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Safety of Low-Dose Oral Food Challenges for Hen's Eggs, Cow's Milk, and Wheat: Report from a General Hospital without Allergy Specialists in Japan

KEITA NAKANISHI[1,*], IKUO OKAFUJI[2], TAKASHI KIHARA[2], YUKINO KAWANAMI[1], AYAKA SHIMIZU[1], SHINPEI KOTANI[1], YOSHIAKI KAMOI[1], and TAKAHIRO OKUTANI[1]

[1]*Department of Pediatrics, Saiseikai Hyogoken Hospital, Kobe, Japan;*
[2]*Department of Pediatrics, Kobe City Medical Center General Hospital, Kobe, Japan*
**Corresponding author*

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An oral food challenge (OFC) is useful for managing food allergies. However, because OFCs have the risk of severe allergic reactions, including anaphylaxis, conducting OFCs under this situation without allergy specialists is difficult. To investigate the safety of a low-dose OFC for eggs, milk, and wheat in a general hospital without allergy specialists. We retrospectively analyzed the medical records of children who were hospitalized in a general hospital without allergy specialists for a low-dose OFC of egg, milk, or wheat between April 2018 and March 2021. The records of 108 patients were evaluated. The median age was 15.8 months (range: 7.5–69.3 months). Challenged foods were eggs (n = 81), milk (n = 23), and wheat (n = 4). Fifty-three (49.0%) patients showed positive allergic reactions. Thirty-five (66.0%) patients showed grade 1 (mild), 18 (34.0%) showed grade 2 (moderate), and none showed grade 3 (severe) reactions. The interventions comprised antihistamines (n = 18), prednisolone (n = 3), inhaled β2-agonist (n = 2). No patients required adrenaline and no deaths occurred. Low-dose OFCs may be safe in a general hospital without allergy specialists. Conducting a low-dose OFC may be essential in food allergy practice.

INTRODUCTION

An IgE-mediated food allergy is a critical problem in children. A total of 5–10% infants are affected by a food allergy in Japan (1). In the United States, as many as 6% of young children are affected by food allergies (2). An IgE-mediated food allergy is suspected in people with a history of allergic reactions to foods, positive blood tests for specific IgE, and positive skin prick tests. However, the oral food challenge (OFC) is considered the most reliable test for the diagnosis of a food allergy (3, 4).

OFC tests have several risks of allergic reactions. The greatest risks from OFCs are anaphylactic reactions or death. Although experienced pediatricians have ample opportunity to provide treatment for acute allergic reactions such as anaphylaxis in the emergency room, their experiences and knowledge alone are not sufficient to provide safe and useful OFCs. According to Japanese guidelines, OFCs should be conducted under the supervision of physicians and nurses who are skilled in the treatment of food allergies and anaphylaxis to ensure safety (3). Because of the risks of OFCs, they can be safely performed under the care of allergists. However, because of the prevalence of allergies in children, not all of them can undergo OFC testing under the supervision of allergists. As a result, OFCs must be performed in general hospitals without allergists and under a system capable of responding to anaphylaxis.

To perform OFCs in the absence of an allergist, methods of reducing the risk of allergic reactions as much as possible need to be determined. A previous report showed that small loading doses reduced the risk of allergic reactions (5).

We conducted a retrospective study to investigate whether a low-dose OFC can be safely performed on hen's eggs, cow's milk, and wheat in a general hospital without allergists on the basis of Japanese guidelines (6).

