



Letter

Probability curves for predicting symptom severity during oral food challenge with milk

Oral food challenges (OFCs) have been used for the accurate diagnosis of food allergies in patients with an allergic history or may have a complete tolerance to certain food allergies. Currently, OFCs are performed in Japan to assess the risks of ingesting causative food agents and prepare treatment plans tailored to the individual.¹ Patients at low risk of severe allergic reactions when consuming allergenic food can evade strict avoidance and might outgrow their food allergy.² Nonetheless, life-threatening events during OFCs should be avoided and anticipated, if possible, before starting the OFC. Although the serum-specific IgE level is a useful parameter in predicting a positive OFC result for several allergenic foods, including cow's milk (CM),^{3,4} it has not been effective in predicting symptom severity during OFCs.⁵ To address this clinical concern, basophil activation tests have been reported as a reliable parameter in predicting severe allergic reactions to peanuts⁶; however, this test remains impractical in clinical settings.⁷ Recently, we reported the use of ovomucoid-specific IgE levels to predict severe allergic reactions during egg white OFCs.⁸ In the present study, we present probability curves predicting induced symptom severity during CM OFCs based on milk-specific IgE levels and report the utility of this approach in food allergy practice.

The present study included Japanese children 0 to 2 years old who underwent CM OFCs at pediatric clinics or during hospital admissions from October 2012 through March 2015, with serum milk-specific IgE levels measured within 3 months. Fourteen institutions participated in this study and used the following OFC protocol: 1, 2, 5, 10, and 20 mL of unheated CM was consumed at 15- to 30-minute intervals. We performed OFCs for a definitive diagnosis of food allergy or to determine tolerance after ingesting an allergic food.¹ Indications for OFC were determined by personal physicians based on the clinical history of food allergy and related specific IgE levels.^{1,3,4} We assessed the severity of the induced symptoms using the grading system of the Japanese Guideline for Food Allergy¹ based on the anaphylaxis severity score of Sampson⁹ and prospectively recorded the results in a single database system. Mild objective symptoms, such as an extremely localized rash, or ambiguous subjective symptoms, such as abdominal pain, that could not be judged as a specific symptom of an OFC were temporarily considered indecisive. Symptoms were carefully assessed with each subsequent dose during the challenge or after symptom recurrence at home. We considered the OFC result negative when at least 38 mL of CM was consumed without any symptoms. Patients without allergic symptoms but unable to consume a sufficient dose were excluded from the study.

Milk-specific IgE levels were measured using the ImmunoCAP test (Phadia AB, Uppsala, Sweden) within 3 months of the OFC. In statistical analyses, milk-specific IgE antibodies were considered 0.17 kU_A/L if the level was lower than 0.35 kU_A/L and 100 kU_A/L if the level was at least 100 kU_A/L. The present study was approved by a local research ethics committee and was conducted according to the principles of the Declaration of Helsinki.

We used logistic regression analysis to assess the association between milk-specific IgE levels and the outcome of OFC. Milk-specific IgE levels were used as a linear parameter in the statistical analyses. Statistical analyses were performed for OFC severity grades higher than 1, 2, and 3. There were no indecisive cases in this study population. Probability curves were drawn based on the results of logistic regression analysis. Statistical analyses were performed using JMP 8.0.2 statistical software (SAS Institute, Cary, North Carolina).

In our study population ($n = 153$, with 1 missing data [$n = 152$] for eczema and asthma), 53 patients (34.9%) had active atopic eczema, 9 (5.9%) were taking medications for asthma, and 6 (3.9%) had a history of anaphylaxis after consumption of CM. Fifty children (32.7%) in our study consumed CM for the first time during the OFC. The median milk-specific IgE level was 1.83 kU_A/L (range 0.17–69.7 kU_A/L). During OFC, induced symptoms higher than grades 1, 2, and 3 were seen in 88 children (57.5%), 47 children (30.7%), and 8 children (5.2%), respectively. According to OFC outcomes, 3 different probability curves were constructed from the same population to predict the results of OFC according to milk-specific IgE levels (Fig 1). A milk-specific IgE level of 52.1 kU_A/L had a 95% probability of predicting symptoms higher than grade 1, and a level of 7.3 kU_A/L had a 5% probability for predicting symptoms higher than grade 3. The goodness of fit of the regression model assessed using the Hosmer–Lemeshow test showed no deviation between the model and the observed event rate ($P > .05$).

We demonstrated that our strategy of using serum-specific IgE levels as an instant parameter to predict severe allergic reactions during OFC⁸ could be applied to CM allergy in Japanese children. A 5% probability for predicting symptoms higher than grade 3 was proposed as a useful indicator for performing OFC in a less intensive setting⁸ and was estimated in the present study of CM allergy. The results of the present study strengthen our strategy in food allergy practice. A limitation of the present study is the target age of the study population. When we extended the target age to at least 3 years, the probability of severe allergic reactions was not well estimated by specific IgE levels. This could be due to an inclusion bias, that is, some patients with milk allergy are remitted before 3 years of age and older patients are a high-risk group for severe

Disclosures: Authors have nothing to disclose.

