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ORIGINAL ARTICLE

Matrix effect on baked milk tolerance in children with IgE cow milk allergy

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Abstract
Background: Children with IgE-mediated cow's milk allergy (IgE-CMA) often tolerate baked milk within a wheat matrix. In our study we evaluated the impact of wheat matrix and of little standardised cooking procedures on tolerance of baked milk. We also tested tolerance versus parmigiano reggiano (PR) and whey-based partially hydrolysed formula (pHF).
Methods: Forty-eight children with IgE-CMA were enrolled. They underwent prick-by-prick (PbP) and open oral food challenge (OFC) with baked cow's milk (CM), both within a wheat matrix (an Italian cake named ciambellone) and without (in a liquid form), with PR and with pHF. After a passed OFC, children continued to eat the food tolerated. In particular, after passed OFC with ciambellone, children were allowed to eat any food containing CM within a wheat matrix, with the only condition that it was baked at 180 °C for at least 30 min. Three months after, parents were asked to answer a survey.
Results: 81% of children tolerated ciambellone, 56% liquid baked CM, 78% PR and 82% pHF. Negative predictive value of PbP performed with tested foods was 100%. No IgE-mediated adverse reactions were detected at follow-up carried out by the survey.
Conclusions: Wheat matrix effect on tolerance of baked milk was relevant in slightly less than half of cases. If our results are confirmed by larger studies, a negative PbP will allow patients to eat processed CM without undergoing OFC. Moreover, in order to guarantee tolerance towards baked milk, strict standardised cooking procedures do not seem to be necessary.

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Introduction

In 2008, Nowak-Wegrzyn et al.[1] reported that 75% of children affected by IgE-mediated cow's milk allergy (IgE-CMA) tolerated baked milk in the form of muffin. These authors obtained similar results in children with IgE-mediated hen's egg allergy (IgE-HEA).[2] This has several implications: it improves the quality of life of young patients, identifies different phenotypes, and perhaps offers new therapeutic possibilities.[3] Therefore, patients' quality of life improved a lot: nowadays baked milk and egg are considered a dietary option for patients with IgE-CMA and IgE-HEA.[4] Moreover, these studies identified several allergic phenotypes and they could offer new therapeutic possibilities to these patients.[3]

Heating certainly plays a key role in achieving tolerance. In fact, high and prolonged temperatures reduce protein allergenicity by destroying conformational epitopes, altering allergens tridimensional structure, so that specific IgE binding capacity decreases.[5] Another theory, proposed to explain baked food tolerance, is the matrix effect.[5] This one would work on proteins, fats and sugars interactions, which are thought to reduce IgE binding to allergen epitopes by covering them.

Further methods of milk processing were tested in vivo. Alessandri et al.[6] reported that 58% of children with IgE-CMA tolerated parmigiano reggiano (PR) 36 months maturated. In fact, during the maturation, milk proteins are gradually and constantly broken down by the proteolytic enzymes of milk rennet and lactic acid bacteria until an almost complete hydrolysis is obtained, especially for caseins.[7] Moreover, other authors found that 60–75% of children with IgE-CMA tolerated partially hydrolysed formulas (pHF),[8–10] which are cheaper and more palatable than extensively hydrolysed ones.

The primary objective of our study was to evaluate the importance of wheat matrix effect on reducing baked CM allergenicity. Secondary objectives were: a) to evaluate negative predictive value (NPV) of prick-by-prick (PbP) performed with differently processed CM; and b) to follow up tolerance maintenance, after patients passed OFCs performed with CM baked in a wheat matrix.

Methods

Eligible patients were children with suggestive history of IgE-CMA of various severity who rigorously avoided CM. They were enrolled, prospectively and consecutively, at the paediatric allergy unit of Agostino Gemelli hospital (Rome), Fatebenefratelli hospital (Benevento), Belcolle hospital (Viterbo), Mazzoni hospital (Ascoli Piceno) and Senigallia civil hospital (Senigallia). Exclusion criteria were: (a) chronic disease or chronic therapies which influenced immune response; (b) need to continue therapy with oral anti-histamines or steroids; and (c) denied informed consent. In all eligible patients, skin prick tests (SPT) were performed, according to international guidelines,[11] with pasteurised CM and commercial extracts (Lofarma, Milan, Italy) of casein, beta-lactoglobulin, alfa-lactoalbumin, negative control and histamine. Patients presenting with positive CM SPT underwent pasteurised CM open OFC, performed and evaluated according to international guidelines.[12] OFC was positive in case of objective and reproducible signs.