MATERIALS AND METHODS

This was a single-center, retrospective study. We included patients who were 6 years old and younger and admitted to our hospital for a low-dose OFC of hen's eggs, cow's milk, and wheat between April 2018 and March 2021. The medical records were analyzed. Data of sex, age, blood tests for total and food-specific IgE (ImmunoCap® assay), a history of atopy dermatitis, asthma, or anaphylaxis to the challenged food, whether the

Phone: +81-78-987-2222 Fax: +81-78-987-2221 E-mail: ypyhc881@yahoo.co.jp

challenged food had been consumed previously, and whether there were any dietary restrictions besides those for the challenged foods of wheat, cow's milk, and eggs were collected. Patients who did not have data of total IgE in a blood test or were negative for food-specific IgE were excluded. Patients whose specific IgE (ImmunoCap® assay) results were >100 UA/mL were also excluded not only because a high specific IgE antibody titer is associated with inducing severe symptoms in the Japanese population (6) but also because we could not accurately measure values of >100 UA/mL. This study was approved by the ethics committee of Saiseikai Hyogoken Hospital, Japan (approval number: #R4-04). In accordance with the guidelines and the institutional ethics review board, the research protocol for the benefit of the patients was published on the Saiseikai Hyogoken Hospital website. This information provided patients with the opportunity to refuse to participate in this study instead of obtaining informed consent directly from the parents. The low-dose OFC had the following objectives. First, a definitive diagnosis of a food allergy was required. Second, as shown in Japanese guidelines, the safe intake quantity and tolerance acquisition judgment had to be determined.

Preparation of low-dose OFCs

To ensure safety, the OFC was conducted by general pediatricians who were skilled in the treatment of anaphylaxis and were experienced as pediatricians for more than 5 years. Emergency agents, such as adrenaline, steroids, antihistamines, inhalation bronchodilators and infusion sets, were prepared. Throughout the OFCs, all of the challenged patients were with their parents, and arterial oxygen saturation was monitored. To assess the OFC test results accurately, all of the patients discontinued antihistamines at 72 hours and leukotriene receptor antagonists at 24 hours before low-dose OFCs. On the day of the OFCs, the general condition of the patients, including atopic dermatitis, asthma, and cough, was checked before the OFCs, and only patients in good condition had a low-dose OFC performed. All of the patients had the objectives and risks of low-dose OFCs explained, and informed written consent was obtained from the parents of all challenged patients.

Low-dose OFC methods

Low-dose OFCs were performed using the open method. We performed challenge doses in accordance with Japanese guidelines as follows (6). Up to one cooked egg yolk, or approximately 1/32 of a cooked whole egg, was used for hen's eggs. Cow's milk up to 3 mL was provided. Udon noodles up to 3.5g (50–75 mg of wheat protein) were used for wheat. Hen's eggs were challenged as boiled eggs, which were boiled for more than 20 minutes. Cow's milk was challenged as itself or yogurt. Wheat was challenged as boiled Udon noodles. Challenged foods were divided into one to four portions. The dosing interval was 30–60 minutes. Observation periods after the final challenge were longer than 2 hours.

Severity of reactions

Allergic reactions were classified as shown in the Japanese guidelines (6), with grade 1 (mild), grade 2 (moderate), and grade 3 (severe). Specific symptoms are as follows: grade 1: skin/mucosal symptoms (e.g. localized erythema, mild itch), gastrointestinal symptoms (e.g. discomfort, mild abdominal pain, nausea), respiratory symptoms (e.g. intermittent cough, rhinorrhea), and neurological symptoms (e.g. tiredness); grade 2: skin/mucosal symptoms (e.g. generalized erythema, severe pruritus), gastrointestinal symptoms (e.g. severe abdominal pain, recurrent vomiting), respiratory symptoms (e.g. repetitive cough, wheezing), cardiovascular symptoms (e.g. tachycardia), and neurological symptoms (e.g. somnolence); grade 3: respiratory symptoms (e.g. persistent severe cough), cardiovascular symptoms (e.g. hypotension, cardiac arrest), and neurological symptoms (e.g. loss of consciousness). Grade 1 symptoms are mainly localized and mild, while grade 3 symptoms are mainly severe systemic symptoms and are life-threatening if not treated. Grade 2 is a condition between grade 1 and grade 3. Because grade 1 symptoms are mild, determining whether an allergic reaction is present is difficult. Grade 2 symptoms are more likely to indicate an allergic reaction. Therefore, we grouped the patients according to the presence of a grade 2 reaction. Clinical symptoms were recorded for the respiratory system, cardiovascular system, skin/mucosal area, gastrointestinal system, and neurological system. The most severe symptoms of each of these were used to determine the degree of allergic symptoms. The clinical criteria for the diagnosis of anaphylaxis were determined by referring to the WAO guidelines (7), which proposed the combination of allergic symptoms that are diagnosed as anaphylaxis.

