

Outcomes of 84 consecutive open food challenges to extensively heated (baked) milk in the allergy office



Amanda Agyemang, MD, Elizabeth Feuille, MD,
Jeanifer Tang, RN, Ingrid Steinwandtner, RN,
Hugh Sampson, MD, and Anna Nowak-Węgrzyn, MD, PhD

Clinical Implications

- Many milk allergic children tolerate oral challenges to baked milk under supervision. Milk serum-IgE antibody levels can identify patients likely to tolerate baked milk during challenges and ultimately incorporate baked milk into their diet.

TO THE EDITOR:

Cow's milk (CM) is among the most common childhood food allergens. A recent Australian birth cohort study found a prevalence of IgE sensitization to CM of 5.6% among infants.¹ Although the majority outgrow cow's milk allergy (CMA) by school age, children with CM specific-IgE (sIgE) antibody levels exceeding 50 kU_A/L may retain CMA into adolescence. Although standard of care has been strict avoidance of all CM products, a majority of CMA children tolerate extensively heated (baked) CM (BM).²⁻⁴ Incorporating dietary BM expands and improves nutrition, and regular ingestion of BM may accelerate acquisition of tolerance to unbaked milk.⁴ In the process of acquiring tolerance to unbaked milk, patients tolerate higher doses of progressively less well-baked CM proteins.^{3,4}

Since 2008, as part of our clinical practice, we have offered BM-oral food challenges (BM-OFC) to select patients with CMA. To provide practitioners with a practical report of the feasibility and safety of BM-OFC conducted in the allergy office, here we retrospectively review outcomes of these BM-OFC, and compare clinical and serologic markers among those tolerating and reacting. The study was approved by the institutional review board of the Icahn School of Medicine at Mount Sinai and a waiver of informed consent was granted. Patients with CMA were offered BM-OFC to muffin based on allergists' interpretation of history and testing (with CM-sIgE generally <15 kU_A/L), and family preference;^{2,5} strict criteria for BM-OFC were not implemented in our clinical practice. BM-OFC were conducted at Mount Sinai Pediatric Allergy Practice by trained staff per standard protocol. Our analysis included all children who tolerated a full serving of BM and all who reacted to any amount of BM during OFC between January 2008 and December 2015. Serum CM-sIgE levels (ImmunoCAP; Thermo Fisher Scientific, Portage, Mich) and skin prick tests (SPT) using CM extract (Greer Laboratories, Lenoir, NC) were performed before OFC.³

The total BM-OFC dose was 1 muffin (1.3 g milk protein; Table E1, available in this article's Online Repository at www.jaci-inpractice.org)^{4,6} given in 4 increasing doses every 15 minutes,

followed by a 2-hour observation. Challenges were stopped and patients were treated (with oral antihistamine, oral steroids, and/or intramuscular epinephrine) per the discretion of the physician if objective signs of reaction developed. Tolerant children were recommended to incorporate baked milk into regular diet.⁶ Statistical significance was calculated using the Mann-Whitney *U* test for continuous variables and mid-P calculation for categorical variables with Graphpad Prism 7 statistical software.

Between January 2008 and December 2015, 84 patients underwent BM-OFC to muffin; 15 subjects who did not consume the full challenge dose for reasons other than allergic reaction were excluded. All of the 69 subjects included in the analysis had milk-sIgE and milk SPT preceding OFC. Most sIgEs and SPT were performed within 1 year and within 6 months before OFC. There were no significant differences in baseline age, gender, or atopic illness between those tolerating and reacting (Table E2, available in this article's Online Repository at www.jaci-inpractice.org).

Of 69 children included in muffin OFC analysis, 72% (n = 50) tolerated a full serving. sIgE levels (kU_A/L) were significantly lower among tolerant children (CM-sIgE median 2.8, interquartile range [IQR] 0.9-5.3) compared with reactors (CM-sIgE median 5.2, IQR 3.6-10.2) (*P* = .003) (Figure 1, Table E2, available in this article's Online Repository at www.jaci-inpractice.org). Sensitivity, specificity, and likelihood ratios of CM-sIgE for muffin OFC are given in Table I.