OFC was not performed in patients who experienced anaphylaxis, as defined by Sampson et al.,[13] within 12 months from our clinical evaluation. We did not establish any positive CM SPT cut-off, as an exclusion criterion for performing an OFC.

We enrolled: (a) children who experienced anaphylaxis within 12 months from our clinical evaluation presenting with a positive CM SPT, (b) children with history of immediate adverse reaction due to CM (not anaphylactic or anaphylactic but occurred more than 12 months before our clinical evaluation), positive CM SPT and failed pasteurised CM OFC.

Among enrolled patients, we performed PbP with baked CM within a wheat matrix in a form of a cake (known in Italy as ciambellone, qualitatively similar to a muffin), baked CM without a wheat matrix (in a liquid form), PR 36 months maturated, whey-based pHF (Mellin HA or Humana HA). Processed CM PbPs were also performed before each specific OFC was conducted. Irrespective of PbP mean wheal diameter, patients underwent open OFC with all the above mentioned forms of processed CM. OFCs were performed on separate days. We established a gap of two weeks between different challenges, so that all tests were performed within three months from the initial assessment.

Ciambellone OFC was considered to be passed if patients assumed a total dose of 170 g (equal to 3 g of CM proteins) without having any adverse reaction. PR OFC was considered to be passed if patients assumed a total dose of at least 10 g (equal to 3 g of proteins) without having any adverse reaction. Baked liquid CM and pHF OFC were considered to be passed if patients assumed a total dose of at least 200 ml (equal to 6 g of proteins) without having any adverse reaction. The above mentioned doses above were chosen based on Italian children's usual intake. It is quite rare that a child under the age of five eats more than 170 g of ciambellone (or muffin) or 10 g of PR.

After passing an OFC and when OFCs' sequence ended, patients were allowed to eat tested food (in case of PR they were allowed to eat exclusively the 36 months maturated type; regarding pHF patients could take only the tested brand). Moreover, they could eat tested food in any physical and emotive state (physical exercise, fever, stressful situations). Regarding ciambellone OFC, after the test was passed, children were allowed to eat every baked food containing CM proteins within a wheat matrix, on condition that the food was baked at 180 °C for at least 30 min. Three months after ciambellone OFC was passed, parents were asked to answer a questionnaire, which was sent via e-mail, in order to report if any adverse reaction occurred at home.

Survey questions are listed in Appendix (see electronic repository).

Statistical analysis

We reported demographic and clinical patients' characteristics as mean and standard deviation for continue variables and percentage for category ones. Percentage differences among populations on PbP and OFC positivity were calculated with chi-square test. We calculated sensitivity,

specificity, positive predictive value (PPV), and NPV of cut-off values of each PbP performed with processed CM. Data were obtained with Statistics for Biomedical Discipline of Stanton A. Glanz ver. 2.0.

Standardisation of procedures

In order to limit any adverse reaction, literature highly recommends to follow strict and precise cooking procedures to make baked CM products with a wheat matrix, such as in the form of a cake.[1,14] In our study, we gave parents minimal cooking rules to follow. For example, we did not mention the baking tray's shape, nor its dimension, although they could both influence food thickness and consequentially change the heating grade. Ciambellone was prepared with 100 ml pasteurised CM, 60 g wheat flour, 40 g sugar, one teaspoon of baking powder. We did not use milk powder as in Italy it is not commonly used to prepare ciambellone or other cakes, moreover it stands as a further form of food processing. The cake was baked at 180 °C for 30 min in pre-heated ventilated oven. Ciambellone's final weight was 170 g and it contained almost 3 g of CM proteins. Baked liquid CM was prepared by placing 300 ml of pasteurised CM (3.6% fat) in a baking dish at 180 °C for 30 min in pre-heated ventilated oven. PR was bought by parents at grocery stores, we did not mention any specific brand, but it had to be 36 months maturated.

PR usually contains 32 g of cow's milk proteins per 100 g. Tested pHFs were Mellin HA (Mellin, Italy) or Humana HA (Humana, Italy). Food was always prepared by parents at home. On one occasion, we prepared ciambellone and baked liquid CM by ourselves, in order to measure food internal temperature. It was made by placing a cooking-thermother (Tescoma) into the inner part of the food, just a few seconds after cooking.

