

Long-term outcomes following baked milk-containing diet for IgE-mediated milk allergy



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Clinical Implications

- Previous studies have reported that most IgE-mediated milk-allergic patients tolerate baked milk products. We found that ingestion of baked milk was safe and well tolerated; however, initial successful challenge does not guarantee ongoing consumption of these products.

TO THE EDITOR:

Cow's milk allergy is the most common IgE-mediated food allergy in childhood, estimated to affect 0.3% to 3% of young children in different countries,^{1,2} and responsible for up to 13% of fatal food-induced anaphylaxis. The overall prognosis is favorable, with most children eventually outgrowing their allergy, although recent studies suggest that tolerance develops at lower rates and with a longer time to resolution than previously believed.³ The elimination of milk products from a child's diet and the persistent fear of accidental exposure have a profound negative impact on quality of life, nutrition, and even on bone density.⁴ Taken together, these observations indicate a need for better alternatives in the active treatment for IgE-mediated milk allergy. An increasing body of evidence has demonstrated that oral immunotherapy (OIT) with incremental doses of raw milk could serve as an emerging interventional treatment modality for milk allergy. However, this modality has many limitations that have retarded acceptance for widescale clinical practice.⁵ There may be an alternative to OIT with raw milk based on the observation that children who eventually outgrew their milk allergy had milk-specific IgE antibodies directed primarily against heat-labile conformational epitopes, whereas persistent milk allergy is characterized by milk-specific IgE antibodies against heat-stable sequential epitopes. Indeed, Nowak-Węgrzyn et al⁶ demonstrated that 75% of IgE-mediated cow's milk-allergic subjects tolerated baked milk (BM) products. Similar findings have been reported in a few additional small studies.^{7,8} However, knowledge regarding the long-term follow-up of these cohort patients is scarce. The aim of this study was to prospectively evaluate the long-term safety and natural course of this intervention.

This was a prospective single-arm interventional trial in children with IgE-mediated milk allergy. Subjects were recruited from 3 pediatric allergy clinics (Tel Aviv Sourasky Medical Center, E. Wolfson Medical Center, and the Haemek Medical Center, Israel) during February 2012 to April 2016. The study was approved by ethical review boards from each medical

institution, and informed consent was obtained. Inclusion and exclusion criteria, design of the study, and food challenges with BM, baked cheese (BC), and unheated milk (UM) are described elsewhere⁹ and in the [Appendix](#) (available in this article's Online Repository at www.jaci-inpractice.org). A sample size of 60 subjects was calculated as necessary to provide 80% power to detect a true difference between the sample proportion (hypothesized to be 0.9) and the known proportion (0.75), using a 2-sided alpha of 0.05 and the test comparing an observed proportion to a known proportion.

Statistical analyses and comparisons of numerical data between the BM-reactive group and the BM-tolerant group were performed with the *t* test for continuous variables with normal distribution and Wilcoxon rank tests for variables with abnormal distribution. Comparisons between categorical variables were performed with the *Z* test. A probability *P* value of less than 5% was considered significant.

Figure 1 describes the flow diagram of the study. A total of 85 children (median age, 5.2 years; range, 15 months to 15 years) were prospectively followed for a median of 29 months (range, 15-50 months). Among 70 (82%) children who initially tolerated BM challenge, 26 (37%) tolerated UM at last follow-up, 16 (23%) tolerated BM/BC, 25 of 70 (36%) avoided all forms of milk despite a successful initial BM or BC challenge at the clinic, and 3 (4%) were lost to follow-up. If we consider all 85 children who participated in the study, then, 26 (31%) tolerated UM at last follow-up, 16 (19%) tolerated BM/BC, 25 of 85 (29%) avoided all forms of milk despite a successful initial BM or BC challenge at the clinic, and 3 (3%) were lost to follow-up.

Fifteen out of 85 (18%) BM participants reacted to the initial BM challenge. The reactions were mild in most cases and only 3 had an anaphylactic reaction. All the subjects who initially failed the BM challenge refused another challenge with BM and completely avoid all forms of dairy products, including 2 of 15 (13%) who reacted to milk after accidental exposure. Predictive parameters for reactivity to initial BM challenge were older age with a median age of 7 years (range, 2.5-15 years) versus 3.5 years (range, 1-14.5 years) (*P* = .02), asthma prevalence (53% vs 14.3%; *P* < .01), a history of respiratory symptoms such as sneezing and rhinorrhea as part of the original allergic reaction to raw milk (67% vs 26%; *P* < .01), and larger skin prick test (SPT) wheal size to casein (median 14 mm vs 6 mm; *P* < .01). In contrast, sex, a history of atopic dermatitis, previous anaphylactic reaction, and SPT wheal size to cow's milk were not significantly different.

