

## Original Article

# Increased Tolerance to Less Extensively Heat-Denatured (Baked) Milk Products in Milk-Allergic Children

Anna Nowak-Węgrzyn, MD, PhD<sup>a</sup>, Kaitie Lawson, MS<sup>b</sup>, Madhan Masilamani, PhD<sup>a</sup>, Jacob Kattan, MD<sup>a</sup>, H.T. Bahnson, MPH<sup>c</sup>, and Hugh A. Sampson, MD<sup>a</sup> *New York, NY; Chapel Hill, NC; and Seattle, Wash*

**What is already known about this topic?** Most milk-allergic children tolerate baked milk.

**What does this article add to our knowledge?** Most muffin-tolerant children progress to pizza or rice pudding, but there is no advantage to frequent escalations.

**How does this study impact current management guidelines?** Escalating every 12 months can be recommended in management of baked milk-tolerant children.

**BACKGROUND:** Most milk-allergic children tolerate baked milk. **OBJECTIVE:** To investigate the effect of more frequent versus less frequent introduction of higher doses of more allergenic (less heat-denatured) forms of milk (MAFM) on progression to tolerance. **METHODS:** Milk-allergic children were challenged with increasing doses of MAFM; baked foods were incorporated into the diet; challenges were repeated at 6- or 12-month intervals over 36 months. **RESULTS:** A total of 136 children (70% males) were enrolled in the active group (median age, 7 years). At baseline, 41 (30%) reacted to muffin, 31 (23%) to pizza, 11 (8%) to rice pudding, 43 (32%) to non-baked milk; and 10 (7%) tolerated non-baked milk. Children who tolerated baked milk but reacted to non-baked liquid milk were randomized to MAFM challenges every 6 months (n = 41) or 12 months (n = 44). At month 36, 61% children in the 6-month and 73% in the 12-month escalation groups tolerated MAFM. Overall, 41 (48%) children who ingested baked-milk diet became tolerant to

non-baked milk; no difference was seen between 6- and 12-month escalations. Among children who reacted to muffin at baseline and continued avoidance, 20% developed tolerance to baked milk and 0% tolerated non-baked milk. None of the 34 children who qualified for inclusion but chose not to take part in the active study became tolerant to any form of milk by history. **CONCLUSIONS:** Majority of children tolerated baked milk at baseline. Baked-milk diets were associated with progressive immunomodulation. Most children who incorporated baked milk into their diet progressed to tolerating MAFM, but there was no advantage to more frequent attempts to escalate to MAFM, per intention-to-treat analysis. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

**Key words:** Milk allergy; Food allergy; Oral immunotherapy; Baked-milk diet; Oral tolerance; Oral immunomodulation

<sup>a</sup>Pediatric Allergy & Immunology, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, NY

<sup>b</sup>Rho, Inc, Chapel Hill, NC

<sup>c</sup>Benaroya Research Institute, Seattle, Wash

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Corresponding author: Hugh A. Sampson, MD, Icahn School of Medicine, Division of Allergy and Immunology, Jaffe Food Allergy Institute, New York City, NY 10029. E-mail: [hugh.sampson@mssm.edu](mailto:hugh.sampson@mssm.edu).

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**Abbreviations used**

AE- Adverse event

CM- Cow milk

CMA- Cow milk allergy

CMP- Cow milk protein

MAFM- More allergenic forms of milk

OFC- Oral food challenge

OIT- Oral immunotherapy

SPT- Skin prick test

Treg- Regulatory T

Cow milk (CM) proteins (CMPs) are frequently the first foreign proteins introduced into the infant's diet and are among common food allergens.<sup>1,2</sup> The natural history of childhood cow milk allergy (CMA) is favorable, with most achieving tolerance by school-age.<sup>3,4</sup> However, serum milk-specific IgE antibody levels exceeding 50 kU<sub>A</sub>/L are associated with an increased risk of persistent CMA into teenage years.<sup>3</sup> Children with IgE antibodies directed predominantly against sequential epitopes of casein and beta-lactoglobulin, and those with antibodies of higher affinity, are more likely to have a persistent and more severe CMA.<sup>5</sup> In contrast, those with IgE antibodies directed predominantly against conformational epitopes and of lower affinity are more likely to have a transient and milder CMA.