Treatment for OFC-induced symptoms

Treatment at the onset of allergic symptoms was carried out in accordance with the guidelines (6). A brief description of the treatment is provided as follows. An intramuscular adrenaline injection was provided to patients with grade 3 symptoms or several grade 2 symptoms. Therapeutic interventions were attempted for each type of symptom in grade 2 allergic symptoms. Antihistamine and prednisolone were used to treat skin symptoms or gastrointestinal symptoms. Inhaled beta-agonists were used to treat respiratory symptoms, while

tachycardia and hypotension were treated with intravenous saline boluses. When patients developed grade 1 allergic symptoms, they were either closely monitored or received the same treatment as those with grade 2 allergic symptoms.

Challenged food load at home after low-dose OFCs

The amount of food loaded at home was checked at an outpatient clinic within 3 months after the low-dose OFC. Challenged food loads at home were instructed only to those who had negative or grade 1 positive allergic reactions in low-dose OFCs. For cases with grade 2 symptoms, the patients were instructed to load only processed products containing very small amounts. To perform home loading, the patient was instructed to load within the amount loaded in the low-dose OFC. The loading method involved not only the loading of the challenged food itself, but also the loading of processed foods containing the challenged food.

Statistical analysis

Statistical analysis was performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (8), which is a graphical user interface for R (www.r-project.org). Data are expressed as the median (range) or number (%). Fisher's exact test was used to analyze categorical variables, and the Mann-Whitney U test was used to analyze non-categorical values. A p value of <0.05 was considered statistically significant.

RESULTS

One hundred twenty patients underwent low-dose OFCs between April 2018 and March 2021. Four patients were excluded because specific IgE concentrations were >100 UA/mL, five were excluded because of negative specific IgE concentrations, and three were excluded because of missing laboratory data (Figure 1). We reviewed 108 low-dose OFCs. The characteristics of the patients are shown in Table I. There were 81 children challenged with hen's eggs, 23 with cow's milk, and 4 with wheat. The rate of female sex was 27.8%. The median age was 15.8 months (range: 7.5–69.3 months). The rate of patients who have completely eliminated the challenged food was 41.7%. The status of the incomplete elimination of challenged foods is as follows. For hen's eggs, only the cooked egg yolk was loaded in 43 cases, and less than 1 g of the cooked egg white was loaded in 7 cases. For milk, 7 cases loaded bread containing a very small amount of milk (less than 0.3 ml per slice) and 6 cases loaded less than 1 ml of milk.