PbP with ciambellone and PR were performed with a special technique in order to improve test's sensitivity and NPV. Ciambellone PbP was conducted adding few drops of water to a little piece of cake, mixing and manipulating the compound until a soft ball-cake was obtained. The latter was pricked with ALK lancet (at least 20 times in different areas), then it was pressed and rubbed on the same lancet. Patient's forearm skin was pricked with the lancet, passing through the soft ball-cake. The last one was finally pressed and rubbed on patient's forearm skin spot. Moreover, PbP were performed twice on both forearms and the two wheal diameters mean was reported. PR PbP was performed in the same way but without water. PbP with baked liquid milk and with pHF were performed in the traditional way.[11] PbP results were considered to be positive if the mean wheal size was $\geq$3 mm greater than with the negative control.

The study was approved by the Ethic Committee of Agostino Gemelli Hospital – Catholic University of Sacred Hearth (Coordinator Center) and other hospitals Ethic Committees. Informed consent was obtained from the patients and/or the guardians.

Table 1 Processed cow's milk PbP and OFC outcomes.

	PbP No. of positive patients/total tested patients (%)	OFC No. of negative patients/total tested patients (%)
Ciambellone	34/48 (71%)	39/48 (81%)°
Baked liquid cow's milk	24/32 (75%)	18/32 (56%)°
Parmigiano reggiano	37/43 (86%)	28/36 (78%)
Partially hydrolysed formula	25/42 (60%)	23/28 (82%)

PbP, prick-by-prick; OFC, oral food challenge.
° $p < 0.05$.

Results

Patients

Forty-eight patients were enrolled between February 1, 2014 and January 31, 2015. 73% were males; mean age ± SD at diagnosis was 13 ± 20 months. 69% of patients received an IgE-CMA diagnosis due to suggestive history, positive CM SPT and failed pasteurised CM OFC; 31% of patients received an IgE-CMA diagnosis due to history of anaphylaxis occurred within 12 months from our evaluation and positive CM SPT. 73% of patients presented with exclusive IgE-CMA, 27% also suffered from IgE-HEA, 8% presented with other food allergies (FA) (fresh fruits, shell fruits, wheat). Fifty-eight percent of them were affected by atopic eczema, 22% suffered from rhino-conjunctivitis and 33% was asthmatic. At our first clinical assessment, the enrolled children presented with the following characteristics: CM PbP mean wheal diameter ± SD: 9 ± 3 mm; SPT casein positivity: 79%, SPT beta-lactoglobulin positivity: 79%, SPT alfa-lactoalbumin positivity: 89%; CM eliciting dose at baseline OFC (mean ± SD) was 35 ± 23 ml.

PbP and OFC results

At our evaluation, tested food internal temperatures were: ciambellone = 102 °C, baked liquid CM = 97.8 °C.

The PbP and OFC results performed with processed CM are listed in Table 1.

OFC performed with processed CM

Ciambellone OFC was passed in 39/48 (81%) patients, baked liquid CM OFC in 18/32 (56%) of patients, pHF OFC in 23/28 (82%) of patients. PR OFC was passed in 28/36 (78%) patients; 2/28 patients (5.5%) passed OFC with 24 months maturated PR and 7/28 (19%) with 30 months maturated PR, as their parents could not find 36 months maturated cheese. A statistically significant difference ($p < 0.05$) was found among OFCs positivity rates, comparing ciambellone and baked liquid CM. In all failed OFCs performed with processed CM, total CM proteins quantity was <3 g. Total CM proteins eliciting dose was always greater in processed CM OFCs than in pasteurised CM OFC.

Among patients who failed one or more processed CM OFC, 9/20 (45%) presented with anaphylaxis with respiratory symptoms, 7/20 (35%) had a generalised non-anaphylactic

Table 2 Sensitisation patterns of main CM proteins compared to OFC outcomes (passed/failed).