Among muffin reactors (n = 19), the most common symptoms were oropharyngeal pruritus (47%) and urticaria (32%) (Figure 1, C). Median cumulative dose before symptom onset was one-fourth muffin (IQR 1/8-1/2). Most reactions (63%) were treated with oral antihistamine. Eight children (12% of all challenged; 42% of subjects who reacted) developed symptoms of anaphylaxis, including one or a combination of the following symptoms: oral pruritus and swelling, vomiting, urticaria, cough with coarse breath sounds, and/or tachycardia. Of these, 6 were treated with intramuscular epinephrine; the remaining 2 were treated with oral antihistamine and oral steroids. None received more than 1 dose of epinephrine. No delayed reactions were reported after the 2-hour observation period. CM-sIgE (kU_A/L) and SPT wheal diameters (mm) were similar among reactors given epinephrine (CM-sIgE median 4.3, IQR 3.6-11.3; SPT median 7.5, IQR 4-13) and reactors not given epinephrine (CM-sIgE median 6.2, IQR 3.4-10; SPT median 9, IQR 8-13) (*P* = .88 and .37, respectively).

In this retrospective study, we describe outcomes of 84 BM-OFC in the allergy office at a food-allergy referral center. As in previous studies, the majority (72%) of milk allergic children included in the analysis who underwent BM-OFC were BM tolerant.^{2,3,7} Among this referral population, 42% of reactors (and 12% of all challenged) developed mild anaphylaxis. All reactions resolved quickly with in-office medications, and no children required monitoring after the 2-hour observation period. Milk-sIgE levels were significantly higher in reactive patients and appear useful in predicting tolerance.^{2,3,5,8,9} In contrast to prior studies,^{2,3,5,8} SPT wheal diameters were similar among those reacting and tolerating BM-OFC, and appear in

