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Received Date : 22-Aug-2016

Revised Date : 30-Dec-2016

Accepted Date : 11-Jan-2017

Article type : Research Letter

Research letter

Title: Use of baked milk challenges and milk ladders in clinical practice: a worldwide survey of healthcare professionals

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Condensed Title: Baked milk challenges & milk ladders

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/cea.12890

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Key recommendations

- **The development of safe home-based, baked milk introduction plans based on individualised risk assessment could help many countries who may not be able to provide food challenge facilities due to limited hospital resources.**
- **Further research is required to explore country-specific advice and compare different settings and clinical practices regarding the use of baked milk challenges.**

Introduction

In previous years, the cornerstone of the management of Cow's Milk Allergy (CMA) was solely based on the strict avoidance of all cow's milk (CM) and foods containing CM from the patient's diet [1]. More recently, the importance of baked milk (BM) introduction into the diet of children with CMA has become well-recognised as a part of CMA management. Current research suggests that 75% of children become tolerant to baked/heated forms of CM such as muffin and waffles before they become tolerant to pure/uncooked forms of CM [2]. It has been demonstrated that children who tolerated BM were 28 times more likely to become tolerant to CM compared to those children who were not able to tolerate these foods [3]. Further, the ingestion and incorporation of BM containing foods into the children's diet seemed to accelerate the resolution of CMA without any adverse effects on children's growth, intestinal permeability, or the severity of coexisting diseases such as asthma, atopic dermatitis and allergic rhinitis [4]. Identification of CMA children who are able to tolerate BM in a variety of forms can also contribute to a liberalised diet that improves the quality of life of patients. This strategy may additionally help to avoid an unnecessary restriction of BM containing foods or to prevent a severe reaction that could be provoked with the uncooked milk; children reactive to BM appear to be at higher risk for systemic reaction than those children that tolerate BM but still remain allergic to uncooked milk [2, 5].

In the UK, CM is one of the most common foods responsible for a fatal anaphylactic reaction in children less than 16 years of age, and food allergy is the main cause of a fatal anaphylactic reaction outside the hospital setting [6, 7]. It is difficult to estimate how many people die each year from food anaphylaxis and to confirm the trigger that caused these tragedies. We are aware of a fatal anaphylactic reaction in a child following eating a milk product outside the healthcare setting in the UK, two years ago. This further emphasises that the decision to challenge at home should not be taken lightly and that there is a risk of severe reactions, even anaphylaxis.

At the time of completion of this survey few guidelines were available on BM introduction. In the UK, the MAP Milk Allergy guidelines provide information on the initial diagnosis and the management of mild to moderate non-IgE-mediated CMA in primary care using a milk ladder (ML) [8]. The British Society of Allergy and Clinical Immunology (BSACI) guidance for home introduction of BM containing foods in IgE-mediated CMA was first published at the end of the survey period [9]. However, there are no studies indicating which patients are optimal candidates for home introduction of BM. Additionally, there is no universal agreement for the criteria used to classify the severity of allergy symptoms as mild, moderate or severe and no reliable biomarkers that can be used to indicate the safety of home introduction of milk containing foods. This study was conducted to explore what guidelines and approaches are currently being used by healthcare professionals (HCPs) across the world and what their experiences have been in introducing a full portion of a BM product as a challenge (BMC) over 1 day or as a more gradual introduction over a number of days/weeks before moving on to other baked milk foods, as per a ML approach.

Methods

A web-based global survey was conducted to capture the views of HCPs using a BMC and/or a ML. An electronic questionnaire (see additional file) was developed consisting of 23 short questions which could be completed within approximately 15 minutes. The main sections of the questionnaire were:

- Characteristics of HCPs including: professional background and level of allergy training, practice setting (private/hospital-primary/secondary/tertiary care) and amount of time spent consulting patients with food allergies, percentage of respondents from various countries and guidelines that HCPs considered before they made the decision about the setting of BMC/ML.
- Were these challenges used and where were these challenges performed?
- What was the HCPs' opinion on the safety of home-BMC and ML?
- What was the HCPs' opinion on parental anxiety in BMC/ML process?
- What symptoms were observed?

An initial pilot testing of the survey was carried out on a group of HCPs practising in different parts of the world to ensure the clarity of questions. Ethical permission of the study was provided by the University of Portsmouth Science Faculty Ethics Committee. HCPs involved in the diagnosis and management of CMA were invited to complete the online questionnaire. The participants were identified through international professional organisations ([a]FAISG, [aa]BSACI, [b]AAAAI, [bb]ADA, [c]INDANA, [cc]ALLSA, [d]ASCIA, [dd]DAA, [e]WAO).

