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Safety and clinical predictors of reacting to extensively heated cow's milk challenge in cow's milk-allergic children

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ABSTRACT

Background: Many children with IgE-mediated allergy to cow's milk (CM) can tolerate CM in baked foods. **Objective:** To define the clinical characteristics and severity of reactions to baked CM in children with CM allergy (CMA) at an oral food challenge (OFC).

Methods: Children with CMA presenting to a tertiary clinic from 2010 through 2013 with complete dietary CM avoidance were offered a baked CM OFC. Challenges were performed with incremental dosages to a total of 1 baked muffin.

Results: Seventy children with CMA underwent a baked CM OFC. Fifty-one children (73%) passed the OFC and successfully incorporated baked CM into their diet. Nineteen children (27%) reacted to their challenge. Of reactors, 4 (21%) developed anaphylaxis and required intramuscular adrenalin. Predictors of clinical reactivity to baked CM were asthma, asthma requiring preventer therapy, IgE-mediated clinical reactions to more than 3 food groups, and those with a history of CM anaphylaxis.

Conclusion: This study identified factors that were predictors of clinical reactivity to baked CM in this cohort of children with CMA. These risk factors do not represent contradictions to a baked CM challenge but may allow for risk stratification of challenges. Given the potential for anaphylaxis, an OFC to baked CM should be done under medical supervision in those children with CMA who have been strictly avoiding all CM.

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Introduction

Food allergy has increased in prevalence over the past 2 to 3 decades, with a recent birth cohort reporting an incidence of more than 10% in Australian infants.¹ Until recently, most guidelines have recommended strict avoidance of the allergen, in all forms and amounts, from the diets of allergic children. This was done partly to decrease the risk of reaction but also because of the belief that accidental allergen exposure might delay the onset of tolerance.² Cow's milk allergy (CMA) is one of the most common food allergies in childhood, and dietary avoidance can be burdensome,^{3,4} because of the ubiquitous nature of CM in Western diets.

Several groups have reported that many children with CMA can tolerate extensively heated CM (in baked products such as cakes

and biscuits) in serving-size quantities.^{5–8} The ability to incorporate extensively heated CM ("baked" CM) liberalizes the diet and may help to decrease anxiety over accidental ingestion. Regular ingestion of baked CM products also may accelerate acquisition of tolerance to CM and/or alter the natural history of the CMA.⁹

Tolerance to baked CM is usually demonstrated at a formal open food challenge (OFC) under medical supervision, given the potential for anaphylaxis.⁷ Previous reported predictors of reaction to baked CM have included serum specific IgE (ssIgE) to heat-stable casein^{6,8} and basophil reactivity.¹⁰ These parameters do not always allow individual determination of risk. Children tolerant to baked CM are reported to have less severe reactions to follow-up whole CM challenge than those reacting to baked CM, suggesting that children with CMA who tolerate the baked CM may represent a different clinical phenotype from their counterparts with baked CMA.⁷ It is unclear whether other clinical characteristics of children with CMA are helpful in predicting the outcome of a challenge to baked CM. Therefore, the authors sought to assess the safety of an OFC to baked CM in children with a high probability of clinical CMA and identify clinical factors that might predict reaction and anaphylaxis at an OFC.

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Table 1

Characteristics of children with a diagnosis of CMA and following strict dietary avoidance of CM

Characteristic	Negative OFC reaction: tolerates baked CM	Positive OFC reaction: all reactions	Relative risk (95% CI)	Positive OFC: anaphylaxis
Patients, n	51	19		4
Age at challenge (y), median (interquartile range)	4.5 (2.5–8)	7.3 (4.9–9.6)		5.2 (2.4–7)
SPT wheal (mm) to CM at OFC, median (interquartile range)	8 (7.0–10.0)	8.5 (7.5–10.0)		8.3 (7.3–8)
SPT wheal (mm) to muffin at OFC, median (interquartile range)	4.8 (3.0–7.0)	5.3 (4.9–7.3)		4.3 (3.0–5.5)
Sex, n (%)				
Male	30 (59)	11 (58)		3 (75)
Female	21 (41)	8 (42)		1 (25)
Other atopy, n (%)				
Asthma, n (%)	23 (45)	18 (95) ^c	12.7 (1.8–90.1)	4 (100)
Asthma, on preventer therapy, n (%)	12 (24)	13 (68) ^b	2.8 (1.3–6.0)	4 (100)
Eczema, n (%)	32 (63)	18 (95)		4 (100)
Food allergy to ≥3 allergen groups (MFA), n (%)	20 (39)	13 (68) ^b	2.4 (1.0–5.7)	4 (100)
Prior anaphylaxis to food other than CM (AnO), n (%)	6 (12)	6 (32)		3 (75) ^{a,b}
MFA + AnO, n (%)	4 (8)	6 (32) ^b	2.8 (1.4–4.5)	3 (75)
Previous reaction to CM, n (%)				
Anaphylaxis	14 (27)	10 (52) ^b	2.1 (1.0–4.5)	2 (50)
Nonanaphylactic reaction	36 (71)	8 (42)		2 (50)
No history of previous exposure to CM, n (%)	1 (2)	1 (5)		0
<12 mo since last clinical reaction to CM, n (%)	22 (43)	4 (21)		1 (25)