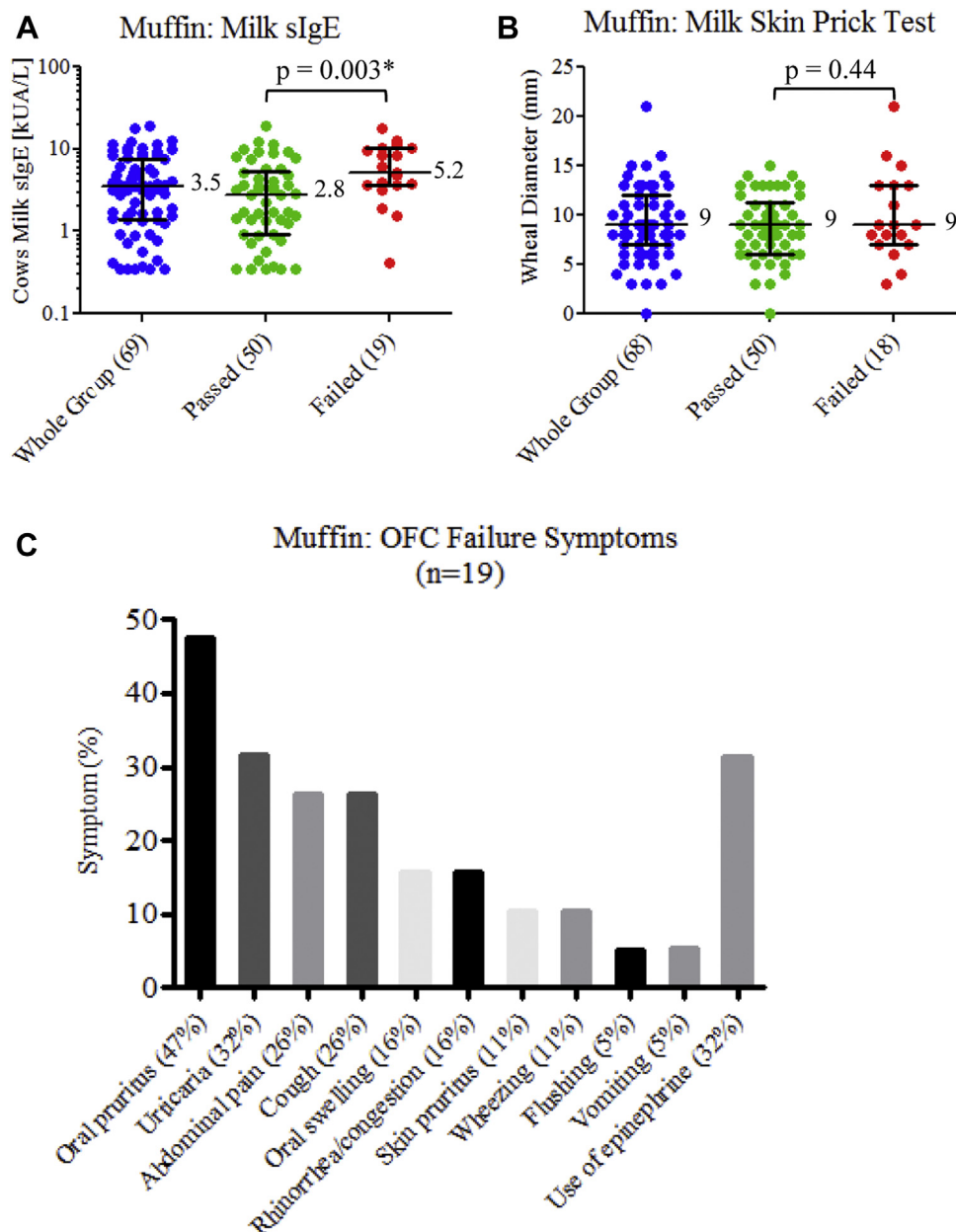


FIGURE 1. Specific IgE, skin prick tests, and symptoms associated with muffin oral food challenges (OFC). Serum cow milk-sIgE (**A**) and skin test results (**B**) before muffin OFC are shown. Median values are labeled and bracketed by interquartile ranges indicated by bars. P values (*significance defined as $<.05$) were calculated using the Mann-Whitney U test. Symptoms during failed OFC are shown in (**C**).

our analysis to have less utility in predicting tolerance when compared with sIgE.

Study limitations include the retrospective design, as well as the lack of follow-up to determine what portion of tolerant children continue to tolerate BM at home and if tolerance to unbaked milk was attained. As subjects were not challenged to unbaked CM to confirm the continued presence of unbaked CMA, we cannot exclude the possibility that some subjects may have already tolerated unheated CM at the time of BM-OFC.

Among patients at this referral center, we anticipate that food allergy is likely to be more prevalent and accompanied by reactions that are more severe than in the typical community-based allergy clinic. This limitation may provide reassurance that we have captured the more severe phenotype of potential reactions during BM-OFC.

In conclusion, we have summarized outcomes of in-office BM-OFC conducted outside the research setting. This study provides further evidence that BM-OFC can be safely conducted

TABLE I. Sensitivity, specificity, and likelihood ratios for various serum milk sIgE of 69 children who underwent muffin-OFC

Milk sIgE (kU _A /L)	Sensitivity	Specificity	Positive LR	Negative LR
1	0.95	0.26	1.28	0.2
8	0.42	0.86	3	0.67
10	0.26	0.92	3.25	0.80

LR, Likelihood ratio; OFC, oral food challenge; sIgE, specific IgE.

Milk serum IgE levels greater than or equal to cutoff values suggested above are associated with positive and negative likelihood ratios specified.

in the allergist's office to identify children with CMA who can tolerate baked milk.

