

A New Model for Conservative Food Challenge in Children with Immunoglobulin E-Mediated Cow's Milk Allergy

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ABSTRACT: **Background:** The diagnostic gold standard for food allergy is an oral food challenge (OFC) with the suspected food. Usually, an OFC is stopped at the onset of mild objective symptoms for fear of severe reactions, but there is no consensus on this issue.

Objectives: To investigate the effectiveness and side effects of a new model of oral milk challenge in order to increase the diagnostic accuracy of cow's milk protein allergy and reduce the number of useless elimination diets. This model is characterized by a conservative diagnostic protocol and "step-up cow's milk dosing." The secondary aim was to investigate possible factors influencing severe reactions.

Methods: Sixty-six children (median age 1 year, range 1–18) with suspected immunoglobulin E (IgE)-mediated cow's milk allergy performed a conservative OFC, i.e., the OFC was continued even in the presence of subjective, even repeated, or mild local or multiple organ objective symptoms. If the first objective reaction occurred when the quantity of milk was > 10 ml, the investigator would decide whether to continue the OFC or prescribe a gradual increase in milk feeding at home.

Results: Symptoms developed during the OFC in 42.4% of the children. Local, generalized and severe generalized reactions developed in 11 (16.7%), 11 (16.7%) and 6 (9.1%) children, respectively. Only 14/28 (50%) who developed objective symptoms during the OFC were considered to be affected by cow's milk allergy. In the remaining 14 both subjective and objective symptoms developed and the OFC was continued without further symptoms. Epinephrine was administered to 6 of the 28 children (21.4%) who developed objective symptoms. All but one had subjective symptoms following the early doses of milk, whereas all children who later tolerated milk had their first subjective or mild symptoms following doses \geq 10 ml.

Conclusions: This new model of OFC criteria led to frequent severe allergic reactions; hence its use in daily practice seems inadvisable. However, our study provides evidence that a severe allergic reaction does not invariably occur if

the offending food continues to be administered after the onset of symptoms. If mild symptoms appear at doses > 10 ml, continued milk administration, on the same day or in subsequent days, seems to facilitate the development of tolerance and may reduce the number of useless elimination diets.

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KEY WORDS: milk allergy, oral food challenge, tolerance

The diagnostic gold standard for food allergy is an oral food challenge with the suspected food. The European Academy of Allergy and Clinical Immunology [1] and other European societies of allergology [2,3] have presented position papers on this procedure but do not detail the signs and symptoms of a positive OFC. Furthermore, they do not distinguish between an OFC performed to establish a diagnosis of food allergy and an OFC to assess tolerance when a patient is suspected to have outgrown his or her clinical allergy.

Usually, an OFC is stopped at the onset of mild objective symptoms for fear of severe reactions. It was recently suggested that an OFC can be stopped and considered positive at the onset of clear, objective and/or repetitive allergic symptoms [4]. However, there is no consensus on this issue and some authors have used a more conservative criterion, such as the development of at least two objective signs of an allergic reaction [5,6]. Moreover, it is not known if a severe allergic reaction invariably occurs if an offending food continues to be administered after the onset of symptoms or, conversely, if it can induce tolerance in children.

Tolerance seems to develop gradually; some children seem to tolerate a small amount of milk, although larger doses still cause symptoms. Furthermore, it is not known whether tolerance is delayed if the intake of milk is increased while tolerance

OFC = oral food challenge

is developing [7]. In this context, it has been reported that a low dose OFC in which increasing doses of milk (up to 30 ml) were administered, followed later at home with increased milk intake taken slowly, allowed the introduction of milk in the diet of children during the development of tolerance [8].

The aim of the present study was to investigate the effectiveness and side effects of a new model of oral milk challenge characterized by a conservative diagnostic protocol in order to decrease the number of incorrect diagnoses of milk allergy, and further up-dosing of cow's milk facilitating the reintroduction of milk in the diet and reducing the number of useless elimination diets. The possible factors influencing severe reactions were also investigated.