Abbreviations: AnO, anaphylaxis to food other than cow's milk; CI, confidence interval; CM, cow's milk; MFA, multiple food allergies; OFC, oral food challenge; SPT, skin prick test.

^aChildren reacting at the CM OFC without anaphylaxis compared with children reacting with anaphylaxis.

^b $P < .05$.

^c $P < .005$.

Methods

Children presenting to the authors' tertiary referral clinic with a clinical diagnosis of CMA and who were completely avoiding all forms of CM in their diet were offered an OFC to extensively heated CM in a muffin (baked CM) at the Children's Hospital at Westmead in Sydney, Australia. CMA in children was defined as a previous convincing clinical reaction to CM within the past 12 months (with evidence of current sensitization based on a positive skin prick test [SPT] reaction or sIgE to CM) or a previous clinical reaction to CM more than 12 months previously and a current SPT reaction to CM with a wheal larger 7 mm in children older than 2 years or larger than 5 mm in those younger than 2 years or no history of exposure and a current SPT reaction to CM with a wheal larger than 7 mm in children older than 2 years or larger than 5 mm in those younger than 2 years. The exclusion criterion was a recent allergic reaction to baked CM within the past 6 months or refusal of consent; children with prior anaphylaxis to CM or baked CM were not excluded. Recruitment and challenges were conducted over a 3-year period from January 2010 until December 2013.

Children were assessed and examined before the challenge to ensure suitability and to confirm coexisting atopy (physician-diagnosed asthma and receiving preventer therapy, allergic rhinitis, and/or eczema). Allergy to foods other than CM was confirmed based on a history of clinical reaction with confirmatory positive testing (SPT or sIgE) to the allergen implicated. SPT was performed on the day of the OFC according to standard guidelines using 10 mg/mL of histamine (Hollister Stier Laboratories, Spokane, Washington) as a positive control. SPT to muffin slurry was performed as previously reported.¹¹ A positive SPT reaction was defined as a wheal at least 3 mm larger than a saline control read at 15 minutes. The OFC to baked CM followed a national protocol using incremental doses of baked muffin.¹² A standard recipe was used for the muffin, baked at 180°C for 20 minutes, with 1 muffin containing 0.5 g of CM protein. The protocol used for the OFC was as follows: children were fed increments of the muffin, starting from 1/16 of a muffin, 1/8 of a muffin, 1/4 of a muffin, to 1/4 of a muffin and then the remainder at 20-minute intervals. The challenge was halted at the onset of objective clinical symptoms, in line with PRACTALL criteria.¹³ Children were observed for another 2 hours after the last

muffin dose. Anaphylaxis was defined according to World Allergy Organization criteria.¹⁴ Children with reactions involving skin and/or gastrointestinal symptoms alone were classified as having mild to moderate reactions. Patients were instructed to avoid all baked CM for 48 hours to detect possible delayed symptoms and then to introduce baked CM (using a muffin containing a similar amount of CM) 2 to 3 times per week. Patients were followed up by telephone 1 week later to confirm ongoing tolerance.

Data analysis was performed using GraphPad Prism 6 (GraphPad Software, Inc, La Jolla, California). Statistical analysis was performed using nonparametric tests: SPT data were compared using the Mann-Whitney *U* test, and categorical data were analyzed using χ^2 test or the Fisher exact test where appropriate. A *P* value less than .05 was considered significant. The study was approved by the ethics committee at the Children's Hospital at Westmead. Written consent was obtained for all food challenges.