Extensive heating, for example, baking, destroys tertiary protein structure and conformational IgE-binding epitopes.<sup>6</sup> We have previously shown that baked CMPs are well tolerated by most milk-allergic children and that children with lower serum casein-specific IgE levels are more likely to be tolerant than children with higher casein-specific IgE levels.<sup>7,8</sup> Baked-milk-tolerant children are characterized by phenotypic heterogeneity regarding the dose and degree of heat-denatured CMP that they tolerate, for example, muffin < pizza < and rice pudding < non-baked liquid milk, reflected by the serum casein-specific IgE levels and basophil activation.<sup>9</sup> The different phenotypes can be partially distinguished by casein- and milk-specific IgE levels, milk-specific basophil reactivity, and milk skin prick test (SPT) mean wheal diameters.<sup>9</sup> Children who ingest baked-milk products are more likely to progress to tolerance of non-baked liquid milk compared with children who maintain strict avoidance.<sup>10</sup> The progression toward tolerance of non-baked liquid milk in children ingesting baked milk is associated with decreased milk SPT wheal diameters, decreased specific IgE levels, and increased specific IgG<sub>4</sub> antibody levels, and decreased basophil reactivity to casein.<sup>7,10</sup> These immunologic changes are similar to the changes observed during oral immunotherapy (OIT) with non-baked milk.<sup>11</sup> We sought to determine whether the more rapid introduction of higher doses of more allergenic (less heat-denatured) forms of milk (MAFM) would result in a more accelerated acquisition of tolerance to non-baked liquid milk.

**METHODS**

We hypothesized that the more rapid introduction of MAFM, defined as escalating to a higher dose every 6 months, would result in a more accelerated acquisition of tolerance to non-baked liquid milk compared with escalating every 12 months. The primary outcome was defined as the odds ratio for progression to tolerance of MAFM in the subjects randomized to escalate their dose every 6 months versus those randomized to escalate every 12 months.

**TABLE I.** Characteristics of the baked foods containing milk

Baked food containing milk	Milk protein dose (g)	Baking temperature (°F)	Baking time (min)
Muffin	1.3	350	≥35
Pizza	4	425	≥13
Rice pudding	7.7	325	≥90
Unheated milk	8	None	None

Secondary outcomes included the degree to which children tolerating various degrees of heat-denatured milk protein developed tolerance over 3 years and the immunologic changes associated with these clinical changes.

**Participants**

Children with CMA were recruited from the pediatric allergy clinics at Mount Sinai and referring allergists from August 1, 2008, to June 30, 2011. The study was approved by the Mount Sinai Institutional Review Board; informed consent was obtained before enrollment. Children aged 4 to 10 years with suspected IgE-mediated CMA were enrolled.

One or more of the following inclusion criteria for enrollment in the study have to be met: In children 4 through 10 years of age: (1) Convincing history of an allergic reaction to milk or a positive double-blind placebo-controlled milk challenge within the past 2 years and either detectable milk IgE or positive SPT result to milk; (2) Serum milk IgE of high predictive value (>14 kU<sub>A</sub>/L) or SPT to milk resulting in a greater than or equal to 10 mm wheal within the past 6 months regardless of clinical history of reactions; (3) Convincing history of an allergic reaction to milk or a positive double-blind placebo-controlled milk challenge more than 2 years ago and either a positive serum milk IgE (<14 kU<sub>A</sub>/L) or positive SPT to milk resulting in a less than 10 mm wheal within the past 6 months (eligible only for the active arm of the study and will undergo a reversed sequence of initial baked-milk challenges). Children were excluded if they had a history (within the past 2 years) of life-threatening anaphylaxis, poorly controlled asthma or atopic dermatitis, eosinophilic esophagitis caused by CM, immunotherapy with anti-IgE antibody within 1 year of enrollment, participation in any food allergy therapeutic trial, or CM IgE levels greater than 35 kU<sub>A</sub>/L (based on our first trial in which we observed that most children with CM IgE levels of >35 kU<sub>A</sub>/L reacted to baked milk, some with anaphylaxis).<sup>7,8</sup>

**Active intervention arm**

Children underwent sequential baseline open oral food challenges (OFCs) to MAFM that were progressively less extensively heat-denatured (baked) and contained higher doses of CMP (Table I) to determine their level of reactivity (Groups 1-5 as shown in Figures 1 and 2.). During the first day, up to 2 foods were tested, muffin and pizza. If a child did not react to pizza, he or she would then return within 2 weeks and undergo rice pudding and non-baked liquid milk OFCs (Figure 1; see Figure E1 in this article's Online Repository at [www.jaci-inpractice.org](http://www.jaci-inpractice.org)). OFCs were stopped at the first objective sign of an allergic reaction. Following baseline OFCs, the children who tolerated at least a muffin but not non-baked liquid milk were randomized to return 6 or every 12 months over a 36-month-period to attempt escalation to the next levels of MAFM. At each escalation visit, the next level of MAFM was challenged first and depending on the outcome, subsequently, the next level up was challenged to

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