PATIENTS AND METHODS

A prospective study was carried out in 66 children (median age 1 year, range 1–18) consecutively attending two pediatric allergy clinics for immunoglobulin E-mediated suspected cow's milk allergy. Children were referred to the clinics because they had had a diagnosis of cow's milk allergy: in six children because of a preceding positive OFC and the others on the basis of a positive skin-prick test and a clinical history suggestive of cows' milk allergy. They were on a milk-free diet for almost 12 months. All children were submitted to a conservative OFC; that is, the OFC was continued even in the presence of subjective, repeated or severe symptoms, or in the presence of mild local or multiple organ objective symptoms (such as mild rhinitis and/or wheals). If the child had a mild reaction to a dose, the next dose was determined at the discretion of the investigator. The options were to increase the dose, to extend the time between doses, or to repeat the current dose. If the first objective reaction occurred to a dose exceeding 10 ml of milk, the investigator could decide whether to continue the OFC or continue cow's milk administration at slowly increasing doses during the subsequent days at home.

An OFC was considered positive if objective symptoms (local or multiple organ) were persistent or consistently worsened with subsequent doses of milk and/or when an immediate reaction involved at least two of the following target organs: skin (generalized pruritus, flushing, urticaria, angioedema), gastrointestinal tract (repetitive vomiting), respiratory tract (rhinorrhoea, marked congestion, sensation of throat pruritus or tightness), cardiovascular (tachycardia = increase > 15 beats/min), or neurological system (change in activity level plus anxiety). This definition corresponds to grade 3 according to Sampson's criteria for food anaphylaxis [9]. Informed consent for the OFC was obtained from the parents or guardians of the infants.

The reactions to the OFC were treated depending on the type and severity of the reaction. Epinephrine, 0.01 mg/kg (maximum 0.3 mg) per dose, was administered intramuscularly every 15 to 30 minutes as needed to reverse symptoms. Patients were observed for at least 4 hours after an allergic reaction.

ORAL FOOD CHALLENGES

Open controlled challenge tests were performed in the allergy clinics. Each patient remained under observance for at least 2 hours after intake of the last milk dose before returning home. An open challenge was carried out with fresh cow's milk (or formula for infants under the age of 12 months). First, a drop of formula was put on the tongue, then increasing doses of formula (0.1 ml, 0.3 ml, 1 ml, 3 ml, 10 ml, 30 ml, 100 ml) were given at 20 minute intervals or until a reaction appeared. All reactions were scored with regard to type, time of onset, and severity. The amount of milk responsible for the development of symptoms was also recorded.

SYSTEMS AND SEVERITY CATEGORIES

Objective symptoms observed during the failed challenges were categorized into four systems: skin, gastrointestinal, respiratory tract, cardiovascular. The skin category included rash, erythema, pruritus, worsening eczema, angioedema, or swelling of the eyes or face. Gastrointestinal symptoms consisted of palatal erythema or hives, vomiting, or diarrhea. Respiratory symptoms included rhinorrhoea, nasal congestion, nasal pruritus, sneezing, cough, wheeze, shortness of breath, stridor or hoarseness. Cardiovascular symptoms consisted of hypotension, light-headedness, syncope or collapse. Subjective symptoms comprised nausea, itching of the palate, tongue or lips, throat pain, and abdominal cramp or pain.

The severity of symptoms was categorized as follows: a) local reactions – any objective symptoms affecting only one system; b) generalized reactions – reactions affecting two or more systems, namely, skin, gastrointestinal and upper respiratory symptoms; c) severe generalized reactions – reactions affecting two or more systems, including cardiovascular or lower respiratory tract involvement.

Skin-prick tests were performed by trained physicians on the volar aspect of the forearm with cow's milk extract, α -lactalbumin, casein, β -lactoglobulin (Lofarma™, Milan, Italy); the prick-by-prick was performed with pasteurized milk. The positive control was carried out with a histamine standard (1 mg/ml) and a negative control with a glycerosaline solution. A wheal \geq 3 mm of the mean wheal diameter tested 15 minutes after the application of the allergen extracts, and after subtraction of each patient's reaction to the negative control, was required for positivity. The results were expressed as the mean wheal diameter in millimeters.