Division of Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, NY

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Conflicts of interest: H. Sampson has received consultancy fees from Allertein Therapeutics LLC, Hycor, and Union Chimique Belge; is employed by and has stock options in DBV Technologies; has received research support from National Institute of Allergy and Infectious Diseases (Consortium of Food Allergy Research, Immune Tolerance Network); and receives royalties from UpToDate. A. Nowak-Węgrzyn has received research support from Nestle, Nutricia, DBV, Aimmune, Thermo Fisher Scientific, and Astellas; has received lecture fees from ThermoFisher Scientific; receives royalties from UpToDate; has received payment for developing educational presentations from Annenberg Center, Nestle. The rest of the authors declare that they have no relevant conflicts of interest.

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Corresponding author: Anna Nowak-Węgrzyn, MD, PhD, Division of Pediatric Allergy and Immunology, Jaffe Food Allergy Institute, Department of Pediatrics,

Icahn School of Medicine at Mount Sinai, 1 Gustave Levy Place, Box 1198, New York, NY 10029. E-mail: anna.nowak-wegrzyn@mssm.edu.

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ONLINE REPOSITORY

TABLE E1. Instructions for an outpatient baked milk oral food challenge

Baked-milk muffin recipe	
Yield	6 muffins, approximately 1.3 g milk protein per muffin
Ingredients	1 cup of milk 2 tbsp. canola oil 1 tsp. vanilla extract 1 egg* or 11/2 tsp. egg replacer if child is allergic to egg† 11/4 cup of flour‡ 1/2 cup sugar 1/4 tsp. salt 2 tsp. baking powder
Instructions	1. Preheat oven to 350°C (do not use a conventional oven) 2. Line a muffin pan with 6 muffin liners. 3. Using a wire whisk, whisk together the liquid ingredients: milk, canola oil, vanilla extract, egg or egg replacer (although the egg replacer is a dry ingredient, please add at this step). Set aside. 4. In a separate mixing bowl, mix together the dry ingredients (flour, sugar, salt, baking powder). 5. Add the liquid ingredients to the dry ingredients. Whisk until combined. 6. Divide the batter into the 6 prepared muffin liners. Depending on the size of your muffin tin, you may need to fill the muffin liners all the way to the top. If you make more than 6 muffins, please note how many muffins you made and bring at least 2 muffins with you on the day of the challenge. 7. Bake for 30-35 min or until golden brown and firm to the touch. 8. After you finish baking, please cut 1 muffin in half. The center should be dry and not wet, moist, or gooey. If it is, please cover the muffins with aluminum foil and bake for another 5-7 min.

*Do not use egg if the child is allergic to egg.

†For example, Ener-G brand egg replacer.

‡Do not use if the child is allergic to wheat.

TABLE E2. Baseline characteristics of participants in muffin on-line oral food challenges (OFC)

	Passed (n = 50)	Failed (n = 19)	P
Baseline characteristics			
Median age in years (IQR)	6.2 (2.9-10.0)	8.0 (3.3-11.1)	.40
Males	34 (68%)	12 (63%)	.70
Asthma	26 (52%)	11 (58%)	.66
Allergic rhinitis	27 (54%)	13 (68%)	.28
Atopic dermatitis	42 (84%)	13 (68%)	.16
History of reaction to milk	49 (98%)	19 (100%)	n/a*
History of anaphylaxis to milk	13 (26%)	5 (26.3%)	.98
Testing: median (IQR)			
Cow milk sIgE, kIU/L	2.8 (0.9-5.3)	5.2 (3.6-10.2)	.003
SPT wheal diameter, mm	9 (6-11)	9 (7-13)	.44

IQR, Interquartile range; SPT, skin prick test.

P values for demographic characteristics were obtained using the mid-P method with odds ratio (OR) calculation. P value for comparison of ages was obtained using the Mann-Whitney U test.

*OR and P value not calculable due to division by 0.

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