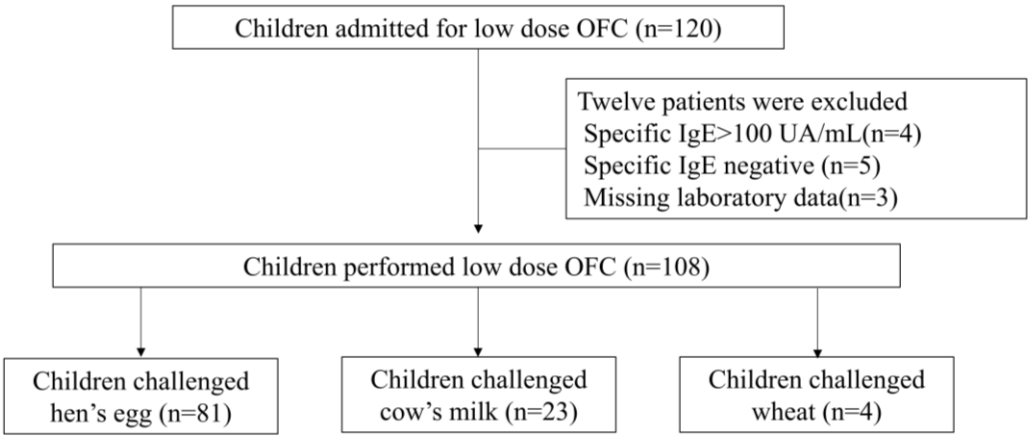

Figure 1. Flowchart of the enrolled participants.
OFC: oral food challenge

Table I. Patients' characteristics

Clinical characteristics	hen's egg(n=81)	cow's milk(n=23)	wheat(n=4)
Age(years)			
<1, n(%)	24(30)	6(26)	0(0)
1-2, n(%)	38(47)	12(52)	3(75)
2-3, n(%)	9(11)	2(9)	1(25)
>3, n(%)	10(12)	3(13)	0(0)
Male, n(%)	58(72)	16(70)	4(100)
total IgE (U/mL), median(range)	76.0(30.0-156.0)	156.0(77.0-373.0)	83.0(35.8-122.5)
specific IgE (UA/mL), median(range)	16.4(5.5-35.8)	15.7(2.9-35.5)	5.5(1.5-11.0)
ovomucoid (UA/mL), median(range)	6.1(1.4-14.0)		
ω5 gliadin (UA/mL), median(range)			4.3(2.2-6.7)
Complete elimination of the challenged food, n(%)	31(38)	10(43)	4(100)
complete elimination only because of positive specific IgE, n(%)	14(17)	4(17)	0(0)
Limited elimination of the other foods in hen's egg, cow's milk or wheat, n(%)	34(42)	18(78)	2(50)
Past history of			
Atopic dermatitis, n(%)	53(65)	18(78)	2(50)
Bronchial asthma, n(%)	7(9)	2(9)	0(0)
Anaphylaxis of the challenged food, n(%)	7(9)	5(22)	2(50)

Among the challenged patients, 67.6% had a past history of atopic dermatitis, and 8.3% had bronchial asthma. Thirteen percent of patients had a past history of anaphylaxis to the challenged food. No patients had a history of severe anaphylaxis requiring adrenaline or an intravenous infusion of normal saline.

Of the 108 patients, 53 (49.0%) had some allergic reactions (Table II). Thirty-three (41%) children challenged with hen's eggs showed positive allergic reactions, 20 (87%) children challenged with cow's milk showed positive allergic reactions, and none of the children challenged with wheat showed positive allergic reactions. Thirty-five (32.4%) patients had a grade 1 allergic reaction, 18 (16.7%) patients had a grade 2 allergic reaction, and no patients had a grade 3 allergic reaction or deaths. Of the allergic reactions, 45 (41.7%) patients presented with skin/mucosal symptoms, 9 (8.3%) had gastrointestinal symptoms, 5 (4.6%) had respiratory symptoms, and none had cardiovascular or neurological symptoms. Regarding treatment for allergic reactions, antihistamines were used in 18 (16.7%) patients, steroids in 3 (2.8%) patients, and bronchodilators in 2 (1.9%) patients, and no patients were treated with adrenaline or an intravenous bolus of saline. None of the patients, except for one patient (challenged with cow's milk) were hospitalized overnight.

Table II. Results of low-dose OFCs

Results of OFC and Treatments	hen's egg(n=81) n(%)	cow's milk(n=23) n(%)	wheat(n=4) n(%)
Low-dose OFC positive	33(41)	20(87)	0(0)
grade 1	24(30)	11(48)	0(0)
grade 2	9(11)	9(39)	0(0)
grade 3	0(0)	0(0)	0(0)
death	0(0)	0(0)	0(0)
Symptoms of			
skin/mucosal	28(35)	17(74)	0(0)
gastrointestinal	8(10)	1(4)	0(0)
respiratory	2(3)	3(13)	0(0)
cardiovascular/neurological	0(0)	0(0)	0(0)
Treatment for allergic synptoms			
antihistamines	11(14)	7(30)	0(0)
steroids	1(1)	2(9)	0(0)
bronchodilators	0(0)	2(9)	0(0)
adrenalines	0(0)	0(0)	0(0)
saline infusions	0(0)	0(0)	0(0)
hospitalization for 1 day	0(0)	1(4)	0(0)
successfully decreased elimination after OFC	64(79)	13(57)	4(100)

OFC: oral food challenge

The characteristics of patients with positive challenge results and those with negative challenge results to hen's eggs, cow's milk, and wheat were compared (Table III). Total serum IgE concentrations were significantly higher in the low-dose OFC-positive group than in the low-dose OFC-negative group (116 [44.0–268.0] U/mL vs. 64 [20.5–137.0] U/mL, $p = 0.02$).