STATISTICAL ANALYSIS

The Kruskal-Wallis test was used to compare age and SPT wheal diameter for milk proteins and milk (PbP) between children who tolerated milk, those who developed allergic reactions, and those who developed anaphylaxis. *P* value of

PbP = prick-by-prick

multiple comparison was adjusted by Bonferroni's correction. The chi-square test (exact test where necessary) was used to compare gender and historical reaction between the three groups. *P* values ≤ 0.05 (two tailed) were considered statistically significant. All analyses were performed using SPSS for Windows (release 17.0; SPSS Inc., Chicago, IL, USA).

RESULTS

PATIENT CHARACTERISTICS

Of the 66 children with cow's milk allergy enrolled in the study, 43 (65.2%) were boys, and the overall median age was 1 year (range 1–18 years). Atopic dermatitis was the most frequent diagnosis (32/66, 48.5%), while gastrointestinal symptoms, urticaria/angioedema, asthma/allergic rhinitis and anaphylaxis were reported in 21 (31.8%), 20 (30.3%), 6 (9.1%) and 9 (13.6%) children, respectively. All children had at least one positive SPT for milk or milk proteins. Mean diameters were larger for cow's milk PbP than for milk proteins [Table 1].

ORAL FOOD CHALLENGE

Subjective symptoms were recorded in 10 children (15.2%). Objective symptoms developed in 28 (42.4%). All children who initially developed subjective symptoms subsequently developed objective symptoms. Skin symptoms were the most frequent objective symptoms (27.3%), followed by respiratory (22.7%), gastrointestinal (18.2%) and cardiovascular (4.5%). Local reactions were seen in 11 OFC (16.7%), whereas generalized reactions and severe generalized reactions were seen in 11 (16.7%) and 6 (9.1%), respectively.

SPT = skin-prick test

Table 1. Main characteristics of historical reactions of the study population

	n = 66	%
Male gender	43	62.5
Age (yrs) median (range)	1 (1–18)	
≤ 3 yrs	45	68.2
SPT ≥ 3 mm	66	100
Diagnosis		
Atopic dermatitis	32	48.5
Urticaria angioedema	20	30.3
Asthma, allergic rhinitis	6	9.1
Gastrointestinal symptoms	21	31.8
Anaphylaxis	9	13.6
Lactalbumin SPT (mm)	3.0 ± 3.1	
Casein SPT (mm)	3.4 ± 2.9	
Beta-lactoglobulin SPT (mm)	3.2 ± 2.5	
Cow's milk PbP (mm)	5.7 ± 2.0	

SPT = skin-prick test, PbP = prick-by-prick

Positive OFC: OFC was considered positive in 14 children (21.2%); thus, only 14/28 (50%) who developed objective symptoms during the OFC were considered to be affected by cow's milk allergy. OFC was considered positive in eight children because of persistent or worsening objective symptoms with subsequent milk doses, and for the onset of cardiovascular or severe respiratory symptoms in six.

Negative and inconclusive OFC: OFC was considered negative in 51 (77.3%), and inconclusive in 1 (1.5%) due to refusal to drink milk. Among the 51 children 38 performed the OFC without any objective symptoms. The remaining 13 children (25.4%) developed both subjective and mild objective symptoms (in 7 cases with local and in 6 with multiple organ targets); however, the OFC was continued. In four children (cases 8, 9, 10, 12) the administration of milk was continued on the same day. Two of these four children (cases 8 and 9) consumed milk until the cumulative dose of 95 and 125 ml, respectively, without side effects. The third child (case 10) developed abdominal pain and itching on the nose following the 10 ml dose. She repeated the same dose without further problem. With the 50 ml dose she felt nausea and a spot of urticaria appeared on the trunk. The fourth child (case 12) retched and refused food at the 10 ml dose. The same dose was repeated with no side effects, but he developed facial urticaria soon after consuming the 30 ml dose. In the remaining nine children, seven developed objective symptoms and milk administration was stopped during OFC at the cumulative amount of 61.4 ml (range 10–144 ml). The last two children (cases 4 and 5) developed slight objective symptoms after having consumed the last dose of 100 ml and were put on a regular intake of cow's milk. All 13 of these children were to continue to consume cows' milk over the subsequent days at the same dosage as the last tolerated dose during the OFC, with small increases every week.