[a] Food Allergy and Intolerance Specialist Group of British Dietetic Association; [aa]British Society for Allergy and Clinical Immunology; [b] American Academy of Asthma Allergy and Immunology; [bb] American Dietetic Association ; [c] International Network for Diet and Nutrition in Allergy; [cc]Allergy Society of South Africa; [d]Dietitians Association of Australia ;[dd] Australasian Society of Clinical Immunology and Allergy;[e] Word Allergy Organisation

A reminder email was sent 4 weeks later. The survey was carried out between January and April 2014. The Bristol Online Survey was used to analyse and describe the results. Descriptive statistics were used to summarise data using a combination of tabulation and graphical description. Further statistical analysis data were entered and analysed using IBM SPSS Statistics for Windows version 22.0. Pearson's chi-square test was used: a) to determine whether or not there was a statistically significant relationship between the use of BMC and ML; b) to test whether or not a statistically significant association exists between the settings (clinical/home) regarding where to perform BMC/ML and the types of CMA (IgE and non-IgE-mediated CMA). A P value less than 0.05 was considered statistically significant.

Results

Characteristics of HCPs study participants

A total of 114 HCPs completed the questionnaire and provided data on their clinical practice regarding using either a BMC and/or a ML in both IgE and non-IgE-mediated CMA. The largest groups of respondents were dietitians with an interest in allergy [52(46%)] followed by paediatric allergists/immunologists [46(40%)]. The majority of participants [106(93%)] indicated that they were involved in the management of IgE and non-IgE-mediated CMA in infancy and childhood. Most of the participants were based in the UK [56(49%)], followed by the US [20(18%)] and were practicing in secondary care/hospital [52(39%)] followed by tertiary care/specialist centre [42(37%)]. HCPs reported that they based their decision regarding BM introduction on an individualised clinical assessment (medical history, SPTs, laboratory tests) and national/regional guidelines. Demographic features of all respondents are shown in Table 1.

Settings (hospital/home) of BMC and ML in children with CMA based on HCPs reports

IgE-mediated CMA

Ninety-three (82%) HCPs indicated that they used BMC to identify patients able to tolerate BM products before tolerating uncooked milk. Fifty two (56%) respondents stated that they conducted these challenges in a clinical setting, 8(9.0%) in a home-based setting and 33(35%) reported using both settings. For ML, 68(60%) HCPs stated that they used this approach to determine the development of tolerance to BM in different forms. Nineteen (28%) respondents reported that they used the ML approach in a clinical setting, 22(32%) in a home setting and 27(40%) in both settings.

Non-IgE-mediated CMA

Eighty-six (75%) of the respondents stated that they used BMC to determine the development of tolerance to BM. Eight (9%) HCPs reported that they challenged their patients in a clinical setting, 51(59%) used home–based challenges and 27(31%) reported using both settings. In terms of using the ladder approach (ML), 77(68%) HCPs reported that they used the ML to identify children able to tolerate a range of BM containing foods. Three (4%) HCPs reported that they used ML in a clinical setting, 56(73%) at home and 18(23%) reported using both settings. Choice of challenge setting (clinic/home) was statistically significant ($p<.001$) associated with the type of CMA (IgE/non-IgE-mediated). A greater number [52(56%)] of hospital-based BMC responses were indicated in IgE-mediated CMA, with a larger number [51(59%)] of home-based BMC in non-IgE-mediated CMA. The decision about where to perform milk ladder challenges (hospital/home) was also statistically significantly ($p<.001$) associated with the types of CMA. A considerable number of respondents used ML challenges/introductions at home in both IgE [22(32%)] and non-IgE-mediated CMA [56(73%)].

However, choosing the safest challenge setting remains a difficult decision that concerns not only HCPs, but also carers. The majority of HCPs [71(62%)] considered the home/outside the clinical setting as a safe place to conduct both BMC and ML in non-IgE-mediated CMA because there is no risk of severe reactions, with an exception in the case of severe forms of non-IgE-mediated diseases, such as Food Protein Induced Enterocolitis Syndrome (FPIES). The most commonly reported symptoms experienced by the patients were reported as atopic eczema and abdominal pain in both hospital and home-based challenges (Table 2). In terms of IgE-mediated CMA, 30(26%) respondents stated that the home environment was a safe place to conduct either approach whereas 65(57%) HCPs considered the home/outside the clinical setting as a non-safe place to conduct both BMC and ML, due to potential severe symptoms (Table 2).