Table III. Comparison of positive low-dose OFCs vs. negative low-dose OFCs

	Results of low dose OFC		
	positive(n=53)	negative(n=55)	
Clinical characteristics			*p*
Male, n(%)	41(77)	37(67)	0.286
age(months), median(range)	16(12.0-27.0)	15(10.5-22.0)	0.221
total IgE (U/mL), median(range)	116(44.0-268.0)	64(20.5-137.0)	0.020*
Past history of			
Atopic dermatitis, n(%)	39(74)	35(64)	0.304
Bronchial asthma, n(%)	5(10)	4(7)	0.74
Anaphylaxis of the challenged food, n(%)	9(17)	4(7)	0.147
Limited elimination of the other foods in hen's egg, cow's milk or wheat, n(%)	31(59)	23(42)	0.123

OFC: oral food challenge. *$p < 0.05$

Specific IgE (hen's eggs, ovomucoid, and cow's milk) concentrations were not significantly different between the two groups. There was no significant difference in sex or age between the two groups. There was no significant difference in the history regarding atopic dermatitis, bronchial asthma, and anaphylaxis to the challenged food between the two groups. Limited elimination of the other foods in hen's eggs, cow's milk, or wheat was also not significantly different between the two groups.

Total serum IgE concentrations were significantly higher in the grade 2-positive group than in the less than grade 2-positive group (163.5 [96.3–266.5] U/mL vs. 79.0 [32.5–156.0] U/mL, $p = 0.0219$) (Table IV). Specific IgE and ovomucoid concentrations in the hen's egg challenged group were also significantly higher in the grade 2-positive group than in the less than grade 2-positive group (42.9 [31.8–56.6] U/mL vs. 15.8 [6.2–36.0] U/mL, $p < 0.01$; 14.0 [11.3–38.0] U/mL vs. 4.9 [1.3–13.1] U/mL, $p = 0.0194$, respectively).

Table IV. Comparison of a positive low-dose OFC of grade 2 vs. less than grade 2

	Results of low dose OFC		
	grade 2(n=18)	less than grade 2(n=90)	
Clinical characteristics			*p*
Male, n(%)	13(72)	65(72)	1
age(months), median(range)	18.5(13.9-26.1)	15.3(11.2-22.7)	0.268
total IgE (U/mL), median(range)	163.5(96.3-266.5)	79.0(32.5-156.0)	0.022*
Past history of			
Atopic dermatitis, n(%)	14(78)	59(66)	0.413
Bronchial asthma, n(%)	1(6)	8(9)	1
Anaphylaxis of the challenged food	4(22)	10(11)	0.245
Limited elimination of the other foods in hen's egg, cow's milk or wheat, n(%)	12(67)	42(47)	0.196

OFC: oral food challenge. *$p < 0.05$

Table V. Results of low-dose OFCs in patients who completely eliminated the challenged food before low-dose OFCs

	hen's egg(n=31)	cow's milk(n=10)	wheat(n=4)
Results of OFC	n(%)	n(%)	n(%)
Low-dose OFCs positive	7(23)	8(80)	0(0)
grade 1	5(16)	4(40)	0(0)
grade 2	2(7)	4(40)	0(0)
grade 3	0(0)	0(0)	0(0)
death	0(0)	0(0)	0(0)
Symptoms of			
skin/mucosal	5(16)	8(80)	0(0)
gastrointestinal	2(6)	0(0)	0(0)
respiratory	0(0)	0(0)	0(0)
cardiovascular/neurological	0(0)	0(0)	0(0)
Treatment for allergic symptoms			
antihistamines	2(6)	3(30)	0(0)
steroids	0(0)	2(20)	0(0)
bronchodilators	0(0)	0(0)	0(0)
adrenalines	0(0)	0(0)	0(0)
transfusions	0(0)	0(0)	0(0)
hospitalization for 1 day	0(0)	1(10)	0(0)
successfully decreased elimination after OFC	29(94)	6(60)	4(100)