At 1 year follow-up, 11 of the 13 of children who tolerated milk after having exhibited objective symptoms continued to consume it and tolerated a regular intake of cow's milk. One of the two remaining children of this group (case 12) tolerated only a cumulative amount of cow's milk < 50 ml, and the other child (case 13) returned to a cow's milk-free diet because of recurrence of allergic symptoms (diarrhea and abdominal pain). None of these 13 children needed epinephrine treatment for allergic symptoms during follow-up [Table 2].

THERAPY ADMINISTERED DURING OFC

Overall, no therapy was administered in half the children affected by objective symptoms. All children whose OFC was considered positive received therapy. Antihistamine and steroids were administered intramuscularly or intravenously in about one-third of cases. Epinephrine nebulization was administered in 10.7% and intramuscular epinephrine in 21.4%.

Table 2. Clinical characteristics of children who tolerated milk after objective symptoms

Case	Gender	Age (yrs)	Lactalbumin (mm)	Casein (mm)	BLG (mm)	Cow's milk PbP (mm)	Milk doses at onset (ml)	Symptoms	Total cumulative milk dose (ml)	Dietary suggestion	Tolerance at 1 yr follow-up
1	M	1	4	4	ND	4	30	LUA	44	Slow increase	Yes
2	M	18	ND	6	7	ND	20	OI, NO, CH	34	Slow increase	Yes
3	M	3	0	0	0	8	100	S, NO	124	Slow increase	Yes
4	M	3	4	9	0	6	100	LUA, NO	144	Free diet	Yes
5	M	1	0	0	3	7	90	LUA	134	Free diet	Yes
6	M	1	0	0	4	4	100	LUA	144	Slow increase	Yes
7	M	5	8	0	8	7	30	LUA	44	Slow increase	Yes
8	F	1	0	3	7	ND	30	LUA	95	Slow increase	Yes
9	F	10	8	2	5	11	40	LUA, OI	121	Slow increase	Yes
10	F	1	7	6	6	6	10	AP, OI, V, LUA	60	Slow increase	Yes
11	M	2	3	7	3	4	10	LUA	10	Slow increase	Yes
12	M	1	5	0	5	6	10	LUA, RM, AV	40	Slow increase	Yes (only for doses < 50 ml)
13	M	6	5	0	5	6	30	OI, LUA	30	Slow increase	No, due to repeated symptoms

PbP = prick-by-prick, BLG = beta-lactoglobulin, ND = not determined, OI = oral itching, AP = abdominal pain, LUA = limited urticaria angioedema, E = erythema, CH = conjunctival hyperemia, V = vomiting, S = sneezing, NO = nasal obstruction, RM = refuse milk, AV = attempt to vomit

FACTORS RELATED TO THE OUTCOME

Continuation of milk feeding despite the onset of symptoms led to a high frequency of severe allergic reactions and seemed to induce tolerance in some of the children. Thus, we tried to identify factors related to this outcome by comparing the characteristics of children who developed allergic or severe allergic reactions with those of children who developed tolerance to milk after objective symptoms. Age, gender and past allergic reactions (atopic dermatitis, asthma, gastrointestinal symptoms and history of anaphylaxis) did not differ in these three groups of children (data not shown).

There was a significant difference in wheal diameter of the SPT for casein and milk (PbP) between children who developed severe allergic reactions and those who developed allergic reactions and tolerance after objective symptoms [Table 3].

All but one of the six children who developed multiple organ reactions with cardiovascular or severe respiratory symptoms had symptoms before the onset of severe allergic reaction. These warning symptoms were only subjective in two children (repeated oral itching starting from the first drop). In one child warning symptoms were both subjective and mildly objective: the child became pale and restless after 0.5 ml, and cried and refused to drink milk after a 3 ml dose. Two children developed mild objective symptoms and only one child developed a severe allergic reaction without any apparent discomfort. He was the youngest child in the study (1 year old).