Discussion

The results from this survey indicate that 32(28%) HCPs reported anaphylaxis in clinic-based BMC and 9(8%) respondents in clinic – based ML challenges, but none at home. This finding is consistent with previous studies, reporting that some children develop anaphylaxis after ingestion of baked milk containing foods such as a muffin/pizza in hospital [3, 10]. Mehr and colleagues identified clinical predictors of reacting to baked cow's milk [10]. These included children with; asthma requiring preventer therapy, IgE-mediated clinical reactions to more than 3 foods, a prior history of anaphylaxis to cow's milk and highly atopic children. They indicated that such children should undergo BMCs in hospital. This study by Mehr involved challenges with increasing amounts of BM being introduced over a number of hours over the same day and 27% of children did not pass these oral food challenges [10]. This shows that baked milk challenges carry a risk in those with IgE-mediated CMA, and in a number of children with non-IgE-mediated CMA. The findings from this survey highlight that there

were no cases of reported anaphylaxis at home during baked milk challenges. This could be due to successful individual risk assessment and choosing an appropriate setting accordingly. This is supported by the fact that there were more IgE-mediated reactions associated with baked milk challenges in the clinical setting compared with the home.

Healthcare systems differ between countries and many European countries may not be able to provide food challenge facilities for all food allergic patients as considerable hospital resources are required [11]. Such challenges are time consuming with long waiting lists, a major problem in many allergy clinics. For practical reasons, allergy services attempt to address this issue by suggesting initial introduction of BM containing foods at home based on a clinical assessment. The findings from our survey indicate that the decision regarding the location of challenges in the majority of cases is based on an individualised clinical assessment looking for such specific parameters as: sIgE levels, skin prick tests, severity of previous symptoms, severe forms of non-IgE-mediated CMA such as FPIES or mixed IgE and non-IgE-mediated CMA. Parents' and children's anxiety is another factor that is considered by HCPs. A considerable number of HCPs reported that the families were anxious when BMC [46(36%)] or ML [41(36%)] were conducted either at home or in a clinical setting. A better understanding of parents' perceptions regarding the use of BM forms would be helpful for HCPs to provide optimal care to children during introduction of BM containing foods.

This survey has clearly highlighted the lack of international guidance on challenge/gradual introduction of baked cow's milk in a matrix (ML). The World Allergy Organization, European Academy of Allergy and Clinical Immunology and PRACTALL consensus report recommends milk challenges in a safe, well-equipped environment that is supervised by a

medical team and have published guidelines for milk oral food challenges but these guidelines do not focus on BMC or a ML process [1, 11, 12]. However, since the survey was completed the BSACI guidelines were published and data from UK respondents may now be different.

In conclusion, our findings suggest that there are a number of inconsistencies between the use of BMC versus ML. We suggest that a larger sample size with a sampling frame inclusive of more countries and clinicians from tertiary, secondary and primary care should be conducted. There is a clear need for universal guidance, taking into account country- specific needs, on the safe introduction of baked milk products.

Acknowledgment

We thank all the healthcare professionals who participated in the survey and made this study possible. We also thank Dr Kate Maslin and Dia Soilemezi for their research contribution in the survey design.

Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Funding

This study was supported by the University of Portsmouth, United Kingdom.

References

1. Fiocchi A, Schunemann H, Brozek J, Restani P, Beyer K, Troncone R, et al. Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA): A summary report. *J Allergy Clin Immunol.* 2010;126(6):1119-U97.

2. Nowak-Wegrzyn A, Bloom KA, Sicherer SH, Shreffler WG, Noone S, Wanich N, et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol.* 2008;122(2):342-7, 7.e1-2.

3. Kim JS, Nowak-Węgrzyn A, Sicherer SH, Noone S, Moshier EL, Sampson HA. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol.* 2011;128(1):125-31.e2.

4. Bartnikas L, Sheehan W, Hoffman E, Permaul P, Dioun A, Friedlander J, et al. Predicting food challenge outcomes for baked milk: role of specific IgE and skin prick testing. *Ann Allergy Asthma Immunol.* 2012;109(5):309-+.