OFC: oral food challenge

However, specific IgE concentrations in the cow's milk challenge group were not significantly different between the two grades (data not shown).

A subgroup analysis was performed for cases of complete elimination of the challenged foods (Table V). There were 45 cases of complete elimination (hen's eggs: 31 cases, cow's milk: 10 cases, and wheat: 4 cases), of which 15 (33%) were positive for the low-dose OFC (7/31 [23%] for hen's eggs, 8/10 [80%] for cow's milk, and 0/4 for wheat). After the low-dose OFC, 39 (87%) patients were able to increase the challenged foods at home (29/31 [94%] for hen's eggs, 6/10 [60%] for cow's milk, and 4/4 [100%] for wheat).

Table VI shows whether the low-dose OFC reduced restriction of the challenged foods at home. Eighty-one (75.0%) patients were able to increase their intake of challenged foods at home after the low-dose OFC test. Children who were able to increase their intake had a significantly lower rate of being positive to the low-dose OFC than children who were unable to increase their intake (33% vs. 96%, $p < 0.01$). A significant difference was found in complete elimination of the challenged food before low-dose OFC between these two groups (48% vs. 22%, $p < 0.024$). When we focused on the results according to the degree of allergic reactions, no significant difference was found in grade 1 between these two groups. However, a significant difference was found in grade 2 between the group of children who were able to increase their intake and the group of children who were not able to increase their intake (2% vs. 59%, $p < 0.01$). There were significant differences in skin/mucosa, respiratory, and gastrointestinal symptoms between the group of children who were able to increase their intake and the group of children who were not able to increase their intake (30% vs. 78%, $p < 0.01$; 0% vs. 19%, $p < 0.01$; 4% vs. 22%, $p < 0.01$, respectively). There was no significant difference in grade 1 skin/mucous membrane symptoms between these two groups. However, the rate of grade 2 symptoms was significantly lower in the group of children who were able to increase their intake than in the group of children who were not able to increase their intake (2% vs. 52%, $p < 0.01$). There were no significant differences between these two groups in the rate of cases with a decrease in total IgE when the change in total IgE before and after low dose OFCs was compared (24% vs. 22%, $p = 1$).

Table VI. Comparison of successfully reduced restriction vs. no reduced restriction on the challenged food after a low-dose OFC.

	After low dose OFC		
Clinical characteristics and Results of OFCs	Reduced restriction (n=81)	No reduced restriction(n=27)	*p*
Male, n(%)	57(70)	21(78)	0.621
age(months), median(range)	15(11.0-21)	19(11.5-29)	0.233
total IgE, median(range)	73(34.0-159)	116(63.5-265)	0.069
Past history of			
Atopic dermatitis, n(%)	51(63)	22(81)	0.098
Bronchial asthma, n(%)	6(7)	3(11)	0.688
Anaphylaxis to the challenged food, n(%)	11(14)	3(11)	1
Limited elimination of the other foods in hen's egg, cow's milk or wheat, n(%)	36(44)	18(67)	0.074
Complete elimination of the challenged food before low-dose OFC	39(48)	6(22)	0.024*
Low-dose OFC positive, n(%)	27(33)	26(96)	<0.01*
grade1, n(%)	25(31)	10(37)	0.636
grade2, n(%)	2(2)	16(59)	<0.01*
grade3, n(%)	0(0)	0(0)	
respiratory, n(%)	0(0)	5(19)	<0.01*
gastrointestinal , n(%)	3(4)	6(22)	<0.01*
skin/mucosa, n(%)	24(30)	21(78)	<0.01*
skin/mucosal symptons of grade 1, n(%)	22(27)	7(26)	1
skin/mucosal fymptons of grade 2 , n(%)	2(2)	14(52)	<0.01*