There was a significant difference (Kruskall-Wallis test, *P* = 0.009) in the mean doses of milk that induced the first subjective or objective symptoms in children who later tolerated

Table 3. Mean SPT wheal diameter for milk proteins and milk (PbP) in children with different OFC outcome

	(1) Severe allergic reactions	(2) Allergic reactions	(3) Tolerance after objective symptoms	<i>P</i> (1 vs. 2)*	<i>P</i> (1 vs. 3)*
Lactalbumin (mean ± SD)	3.0 ± 4.6	4.6 ± 4.1	3.6 ± 3.1	1.000	1.000
Casein (mean ± SD)	7.1 ± 2.0	1.7 ± 2.2	2.8 ± 3.2	0.006	0.034
Beta lactoglobulin (mean ± SD)	3.2 ± 3.0	4.8 ± 0.7	4.4 ± 2.5	1.000	0.976
Milk (PbP) (mean ± SD)	10.1 ± 3.4	5.6 ± 1.6	6.2 ± 2.0	0.036	0.048

* After Bonferroni's correction

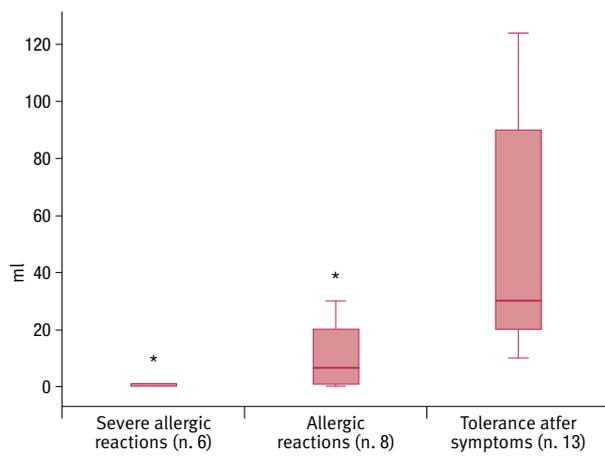
milk (48 ± 40 ml) as compared to children who developed allergic reactions (19.3 ± 34.0) and those who developed severe allergic reactions (16.9 ± 40.6 ml) [Figure 1].

DISCUSSION

In this study we investigated a new model of OFC. We considered the OFC positive based on more conservative criteria, and we allowed the possibility of interrupting the OFC and continuing the administration of milk in the subsequent days if at least 10 ml of milk was tolerated, facilitating introduction of milk in the diet.

This new protocol has been burdened by a high frequency of severe generalized reactions (21.4%) and the use of epi-

Figure 1. Doses of milk (median and range) inducing the first subjective or objective symptoms in children



nephrine (21.4%). This could be explained by the conservative diagnostic criterion: i.e., the OFC was not stopped at the onset of objective symptoms, hence there was a higher possibility of a severe allergic reaction. Therapy was administered in about half the children. In accordance with other studies [10,11], antihistamine was the most frequent drug administered during OFC. However, intramuscular epinephrine was used frequently (21.4%); this percentage is higher than the 11% reported by Perry et al. [12] and by Jarvinen et al. [13], although epinephrine seemed to be underused in our centers, being administered in only five of the six children with severe generalized allergic reactions.

On the other hand, only about half the children (14/28) in the conservative criterion group were considered to be allergic to cow's milk at the end of the OFC, irrespective of the presence of objective symptoms. Had the OFC been considered positive at the onset of objective symptoms, 14 children would have been wrongly diagnosed as allergic and would have received a useless prescription of elimination diets. Thus, to continue the administration of milk after the onset of objective symptoms increased the risk of severe allergic reactions in some children, but in others it seemed to induce tolerance. In fact, further symptoms did not develop in five children despite the administration of increasing amounts of milk on the same day until the maximum dose of 100 ml.

Among children who continue to consume milk despite subjective or mild objective symptoms, it seems impossible a priori to distinguish those who will develop tolerance from those who will develop a severe reaction. A larger mean wheal diameter of milk SPT correlates with a positive challenge but it seems not to be predictive of a severe reaction [10-14]. In this study population the mean wheal diameter of casein SPT and milk PbP was larger in children who developed severe allergic