Processed cow's milk OFC (no. pts)	Positive to casein (%)	Positive to beta-lactoglobulin (%)	Positive to alfa-lactoalbumin (%)
Ciambellone			
Failed OFC (9)	9/9 (100%)	7/9 (78%)	9/9 (100%)
Passed OFC (39)	28/39 (72%)	30/39 (77%)	33/39 (85%)
Baked liquid cow's milk			
Failed OFC (14)	12/14 (86%)	11/14 (79%)	13/14 (93%)
Passed OFC (18)	12/18 (67%)	15/18 (83%)	17/18 (94%)
Parmigiano reggiano			
Failed OFC (8)	8/8 (100%)	7/8 (88%)	8/8 (100%)
Passed OFC (28)	18/28 (64%)	21/28 (75%)	24/28 (86%)
Partially hydrolysed formula			
Failed OFC (5)	4/5 (80%)	4/5 (80%)	5/5 (100%)
Passed OFC (23)	17/23 (74%)	19/23 (83%)	20/23 (87%)

OFC, oral food challenge.

adverse reaction and 4/20 (20%) experienced a single-organ adverse reaction, such as isolated urticaria, repeated vomiting or rhinitis.

Not every child performed all tests, only 23/48 (48%) tested everything. This was mainly due to: (a) parents logistical problems (90%); (b) parents fear of adverse reactions (10%).12/23 (52%) passed all OFCs without any adverse reaction. 11/23 (48%) children failed some of the OFCs: three failed OFC with baked liquid CM; two failed OFC with ciambellone, baked liquid CM and PR; two failed OFC with pHF; two failed OFC with PR and pHF; one failed OFC with PR and baked liquid CM; and one failed OFC with baked liquid CM and pHF. No statistically significant difference was found among sensitisation profiles between 12 ''total tolerant'' children and 11 ''partially tolerant'' ones.

We investigated the occurrence of asthma, history of previous CM anaphylaxis, multiple food allergies and/or inhalant allergies, between patients who failed or passed ciambellone OFC. These factors were found to be good predictors of adverse reaction at OFC towards baked hens' egg or CM, by Mehr et al.[15] Since no statistically significant difference was found between the groups, our data do not confirm what Mehr et al. [15] previously reported.

PbP performed with processed CM

Sensitisation profiles compared to the outcomes of various processed CM OFCs are listed in Table 2. Negative casein SPT always predicted passed ciambellone and PR OFCs. Moreover, negative lacto-albumin SPT predicted in 100% of cases tolerance towards ciambellone, PR and pHF.

OFCs were always failed if PbP mean wheal diameters were: ciambellone >7 mm (sensitivity = 22%, specificity = 100%, positive predictive value [PPV] = 100%, negative predictive value [NPV] = 84%), baked liquid CM >7 mm (sensitivity = 58%, specificity = 100%, PPV = 100%, NPV = 77%), PR >8 mm (sensitivity = 50%, specificity = 100%, PPV = 100%, NPV = 87%), pHF >7 mm (sensitivity = 20%, specificity = 100%, PPV = 100%, NPV = 85%). OFCs were always passed if PbP mean wheal diameters were: ciambellone <3 mm (sensitivity = 100%, specificity = 55%, PPV = 35%, NPV = 100%), baked liquid CM <4 mm (sensitivity = 100%, specificity = 59%, PPV = 63%, NPV = 100%), PR <4 mm (sensitivity = 100%, specificity = 33%, PPV = 31%, NPV = 100%), pHF <3 mm (sensitivity = 100%, specificity = 52%, PPV = 31%, NPV = 100%).

Regarding ciambellone OFC, we could not establish any cut-off value, since when performing casein, beta-lactoglobulin and alfa-lactoalbumin SPTs, PPV > 95% was never reached. On the other hand, NPV (always basing on ciambellone OFC) was 100% in the case of casein SPT mean wheal diameter <3 mm and alfa-lactoalbumin <5 mm.

Follow-up after passing ciambellone OFC

Thirty-nine patients passed ciambellone OFC and all patients answered our survey. Thirty percent of them declared that they did not eat any baked food containing CM, except biscuits (with very small CM amount). Three percent of patients kept on eating ciambellone prepared exclusively with our recipe. Seventy-seven percent of patients consumed CM baked within wheat matrix in the form of various foods. These ones were made following different cooking procedures, but always respecting the given heating time and temperature (at least 180 °C for 30 min minimum). Regarding food quantity, patients took doses comparable to usual daily intake according to food type and children age.

Children ate baked CM foods (i.e. cakes, biscuits and other baked products) whenever they liked. For instance, they took these products while they were ill or during physical exercise.