Results

Eighty-six children with a diagnosis of CMA and following strict dietary avoidance of CM were identified, and 70 met the inclusion criteria and were recruited to the study (median age 5.3 years; Table 1). Only 2 children were avoiding CM based on sensitization alone. Twenty-four children (34%) had a history of anaphylaxis to CM. Forty-one children (59%) had a diagnosis of asthma and 23 (33%) were using an asthma preventer. Twelve children (17%) had experienced anaphylaxis to CM and at least 1 other food. Thirty-three children (47%) had a clinical history of immediate IgE-mediated reactions to at least 2 other food groups, in addition to CM.

Challenge Outcome

Nineteen children (27%) reacted to their challenge (Table 1). Four children had anaphylaxis (Table 2). Fifty-eight percent of children with prior anaphylaxis to CM tolerated the baked CM. The size of the SPT wheal to CM or to muffin slurry was not predictive of outcome ($P > .05$; Table 1, Fig 1). An SPT wheal smaller than 7 mm in children with CMA older than 2 years did not predict tolerance to baked CM ($P = 1$). Children with a history of asthma ($P < .005$), using an asthma preventer ($P < .05$), a history of anaphylaxis to CM

Table 2
Challenge outcome for anaphylaxis: characteristics

Age (y)	History of CM reactions	Symptoms at baked CM OFC	Eliciting dose (muffin)	Onset of symptoms (h)
5.5	anaphylaxis	sudden lethargy, pallor, tongue swelling, urticaria	1/16	<1
4.9	anaphylaxis	vomit, cough, wheeze, angioedema, urticaria	1/8	<1
1.5	generalized	wheeze, noisy breathing, hoarse voice, intermittent cough	1/4	<1
7.5	generalized	wheeze, cough, shortness of breath	1	1–2

Abbreviations: CM, cow's milk; OFC, oral food challenge; SPT, skin prick test.

at any previous exposure ($P < .05$), and with IgE-mediated allergy to at least 3 food groups ($P < .05$) were more likely to have a positive challenge outcome. Age at the OFC, time since the last clinical reaction, previous anaphylaxis to other foods, and/or other atopic condition (eczema) were not predictive of challenge outcome ($P > .05$; Table 1).

Symptoms Elicited during Positive Challenges

Of those children who reacted, 4 (21%) experienced anaphylaxis to baked CM, according to World Allergy Organization criteria (6% of total cohort), and all 4 required intramuscular epinephrine. The eliciting dose of CM protein ranged from less than 50 mg to 500 mg of CM protein (median 95 mg). The interval from the start of the OFC to the onset of symptoms was shorter than 1 hour in 3 children and 1 to 2 hours in the other child. All 4 children had asthma (and were on preventer therapy) and food allergy to at least 2 other food groups; 3 had a history of anaphylaxis to other foods. Of those children who reacted at the CM OFC, a history of anaphylaxis to other foods was associated with anaphylaxis to baked CM at the OFC ($P < .05$). Two of the 4 children had a history of anaphylaxis to CM, and the remaining 2 children experienced widespread urticaria and angioedema with no respiratory or cardiovascular symptoms with previous CM exposure.

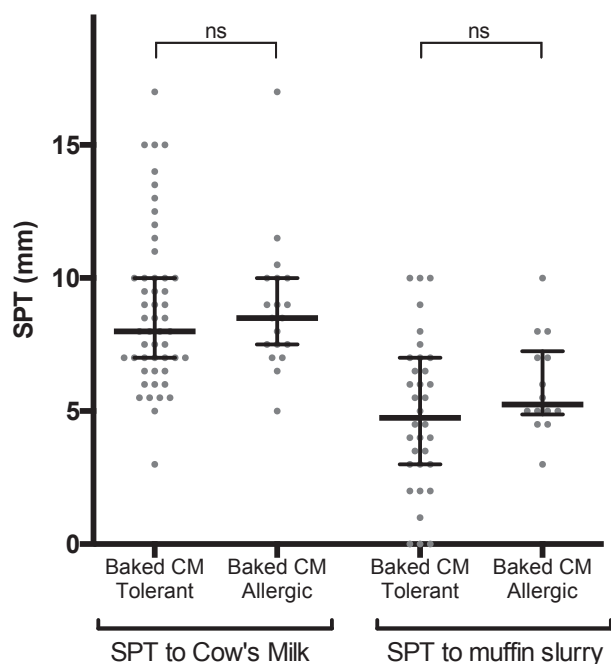


Figure 1. Skin prick test (SPT) wheal size to cow's milk (CM) and baked CM muffin at an oral food challenge by challenge outcome. Data are shown as median and interquartile range. ns, not significant.