OFC: oral food challenge. *$p < 0.05$

DISCUSSION

In the current study, by restricting the challenged foods' dose to a low amount, the OFC was able to be safely performed on the basis of the guidelines (6) in a general hospital where allergy specialists were not present. To date, there have been numerous reports on OFCs from hospitals with allergy specialists, but there have been no reports from hospitals without allergy specialists. OFCs are considered essential tests in food allergy practice (4). We believe that this study is important because it showed that the OFC can be safely performed in general hospitals without allergy specialists if the Japanese guidelines are followed.

A low-dose OFC is often performed in patients where the risk is considered high on the basis of a risk assessment before the OFC for safety (9). A history of severe symptoms, such as anaphylaxis or shock, the type of food, high specific IgE concentrations, and medical conditions, such as bronchial asthma, allergic rhinitis, and atopic dermatitis, all increase the risk of OFCs (10).

The recently revised guidelines define low-risk groups by different types of foods according to the history of allergic reactions and low specific IgE concentrations. With regard to hen's eggs, the cut-off point for specific IgE for ovomucoid is <3.5 UA/mL. With regard to cow's milk, the cut-off point for specific IgE is <3.5 UA/mL. With regard to wheat, the cut-off point for specific IgE is <0.7 UA/mL and that for specific IgE for ω5-gliadin is <0.35 UA/mL. In the population with complete elimination, one patient in the hen's egg group, one in the cow's milk group, and zero in the wheat group were considered to be in the low-risk group in this study. Of these, the hen's egg case and the wheat case were negative in the low-dose OFC, while the case in the milk group had a positive low-dose OFC with grade 2. These findings suggested that the OFC should be performed with caution, even if it is a low-dose test, because determining the risk alone may not be possible. The non-low-risk groups as defined by the recently revised guidelines (i.e., the intermediate-risk and high-risk groups), comprised 30 children with the hen's egg challenge, 4 with the cow's milk challenge, and 4 with the wheat challenge in this study. Of these, 7/30 cases in the hen's egg group were positive (grade 1: 5 cases, grade 2: 2 cases), 3/4 cases in the milk group were positive (grade 1: 2 cases, grade 2: 1 case), and zero cases in the wheat group were positive for the low-dose OFC. Therefore, in high-risk patients, the low-dose OFC can be safely performed with caution, even in a general hospital without any experts.

A risk assessment should be performed before OFCs, and if any conditions, such as a history of severe symptoms or complications, are clearly present, the OFC should be performed at a special training facility (3). However, in patients who do not clearly fulfill either of these conditions, low-dose OFCs could be considered to be performed at a non-specialized facility. In this study, 14 patients (7 with hen's eggs, 5 with cow's milk, and 2 with wheat allergies) had a history of anaphylaxis. None of the patients had a history of adrenaline administration, and a low-dose OFC was performed on the basis of the absence of a history of severe allergy. In the group with a history of anaphylaxis in this study, 5/7 patients (grade 1: 3 patients, grade 2: 2 patients) were positive in the hen's egg group, 4/5 patients (grade 1: 2 patients, grade 2: 2 patients) were positive in the cow's milk group, and none were positive in the wheat group. Therefore, these findings suggest that the low-dose OFC

can be safely performed, even in patients with a history of mild anaphylaxis, in a general hospital without allergy specialists. In patients who are considered high risk, parents should receive a full explanation, and a careful decision should be made regarding whether to actually perform an OFC and whether to perform an OFC at a specialized facility.