Among these patients, only one showed up with atopic dermatitis, which occurred 2 h after eating ciambellone. However, his parents continued administering ciambellone and atopic dermatitis did not appear anymore. Another child presented with asthma 8 h after eating ciambellone, his parents related this episode to processed CM, so they stopped administering it to their son. It should be noted that, this patient had always suffered from inhalant-induced asthma.

Discussion

Our results confirm that, in children with IgE-CMA, prolonged and extensive heating increases tolerance towards

CM proteins. Certainly, these results are only applicable to populations similar to that studied.

An interesting finding of our study is that more than 50% of children with IgE-CMA did not need a wheat matrix to tolerate baked CM. In the worst scenario analysis, there would still be a significant proportion of children who tolerate baked milk without wheat matrix (18/48 children = 37.5%).

Tolerance seems to be mainly related to prolonged heating. Comparing CM baked with a wheat matrix and CM baked in a liquid form (without wheat matrix), internal temperatures were not very different: we measured 102 °C for ciambellone and 97.8 °C for liquid baked CM. Moreover, we measured temperature of CM boiled for 10 min and it reached 97.9 °C from starting to boil. Therefore, CM allergenicity is influenced not only by heating degree, but also by heating time. To eliminate detectable IgE binding, a temperature of ≥95 °C prolonged for at least 30 min is necessary.[16]

Our results give some practical benefits to children with IgE-CMA. For example, they could have breakfast with baked liquid CM, this fact would be convenient in terms of cost saving, palatability and social life. Similar profits can be enjoyed by infants with IgE-CMA under six months of life. In our study, only few of them failed pHF OFC. pHFs have a better palatability than extensively hydrolysed formulas and cost less. However, in this case parents should use only pHF brand tested at OFC, as the grade of hydrolysis differs from one brand to another.

The ciambellone recipe used in our study was simple, the only thing we stressed about was baking at a temperature of 180 °C for 30 min in a pre-heated ventilated oven. We did not mention anything about baking trays, or about cake thickness, as other authors did.[14] Moreover, children who passed ciambellone OFC were allowed to eat every food prepared with CM baked with a wheat matrix on condition that it should be baked in a pre-heated ventilated oven at 180 °C for at least 30 min. We did not ask parents to pay attention to the culprit food's position in commercial ingredients lists. Some authors suggested it,[17] as this fact could influence the quantity of offending food contained in the product. During the follow-up period, any IgE-mediated adverse reaction occurred. Therefore, strict standardisation does not seem necessary to maintain tolerance.

Our study was in line with Alessandri et al.[6] results. PR was tolerated by the majority of children. On this matter, we noticed that allergic children could tolerate not only 36 months maturated cheese, but also 30 months maturated (which is cheaper and easier to find).

Some authors evaluated the utility of SPT performed with processed food. Hong et al.[18] evaluated tolerance towards boiled milk in patients suffering from IgE-CMA and tested skin reactivity to boiled commercial extract. Three patients were evaluated: the one who passed boiled milk OFC was the only presenting with the lowest boiled extract SPT mean wheal diameter (3 mm vs 9 mm). Faraj et al.[19] were the first to study muffin PbP NPV. These authors enrolled 58 children with IgE-HEA or IgE-CMA presenting with a negative muffin PbP. Enrolled patients underwent muffin OFCs: 3/58 OFCs failed and PbP's NPV was 94.8%. In Tan et al.[20] the study muffins' PbP NPV was 88%. In our study every negative PbP corresponded to a passed OFC, as a result NPV was 100%. We believe the keystone is the PbP technique. It is known that PbP is effective when performed with liquid or highly water-containing food, while muffin (as ciambellone) is a quite dry product. To solve this problem, Faraj et al.[19] mixed 1 g of muffin with 10 ml of water using a tongue depressor; they put a drop of this solution on patients' forearm skin and pricked it with a lancet passing through the drop. Despite all this, our concern is about the possibility that the lancet passed through the slurry without capturing any muffin particle (as it was mixed in 10 ml of water). This last fact could give false negative results. In the methods section, we described point-by-point techniques we used to perform solid food PbP. Further larger studies would allow patients to avoid an OFC in case of a negative PbP.