BM CONSUMPTION—LONG-TERM FOLLOW-UP

Thirteen out of 70 BM-tolerant children (19%) had eventually stopped consuming BM products. Reasons for stopping were mild skin rash or tingling oral sensation in 5, gastrointestinal symptoms in 4, and rhinorrhea in 1. The rest, 3 of 13 (23%), described aversion, emotional distress, or anxiety from a potential reaction. The parents refused to repeat the challenge and preferred to avoid all forms of milk products in their children's diet. Two participants were lost to follow-up. The BM dropout group (*N* = 13) was compared with the group of patients who continue to consume BM products in

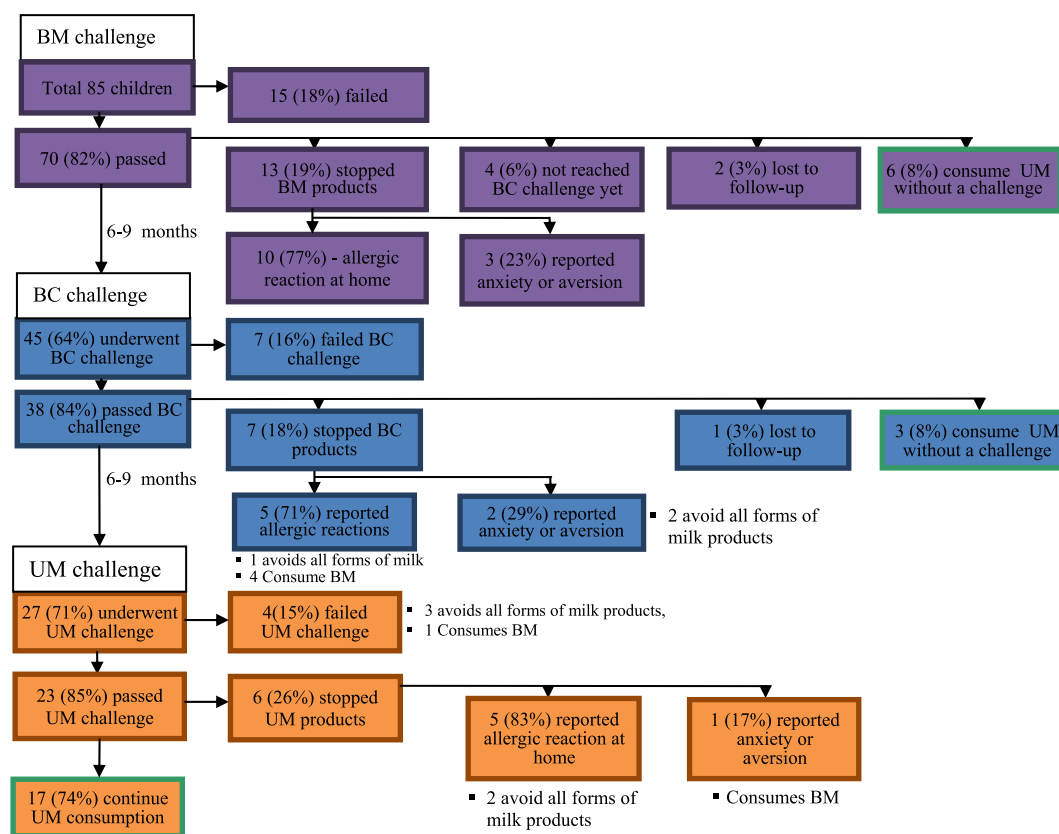


FIGURE 1. Flow diagram of the study. *BM*, Baked milk; *BC*, baked cheese; *UM*, unheated milk.

their diet ($N = 55$). SPT wheals to both cow's milk—median of 20.5 mm (range, 8–40 mm) versus 10 mm (range, 0–33 mm) ($P < 0.01$)—and to casein—median of 7.5 mm (range, 6–18 mm) versus 5 mm (range, 0–15 mm) ($P = .04$)—were significantly larger in the dropout group. Other parameters, including age, sex, and a history of atopic dermatitis, asthma, respiratory symptoms, and anaphylaxis as part of the original allergic reaction to raw milk, were not significantly different.

BC CHALLENGE

Forty-five out of 70 BM-tolerant children (64%) participated in the BC challenge and 38 (84%) tolerated it. The allergic reactions of the 7 subjects who failed the initial BC challenge included urticaria or angioedema in 4, gastrointestinal symptoms in 2, and respiratory symptoms in 1. None developed anaphylaxis. Currently, 3 (43%) of those failing the initial BC challenge continue to consume BM products, and 4 (57%) avoid all forms of milk products. One patient was lost to follow-up after a successful BC challenge.

BC CONSUMPTION LONG-TERM FOLLOW-UP

Three of the 38 (8%) children who initially tolerated BC challenge currently consume UM products, before the UM challenge at the clinic. Seven (18%) stopped regular consumption of BC products: because of gastrointestinal symptoms in 4, oral sensation and rash in 1, and 2 did not report specific reasons

for discontinuing the diet. Of these 7 patients, 4 continue consuming BM products in their diet.