reactions than in children with allergic reactions or tolerance after objective symptoms. Furthermore, also the amount of milk that evoked the onset of the first allergic symptoms was related to the OFC result. All but one of the children who developed severe allergic reactions had subjective symptoms or slight objective symptoms at the early doses of milk (few drops or a few milliliters), whereas all the children who later tolerated milk had their first subjective or mild symptoms at doses ≥ 10 ml. The only child who developed a severe allergic reaction without any apparent discomfort was the youngest (one year old), and it is conceivable that his young age may have hindered the identification of subjective symptoms. In accordance with our results, Kok et al. [15] recently reported that oropharyngeal symptoms frequently predict the development of objective symptoms in double-blind placebo-controlled food challenges to cow's milk. Thus, we suggest that physicians be particularly alert to subjective oropharyngeal symptoms during milk OFC in the first years of life if symptoms developed at the early doses. The importance of the dose is supported by the fact that the only two children who at 1 year follow-up had reduced tolerance to milk or were on a milk-free diet developed the first symptoms at very low doses, namely 10 and 30 ml, respectively. In addition, there was a significant difference in the mean doses of milk that induced the first subjective or objective symptoms in children who later tolerated milk as compared to those who developed allergic reactions or those who developed anaphylaxis. Two previous studies of the relationship between the amount of food triggering a reaction and severity of reaction produced contrasting results. Perry and co-authors [10] reported that severe reactions during OFC were significantly related to reacting to a lower dose of the challenge food, whereas Jarvinen et al. [11] found that the amount of food triggering a reaction did not differ between children who received epinephrine and those who did not. This discrepancy may be due to methodological differences between the studies. Lastly, in our study, we considered the amount of milk triggering the first reaction, taking into account both subjective and objective symptoms.

Today, OFC is performed to obtain a clear yes/no response, and if any objective symptoms or repeated severe subjective symptoms arise it is usually stopped and considered positive to avoid more severe allergic reactions. This seems appropriate if the OFC is done to confirm the allergy in a child with suspected milk allergy. It might be less appropriate, however, if the OFC is performed to demonstrate the development of tolerance in children on a long-standing cow's milk-free diet. In fact, it is likely that tolerance develops gradually, probably starting at the lowest doses of milk, which is in line with Carl Nilsson Linnaeus' adage *natura non facit saltus*. A number of recent studies have challenged the dogma that strict avoid-

* Translated from the Latin as: Nature makes no leaps

ance hastens recovery from food allergy [16,17]. Studies on oral desensitization for milk showed that the continued administration of milk promotes the development of tolerance in some children [18,19]. This observation suggests that once tolerance for low doses is established, continued graded exposure favors the maintenance of tolerance rather than sensitization [20], and recent DRACMA Guidelines suggest that “when the diagnostic challenge indicates that the child is tolerating small doses of cow’s milk, complete avoidance may not always be required” [21]. Our results support the hypothesis that tolerance develops gradually, starting with the lowest doses. It is tempting to speculate that in children who continued the OFC despite objective symptoms, tolerance was achieved as occurs in rush immunotherapy, i.e., by making effector cells less responsive or non-reactive by the continuous administration of incremental doses of milk, and then maintained by the continuing administration of milk [22].

A limitation of this study is that we did not confirm the diagnoses of food allergy using double-blind placebo-controlled food challenges. However, an open OFC is considered to be sufficient when dealing with immunoglobulin E-mediated acute reactions manifesting as objective signs, such as in our study population. Moreover, the median age of our study population was rather low (1 year) and hence it is unlikely that the development of symptoms had a psychological basis, and investigators reported both subjective and objective symptoms.

In conclusion, our new conservative diagnostic criteria led to frequent severe allergic reactions; therefore, its use in daily practice seems inadvisable. However, our study, for the first time (to the best of our knowledge), provides evidence that a severe allergic reaction does not invariably occur in children with suspected/confirmed immunoglobulin E-mediated cow’s milk allergy who were on a milk-free diet for almost 12 months, if the offending food continues to be administered after the onset of symptoms. Continuing milk administration, on the same day or in subsequent days, if mild symptoms emerge at doses higher than 10 ml, appears to facilitate the development of tolerance and may obviate useless elimination diets. On the contrary, continuing milk administration should be avoided if subjective or mild objective symptoms appear at the first drops of milk, because there is a high risk of a severe allergic reaction. Finally, OFC should be undertaken only in a fully equipped clinical setting because severe adverse reactions can occur, even without warning symptoms. Other studies are required to verify our findings, which, if confirmed, may help to establish new guidelines on how to perform OFC to demonstrate milk tolerance in children.

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