The remaining 15 children had mild to moderate allergic reactions with skin and/or gut symptoms only. The most commonly reported symptoms were urticaria and/or angioedema (47%), itchy mouth and/or itchy or tight throat (53%), abdominal pain (20%), and vomiting and/or acute-onset diarrhea (13%). Eighty-seven percent of reactions occurred within 1 hour, and the remainder (2 children with urticaria and angioedema) occurred within 2 hours of the OFC initiation. Three children passed the OFC but developed symptoms at home with ongoing exposure 1 week later (itch, abdominal pain, and flaring of eczema). These 3 children were reported to be ingesting the same amount of muffin and CM protein, baked for the same time, as they had been exposed to at the OFC.

Discussion

It is increasingly common practice in the management of children with food allergies to aim for liberalization of the diet where possible. This is done to improve quality of life, to potentially hasten natural resolution^{9,15} of IgE-mediated food allergy, and/or to act as immunotherapy to alter the natural history of persistent disease.¹⁶ Therefore, the task of selecting which patients who are less likely to react to heat-modified allergen at an OFC is an increasingly commonplace scenario faced by the allergist caring for children with food allergy.

Up to 75% of children with CMA tolerate baked or heat-modified CM, a finding confirmed in this study. These rates are very similar to the proportion of children with egg allergy who are tolerant to baked egg challenges, as the authors¹² and others^{5,17,18} have shown.

Several parameters have been reported to be associated with a higher risk of reacting to a heat-modified CM OFC; however, these are not sufficiently sensitive or specific enough to replace the OFC for many children with CMA. In a study of 100 children with CMA, a larger SPT wheal reaction to CM and higher milk-specific and casein-specific IgE levels were reported in children reacting to extensively heated milk.⁷ The researchers did not find an association between a history of anaphylaxis to milk and current asthma and did not report on the use of an asthma preventer or the presence of multiple food allergies (to ≥ 3 food groups). Although the authors were not able to measure asthma control directly in the present cohort, the association between reactions at a baked CM OFC and asthma with preventer use may indicate that persistent asthma is a risk factor for reacting. Some differences between the previous and present findings may relate to the older age of the previous cohort (median 7.5 years) compared with the present cohort (median 5.2). Indeed, the researchers specifically commented that their findings could not be readily applied to the younger child with CMA. In a larger follow-up study of 225 children with CMA (including 97 children with CMA from the original study), a casein sIgE level higher than 20.2 kU/L was reported to have a positive predictive value of 69% for determining reactions at a baked CM OFC.⁶ Decreased in vitro basophil activation and tolerance to baked CM have been reported, but the utility of an OFC in the day-to-day selection of children who might tolerate baked CM has not been established.¹⁰ In a small retrospective review of 35 younger children with CMA (median age 3.7 compared with 8.9), those with greater whole-milk SPT, casein SPT, and sIgE reactions were more likely to react at a baked CM challenge.⁸ An SPT wheal to CM smaller than 7 mm was associated with baked CM tolerance in this group. The investigators did not find a relation between asthma and anaphylaxis at first known exposure, although the sample size may have not allowed for these associations to be examined. The authors found no association between baked CM challenge outcome and size of a CM SPT wheal reaction in the present population and no good negative predictive value of a CM SPT wheal reaction smaller than 7 mm. Very few children older than 2 years in the present cohort had a CM SPT wheal smaller than 7 mm,

reflecting the highly atopic nature of these patients. The authors did not find that SPT muffin slurry was predictive of baked CM challenge outcome. This is in contrast to the finding by Faraj and Kim¹⁹ who reported a high negative predictive value for a negative SPT reaction to baked CM muffin slurry in 14 children with sensitization to CM. These differences may relate to different inclusion criteria, with the possibility that not all CM-sensitized children were allergic at the time of the baked CM challenge. Overall, the sensitivity and specificity of currently available in vitro and in vivo tests are not sufficiently high to allow for the safe introduction of baked CM within the home environment in the absence of an initial baked CM OFC under medical supervision.