Lee et al.[21] followed up 126 children with IgE-CMA or IgE-HEA, who passed muffin OFC. 27/98 patients stopped muffin ingestion: 10 of them did not eat any baked good at all, 17 continued to eat only biscuits with small amount of offending food proteins. In all cases, patients presented with mild gastro-intestinal tract symptoms, such as abdominal pain. In our study no child presented with symptoms associated to certain IgE-mediated adverse reaction. Note also that our children were allowed to eat every baked food containing CM proteins within a wheat matrix in any physical and emotive state. The results of these two studies are encouraging about the safety of CM baked with a wheat matrix ingestion in real life after passing an OFC.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appears in this article.

Right to privacy and informed consent. The authors declare that no patient data appears in this article.

Protection of human subjects and animals in research. The authors declare that no experiments were performed on humans or animals for this investigation.

Conflict of interest

The authors have no conflict of interest to declare.

Appendix 1. Follow-up questionnaire

1. Name and Surname
2. Date of birth
3. How long has it been since your child underwent his/her ciambellone OFC?
   - 3 months
   - 3–6 months
   - >6 months
4. Can your child now eat dairy products in all forms and grades of heating?
   - Yes; eating cow's milk both processed (ciambellone, cakes, biscuits, cream) and raw (ice-cream, other dairy products made with fresh cow's milk)
   - No; still avoiding dairy except baked cow milk products, such as ciambellone, cakes, muffins, biscuits and extensively heated cow milk without a wheat matrix (baked in a liquid form).

- No; avoiding dairy except baked in biscuits
- No; avoiding all forms of dairy, including baked products.

5. To date, does your child eat ciambellone prepared exclusively following our recipe or even other baked products?
   - Yes; only eating ciambellone prepared following medical recipe.
   - No; also eating other baked products.
6. How often does your child eat baked milk (such as in a form of ciambellone or other baked products)?
   - Daily
   - Once in a week
   - Once in two weeks
   - Less than once per month
   - Never
7. How long after the ciambellone OFC did your child continue to have it in his or her diet?
   - Stopped directly after the OFC
   - Less than a month
   - Between one and six months
   - Just few days, I started feeding him/her very soon.
8. On average, does your child still eat approximately the same amount of baked milk as he or she consumed during his or her OFC?
   - Yes
   - No; he or she eats less
   - No; he or she eats more
   - No; he or she does not eat muffin at all
9. Did your child have any symptoms that you thought might have been caused by the ciambellone after you got home from the OFC?
   - Yes
   - No
10. If yes to Question 9: what were these symptoms?
    - Itchy mouth or tingling mouth or throat between 2 and 8 h
    - Itchy mouth or tingling mouth or throat >8 h
    - Hives between 2 and 8 h
    - Hives >8 h
    - Occurrence or worsening of eczema between 2 and 8 h
    - Occurrence or worsening of eczema >8 h
    - Abdominal pain between 2 and 8 h
    - Abdominal pain >8 h
    - Vomiting between 2 and 8 h
    - Vomiting >8 h
    - Diarrhoea between 2 and 8 h
    - Diarrhoea >8 h
    - Cough or wheeze between 2 and 8 h
    - Cough or wheeze >8 h
11. If yes to Question 10: did these symptoms influence your child's diet?
    - Yes; I completely stopped giving baked milk in all its forms.
    - No; I continued with approximately the same amount of ciambellone as the challenge
    - No; but I reduced the amount of cow's milk in the mixture or the amount of ciambellone
    - No; but I changed to cow's milk in biscuits
12. Did your child show any symptoms in the months after you continued baked milk in his or her diet that you thought were related to the baked milk?
    - Yes
    - No
13. Please report culprit food (ciambellone/cakes/croissant/other commercial baked products)
14. Has your child ever eaten baked milk (ciambellone or other baked products), while she/he was in a fever?
    - Yes
    - No
15. If yes to Question 14, did any adverse reaction occur? Please, state below culprit food and type of problem (for example: ciambellone → worsening of eczema).
16. Has your child ever eaten baked milk (ciambellone or other baked product), within 2 h before or after performing physical activity?
    - Yes
    - No
17. If yes to Question 16, did any adverse reaction occur? Please, state below culprit food and type of problem (for example: ciambellone → worsening of eczema).
18. How useful was the ciambellone OFC in relieving your concerns relating to your child's cow's milk allergy?
    - A lot
    - A little bit
    - Not at all
19. If your child passed OFC, how useful was being able to add baked milk into your child's diet?
    - A lot
    - A little bit
    - Not at all
    - I was not able to introduce because of ongoing symptoms

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