5. Nowak-Wegrzyn A, Bloom K, Sicherer S, Shreffler W, Sampson H. High failure rate during oral food challenge to baked milk in children with high serum cow's milk (CM)-Specific IgE antibody level. *J Allergy Clin Immunol*. 2008;121(2):S247-S.

6. Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol.* 2015;135(4):956-63.e1.

7. Wang J, Sampson H. Food anaphylaxis. *Clin Exp Allergy*. 2007;37(5):651-60.

8. Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy - a UK primary care practical guide. *Clin Transl Allergy.* 2013;3(1):23.

9. Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, et al. BSACI Guideline for the Diagnosis and Management of Cow's Milk Allergy. *Clin Exp Allergy*. 2014; 44, 642–672 .

10. Mehr S, Turner PJ, Joshi P, Wong M, Campbell DE. Safety and clinical predictors of reacting to extensively heated cow's milk challenge in cow's milk-allergic children. *Ann Allergy Asthma Immunol.* 2014;113(4):425-9.

11. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69(8):1008-25.

12. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma &

Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol.* 2012;130(6):1260-74.

Table 1: Demographic characteristics of respondents

Characteristics	Options	Respondents (n=114) (%)
Professional background	Dietitians Paediatric Allergist/Allergist/Immunologist Paediatrician with Allergy interest Other*	52(46) 32(28) 14(12) 16(14)
Practice Settings	Secondary Care/Hospital Tertiary Care/Specialist Centre Private Practice Primary Care/Community Other**	52(39) 42(37) 19(14) 16(12) 4(3)
Allergy training	Work-based experiential learning Speciality in Allergology/Immunology Postgraduate Dip in Allergy MSc in Allergy PhD in Allergy Postgraduate Cert in Allergy Other***	50(38) 36(27) 10(8) 8(6) 8(6) 4(3) 16(12)
Food allergy weekly workload	>50% <50%	62 (54) 52 (46)
CMA patients seen by HCPs	Infants/children Adults	106(93) 37 (32)
Participated countries	United Kingdom North & South America Oceania, Africa, Asia Europe	56(49) 24 (21) 20(18(14(12)
Guidelines for hospital -BMC	Medical history/SPT/IgE Regional/National International Hospital policy	40(35) 24(21) 12(11) 9(8)
Guidelines for home-BMC	Medical history/SPT/IgE Regional/National International Hospital policy	39(34) 26(23) 6(5) 5(4)
Guidelines for hospital-ML	Medical history/SPT/IgE Regional/National International Hospital policy	24(21) 26(23) 4(4) 3(3)
Guidelines for home-ML	Medical history/SPT/IgE Regional/National International Hospital policy	22(19) 30(26) 4(3) 4(3)

**Other: Pharmacists, Nutritionists, Allergy Paediatric Nurses, Physicians, General Practitioners*
***Other: Ministry of Health & Welfare, Research*
****Other: Research, Continued Professional Development (CPD) & Continuing Medical Education (CME) resources, allergy training, completed allergy modules*

Table 2: Summary of the most frequently reported symptoms by the HCPs for BMC & ML

Clinical Symptoms	IgE-mediated CMA			
	Clinical setting *N (%)		Home *N (%)	
	BMC	ML	BMC	ML
Urticaria	68 (60)	34(30)	32(28)	25(22)
Vomiting	55 (48)	24(21)	33(29)	22(19)
Angioedema	49 (43)	23(20)	10(9)	9(8)
Runny nose & eyes	49 (43)	19(17)	13(9)	12(11)
Nausea	48 (42)	20(18)	16(14)	22(19)
Wheezing	39 (34)	15(13)	3(2)	4(3)
Diarrhoea	34 (30)	17(15)	42(37)	35(31)
Anaphylaxis	32 (28)	9(8.0)	-	-
	Non-IgE-mediated CMA			
	Clinical setting *N (%)		Home *N (%)	
	BMC	ML	BMC	ML
Atopic eczema	20(18)	8(7)	43(38)	37(32)
Abdominal pain	18(16)	4(3)	41(36)	32(28)
Diarrhoea	15(13)	6(5)	37(32)	35(31)
Gastro-oesoph. reflux	12(11)	4(3)	32(28)	30(26)
Colic	7(6)	2(1)	22(19)	17(15)
Food aversion	6(5)	4(3)	17(15)	12(10)
Constipation	5(4)	4(3)	43(38)	29(25)

**N: number of responses*