The mechanism by which children with CMA might tolerate baked CM (but not other forms of CM) is likely to be related to several factors, including the protein denaturation resulting in conformational changes in the major allergenic epitopes.²⁰ Tolerance to baked CM may reflect the nature of the CMA, with some evidence to suggest that those who are tolerant to heated CM represent a (large) subgroup of children who have transient, rather than persistent, CMA.⁹ To some extent, this is supported by the present data, which show that those children who reacted to baked CM were generally more atopic, with multiple other food allergies and asthma and a higher rate of previous CM anaphylaxis. The authors did not find a significant difference in the age of the children or the time since the last clinical reaction between those who reacted to baked CM and those who were tolerant; however, the median age was younger in the tolerant group (4.5 years) than in the reactive group (7.3 years). Children who tolerate baked CM may represent a more persistent CMA phenotype. A larger cohort might be able to answer this question more adequately.

A smaller amount of total CM protein was used in the present baked CM OFC (0.5 g) than in other studies^{6,8}; however, those studies reported a rate of reaction very similar to those of other studies, suggesting that heat modification of an allergen and the physicochemical properties of the wheat matrix²¹ rather than dose is the likely predominate factor in determining allergenicity of baked CM. The amount of CM protein used in the present muffins reflects a standard Australian serving size of CM protein in cake and muffins.

When the present data were compared with outcomes from baked egg challenges conducted under the same conditions over a similar period at the current authors' institution,¹² there were several notable differences. Although the overall rates of reacting were similar between the baked egg and baked CM cohorts, proportionally more children required epinephrine in the baked CM group, although this did not reach statistical significance ($P = .054$). The authors also were able to stratify the risk of reaction to baked CM by the presence of asthma, current use of an asthma preventer, and a history of anaphylaxis at a previous exposure to native CM, whereas these factors were not useful in determining the likelihood of a reaction to baked egg. Multiple IgE-mediated food allergies appear to be a good indicator for risk of reacting to a heat-modified allergen and were identified as a risk factor for reaction in the baked egg and baked CM study populations.

A potential limitation of this study is that children were not all formally challenged to conclusively establish CMA at entry, before the OFC to baked CM. Although this would have strengthened the study, it was considered unethical to challenge children with a very high probability of clinical reaction, including 34% with a history of anaphylaxis to CM. The cohort is highly atopic and reflects a tertiary center population. There are children with CMA who do not require tertiary care, and the safety of baked milk challenges in this population cannot be easily inferred from the result of this study alone. Because of the ubiquitous nature of CM in prepared and packaged foods, a careful and thorough dietary history in children with CMA often discloses tolerance to baked milk products. This cohort was

specifically avoiding all forms of CM, with no prior exposure to baked milk products, and thus potentially represents the more severe end of the spectrum of CMA.

This present series is second in size only to the large Mt Sinai cohort,⁶ and the authors believe it provides valuable additional information about risk stratification for children for whom a baked CM challenge is being considered. Those children with the combination of multiple IgE-mediated food allergies, asthma, and prior anaphylaxis to other foods appear particularly at risk of reacting, and with anaphylaxis, to baked CM. Although a history of CM anaphylaxis was associated with reacting at the baked CM challenge, more than 50% of those with such a history were tolerant to baked muffin at challenge in this population. This suggests that anaphylaxis to nonextensively heated (ie, native) CM is not a contraindication to the introduction of baked CM. The benefits of introduction, for decreasing anxiety relating to accidental exposure, may indeed be even greater in these children with a history of anaphylaxis, in whom the severity of a past reaction and the length of dietary exclusion have been shown to be associated with a lower quality of life.³

This study has shown the relative safety of an OFC to baked CM in children with CMA, including those with a previous reaction to baked CM or anaphylaxis to whole CM. Based on the present population of children with known CMA, in whom no history of tolerance to baked milk was obtained, the authors recommend that the initial introduction of baked CM should occur under direct medical supervision in an environment where severe reactions can be managed appropriately. Particular caution should be exercised in those children with CMA who have a combination of asthma, multiple food allergies, and a history of anaphylaxis to CM and other foods.

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