<http://dx.doi.org/10.1016/j.anai.2015.06.019>

1081-1206/© 2015 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

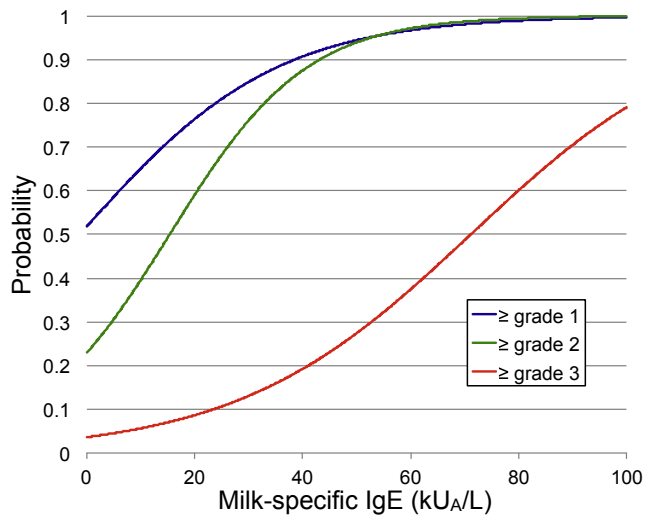


Figure 1. Probability curves for milk-specific IgE levels in patients 0 to 2 years old (n = 153). Fitted predictive probability curves predicting the outcomes after an oral food challenge with cow's milk are shown.

reactions, although the probability depends on the characteristics of the study population. Apart from this limitation, many CM OFCs are performed before 3 years of age¹ and our study population was comprised of patients from many first-line institutions of food allergy, demonstrating the applicability of this strategy to a common clinical practice.

Using this strategy, we are able to provide more accurate pre-OF risk guidelines to patients with CM allergy.

Mizuki Yoneyama, MD*
Takayasu Nomura, MD, PhD†
Taisuke Kato, MD‡
Takehiro Sobajima, MD§
Hisashi Tanida, MD¶||
Takehiro Morishita, MD¶¶
Shiro Sugiura, MD, MPH#
Yuichiro Suda, MD**
Yasutaka Hirabayashi, MD††
Chieko Misawa, MD‡‡
Naomi Kamioka, MD*,†
Hidenori Tanaka, MD§§
Mihoko Mizuno, MD|||
Akihiko Terada, MD, PhD¶¶¶
Yasushi Kanda, MD, PhD##
Shinji Saitoh, MD, PhD†
*Department of Pediatrics
Nagoya City West Medical Center
†Department of Pediatrics and Neonatology
Graduate School of Medical Sciences
Nagoya City University
Nagoya, Japan

‡Department of Pediatrics
Gamagori City Hospital
Gamagori, Japan
§Department of Pediatrics
Seirei Mikatahara General Hospital
Hamamatsu, Japan
||Department of Pediatrics
Holy Spirit Hospital
Nagoya, Japan
¶Department of Pediatrics
Shizuoka Saiseikai General Hospital
Shizuoka, Japan
#Department of Pediatrics
Toyohashi Municipal Hospital
Toyohashi, Japan
**Department of Pediatrics
Miyoshi Municipal Hospital
Miyoshi, Japan
††Hibarigaoka Kids Allergy Clinic
Nagoya, Japan
‡‡Department of Pediatrics
Gifu Prefectural Tajimi Hospital
Tajimi, Japan
§§Department of Pediatrics
Komaki City Hospital
Komaki, Japan
|||Department of Pediatrics
Daido Hospital
Nagoya, Japan
¶¶Terada Kid's Allergy & Asthma Clinic
##Department of Pediatrics
Japanese Red Cross Nagoya Daini Hospital
Nagoya, Japan
tnomura@med.nagoya-cu.ac.jp

References

- [1] Urisu A, Ebisawa M, Ito K, et al. Japanese Guideline for Food Allergy 2014. *Allergol Int*. 2014;63:399–419.
- [2] Leonard SA, Caubet J-C, Kim JS, et al. Baked milk- and egg-containing diet in the management of milk and egg allergy. *J Allergy Clin Immunol Pract*. 2015;3:13–23.
- [3] Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol*. 2001;107:891–896.
- [4] Komata T, Soderstrom L, Borres MP, et al. The predictive relationship of food-specific serum IgE concentrations to challenge outcomes for egg and milk varies by patient age. *J Allergy Clin Immunol*. 2007;119:1272–1274.
- [5] Sicherer SH, Wood RA; American Academy of Pediatrics Section on Allergy And Immunology. Allergy testing in childhood: using allergen-specific IgE tests. *Pediatrics*. 2011;129:193–197.
- [6] Santos AF, Du Toit G, Douiri A, et al. Distinct parameters of the basophil activation test reflect the severity and threshold of allergic reactions to peanut. *J Allergy Clin Immunol*. 2015;135:179–186.
- [7] Bird JA, Lack G, Perry TT. Clinical management of food allergy. *J Allergy Clin Immunol Pract*. 2015;3:1–11.
- [8] Nomura T, Kanda Y, Kato T, et al. Probability curves focusing on symptom severity during an oral food challenge. *Ann Allergy Asthma Immunol*. 2014;112:556–557.
- [9] Sampson HA. Anaphylaxis and emergency treatment. *Pediatrics*. 2003;111:1601–1608.