In this study, the rate of a positive low-dose OFC was low at 41% in patients who were challenged with hen's eggs. The reason for this finding is thought to be that, in 29/81 (36%) of the low-dose OFCs for hen's eggs, well-boiled yolk challenge tests were performed. Well-boiled egg yolk has been reported to be less allergenic than egg white (11). With regard to allergic symptoms, gastrointestinal symptoms were more common in the hen's egg challenge (8/81 [10%]). This result is consistent with a previous report (12). The rate of a positive low-dose OFC was 87% in patients challenged with cow's milk. There were no grade 3 symptoms, but one patient was hospitalized for one night because her grade 2 skin symptom persisted for more than 2 hours after taking antihistamines and steroids. She was managed as an inpatient because of the risk of biphasic allergic reactions. Because cow's milk is listed as a food requiring caution in a guideline (3), even low-dose OFCs should be conducted carefully. In this study, respiratory symptoms were more common in the cow's milk challenge (3/23 [13%]). This result is also consistent with previous reports (13). In this study, all of the patients who had the wheat challenge had no allergic reactions, but wheat is also listed as a food requiring caution in a guideline (3).

Japanese guidelines recommend that the OFC be performed in patients with or the suspicion of an IgE-dependent hen's egg allergy, and in those with a cow's milk allergy to avoid complete elimination (3). Studies have shown the usefulness of a small-dose of OFC for hen's eggs, cow's milk, and wheat (13–15). In this study, after low-dose OFCs, 81 (75.0%) patients were able to increase the amount of challenged food at home. In the case of complete elimination, 87% of the children were also able to increase their intake of the challenged foods at home. Patients who were challenged with hen's eggs were able to increase the load at a higher rate, possibly because well-cooked egg yolks are less likely to cause allergic reactions. The reason why a relatively large number of patients who were challenged with cow's milk were able to increase their load at home, despite the high percentage of positive low-dose OFCs, may be that they were able to proceed with home loading with processed products containing trace amounts. In patients with the wheat challenge, all of them could proceed with home loading because of negative results in the low-dose OFC.

A systematic review of hen's egg and cow's milk allergies reported that the OFC was useful to avoid complete elimination of hen's eggs and cow's milk (16, 17). Cochrane reviews showed that oral immunotherapy was more likely to be useful in hen's eggs and cow's milk than continued complete elimination (18, 19). Especially in cases with severe allergy, oral immunotherapy may be essential. In this study, home loading after the low-dose OFC was guided not only by hen's eggs, milk, and wheat, but also by processed foods, such as bread containing trace amounts of each. By adopting different methods for home small-volume loading, the amount of home loading may have increased, even after low-dose OFCs instead of oral immunotherapy in cases who were thought to have severe allergy. A prospective study is required to verify this possibility.

Based on the present study, the selection criteria for performing low-dose OFCs of hen's eggs, cow's milk and wheat at a general hospital without allergy specialists are: 1) no history of life-threatening anaphylaxis and 2) no complications such as severe asthma or severe atopic dermatitis. Risk factors associated with inducing severe symptoms are described in the guidelines (6), therefore, the guidelines should be followed. In addition, allergy specialists should be consulted.

There are several limitations to this study. First, this was a single-center, retrospective study with a small number of cases. The reason may be a small number of cases why there were no significant differences in the rate of cases with a decrease in total IgE between the group of children who were able to increase their intake and the group of children who were not able to increase their intake after low-dose OFCs when the change in total IgE before and after low-dose OFCs was compared. Second, there were only four wheat-challenged patients. Third, the total number of low-dose OFCs and the loading interval were not standardized. Fourth, our study might have included patients who did not require a low-dose OFC, but could have been safe with a moderate-dose OFC. Fifth, after the low-dose OFC, whether a restriction of the challenged food was subsequently removed in the long term is unclear, even in patients where it could be increased soon after the low-dose OFC. Oral immunotherapy may be necessary in collaboration with a specialized facility to remove this restriction.

In conclusion, a low-dose OFC can be safely performed at a non-specialized facility on the basis of guidelines. After a low-dose OFC, many patients are able to increase their home load not only by challenged foods but also by ingesting processed foods containing small amounts of the challenged food even in cases who were thought to have a severe allergy. Further studies are required to determine whether children with food allergies can safely increase their intake and whether their allergies can disappear after low-dose OFCs in the long term.

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