UM CHALLENGE

Twenty-seven out of 38 (71%) BC-tolerant children participated in the UM challenge, and 23 (85%) passed it. Four patients (15%) developed immediate allergic reactions including rash in 1, gastrointestinal symptoms in 1, and anaphylactic reactions treated with epinephrine in 2.

UM CONSUMPTION LONG-TERM FOLLOW-UP

Six of 23 (26%) stopped UM consumption: because of mild rash and pruritus in 4, gastrointestinal symptoms in 1, and another 1 with no apparent reason. Of these 6 patients, 3 currently consume BM, 1 BC, and another 2 avoid all forms of dairy products. The rest (17 [74%]) of the patients continue to consume UM products. Three out of 4 patients who failed the initial UM challenge currently avoid all forms of dairy products and 1 consumes BM.

Our study demonstrated the relative safety of BM-containing diet for IgE-mediated milk allergy and similar short-term gains noted in other studies,^{7–9} but raises questions about the long-term consequences of BM ingestion in our patients who were followed-up for a median of 29 months. Previous studies reported dropout rates of only 6% to 12% after initial successful BM challenges,^{7–9} whereas we have found that more a third of our patients who initially tolerated BM, BC, or UM challenges later avoided consumption of milk products. In this group of

intolerant patients, 20 of 26 (77%) developed mild allergic reactions manifested mostly as gastrointestinal and dermatological symptoms. The rest of this group (6 of 26 [23%]) reported nonspecific symptoms such as aversion or anxiety, emphasizing the challenges of strict adherence to proper food preparation and selection and the significant psychological and emotional impact of food allergy on milk-allergic patients' lives.

In our cohort, the predictive parameters of reactivity to initial BM challenge include older age, asthma, respiratory symptoms such as sneezing and rhinorrhea as part of the original allergic reaction to raw milk, and a larger SPT wheal size to casein.

In conclusion, we found a somewhat higher proportion of subjects who did not react to initial BM challenge than reported in the literature. However, initial successful challenge with BM/BC does not ensure ongoing tolerance to these products. Indeed, more than a third of our patients ceased consuming milk products, a value considerably higher than that reported in the literature. Better predictors of response are needed to provide guidance for patient selection and improved long-term outcomes.

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APPENDIX

Inclusion criteria included children between the ages of 1 and 18 years, with a positive SPT or detectable serum milk-specific IgE, and a history of an allergic reaction to milk within 6 months before study entry or milk-specific IgE levels or SPT responses greater than 95% of predicted value for clinical reactivity.

Determination of allergy based on tests was as follows: IgE level of more than 5 kUA/L if 2 years or younger; an IgE level of more than 15 kUA/L and mean SPT wheal diameter size of 8 mm or more if older than 2 years. Exclusion criteria included a negative SPT response and undetectable milk-specific IgE levels, unstable asthma, a previously diagnosed food-induced eosinophilic gastroenteropathy, a recent reaction (within 6 months) to BM products, or pregnancy.

The design of the study was based on the initial BM oral challenge. Subjects were categorized as BM reactive or BM tolerant. BM-reactive subjects were instructed to completely avoid all forms of milk, whereas BM-tolerant subjects were instructed to incorporate BM products daily into their diet and after 6 to 9 months were offered challenges to BC products. After 6 to 9 months, BC-tolerant children were offered a challenge to UM. Long-term adherence to milk products consumption as well as late-onset adverse events to these products were evaluated by phone call every 6 months in addition to the regular visits in the clinics.

BM was given in the form of a muffin or cake. Each muffin (or an equivalent piece of cake) contained approximately 1.3 g of milk protein. The muffins/cakes were baked at 180°C for 30 minutes, and were based on a recipe kindly received from HA Sampson's group at the Mount Sinai Jaffe Food Allergy Institute. BM-tolerant subjects were instructed to ingest 1 to 3 servings per day of home-baked products with an equivalent amount of milk protein or store-bought BM products with milk listed as a minor ingredient (third or less). BC was given in the form of well-cooked cheese on a pizza (Maadanot Factory) or in a pastry that was baked at 220°C for 13 minutes or longer. BC-tolerant subjects were instructed to eat any brand of well-cooked cheese products 4 to 7 times weekly and limited to 1 daily serving. UM was given in the form of skim milk or yogurt. A challenge included 240 mL of skim milk (or other products containing 8-10 g of UM protein, such as yogurt). Food challenges were performed according to previously published protocol. Challenges were administered under a physician's supervision (unblinded) in the clinical research units. Muffin (BM challenge) or pizza (BC challenge) was eaten in 4 equal portions over 1 hour. Skim milk (UM challenge) was administered in gradually increasing doses. Subjects were monitored during and up to 4 hours after completion of the challenge. Challenges were discontinued at the first objective sign of a reaction or because of convincing persistent subjective symptoms, and appropriate treatment was initiated immediately.

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