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Diagnosed child, treated child: food challenge as the first step toward tolerance induction in cow's milk protein allergy

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Key words

Cow milk allergy, food challenge, tolerance induction

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Summary

Background: *food challenge is required to assess tolerance in cow milk (CM) allergy. A positive challenge contraindicates the reintroduction of CM. Specific oral tolerance induction (SOTI) is a promising treatment.* ***Methods:*** *all children admitted for a challenge were prospectively enrolled. To those tolerating between 2 and 150 ml a SOTI protocol was offered. Outcome, adverse reactions, parents' satisfaction were recorded.* ***Results:*** *out of 245 challenged patients, 175 reacted. 122 out of 125, able to tolerate a minimum dose of 2 ml, underwent SOTI. After one year 75.4% were in an unrestricted diet, 16.1% tolerated between 5 and 150 ml, 8.5% stopped SOTI. Side effects were mild, parents' satisfaction was very high.* ***Conclusions:*** *the majority of children tolerating limited amounts of CM at the challenge acquires tolerance with SOTI without relevant side effects. Maintaining on an exclusion diet partially tolerant children should be considered debatable.*

Background

Food allergy and anaphylaxis in children are increasing (1). Cow milk (CM) is the main offender in Europe (2). The natural history of CM allergy seems also to be changing in the last decades. Actually the rate of spontaneous achievement of tolerance seems to be slower. Skripak et al reported a strikingly 20% of not tolerant patients at 16 years of age (3). According to DRACMA guidelines a child is considered tolerant only when a significant amount of milk (e.g a normal serving for his age) is tolerated (2). A positive challenge (milk assumption evoking an objective reaction) is considered an absolute contraindication to the reintroduction of CM, so that in case of a positive challenge food avoidance should be reinforced and recommendation for follow-up visit and evaluation after 12 months should be provided (2, 4). Specific oral tolerance induction (SOTI) is a promising approach for the treatment of food allergy (5-14) and contact with allergen seems to play a pivotal role in the acquisition of tolerance (15, 16). Since 2002 we empirically started to offer a home SOTI protocol to all patients who tested positive at the challenge for 4 ml or more of pure milk.

Methods

This was an observational prospective study. The study involved children with CM allergy admitted to the Department of Allergology during the period between January 2005 and April 2010. All children between the age of 1,5 and 14 years with a history of one or more allergic reaction in close connection with the ingestion of CM that had a positive skin prick or positive RAST and /or a positive previous oral challenge underwent an oral challenge to evaluate the persistence of allergy or, conversely, the acquisition of tolerance. The challenge was preceded in all cases by a determination of total serum IgE, specific IgE to CM proteins (RAST, FEIA CAP System, Pharmacia & Upjohn AB, Uppsala, Sweden) and by a skin prick test (Lofarma, Milano, Italy).
Before starting the challenge a venous access was obtained in each patient and drugs to treat any allergic reaction were prepared. Written informed consent was obtained from all parents both for the challenge and eventual study enrollment. Patients with acute illness or taking drugs able to modify the reaction (antihistamines) were excluded. The institute's Ethical Committee approved the study and the home SOTI protocol.

Challenge protocol

An open challenge was performed by offering progressive increasing amounts of pure fresh pasteurized CM, starting with one drop up to a maximal dose of 150 ml. In order to restrict the challenge duration the interval between the doses was gradually increased with the increasing amount of milk given, starting with 10 minutes for smaller quantities up to 20 minutes to the larger doses (Tab. 1)
In case of mild and transient reactions (throat and/or tongue itching, mild rhinitis and/or conjunctivitis mild urticaria, mild abdominal pain) the challenge was continued, slightly delaying the time of the next dose or repeating, in doubtful cases, the dose already administered. In the case of persistent or more severe symptoms the challenge was discontinued (diffuse urticaria, persistent gastric pain or vomiting, respiratory symptoms, hypotension).
Results of challenge were divided into three categories:

a) positive: presence of reaction that would result in termination of challenge;
b) negative: achievement of the maximal dose without any reaction;
c) suspended: the child was tired and no longer collaborating, in agreement with the parents the challenge was stopped even without any reaction.

Table 1 - Cow's Milk challenge scheme

Dose	Time	Dose	Time
1 drop	0	4 ml	70 minutes
2 drops	10 minutes	8 ml	85 minutes
4 drops	20 minutes	16 ml	100 minutes
8 drops	30 minutes	32 ml	120 minutes
16 drops	40 minutes	64 ml	140 minutes
2 ml	55 minutes	150 ml	160 minutes

Prescription after challenge

Three hours after the last dose the patient, if asymptomatic, was discharged with instructions to the after-care. Patients not able to tolerate a minimum dose of 2 ml were prescribed to continue the exclusion diet or were offered to be scheduled for an intra-hospital SOTI. Patient reaching the maximal dose without reactions were considered tolerant and allowed to introduce CM in diet without limitations. To patients able to tolerate 2 ml or more, but not reaching the maximal dose because of reactions, an home protocol of SOTI was offered. Children who suspended the challenge without reactions were not included in the study. In these cases an incremental home reintroduction starting with the last tolerated dose was recommended.

Home SOTI protocol

Each patient was discharged with written instructions on how to gradually increase the dose of CM (Tab. 2).
Empirically we decided that the starting dose, from the day after the challenge, corresponded to that prior to the last tolerated dose without symptoms.
The increase in CM was flexible and could be adapted to the patient's tolerance and symptoms by slowing down the rate of increase or keeping it a fixed dose for weeks or even months at a time, in the case of recurring symptoms . An equivalency table outlining the conversion of CM to cheese and yogurt was provided for the patients, in order to give them the possibility to vary their diet (17). Due to the significant amount of CM required to convert the CM dose to a small portion of cheese, the patients had to reach 80 ml of CM before being able to use this option. Cheese could be used to replace a CM dose or could be added to a smaller CM dose.

General recommendations for home CM assumption: According to our protocol (17) parents were told to keep the child under observation for 3 hours following the ingestion of CM and to avoid physical activity during this 3 hours period. In case of a respiratory infection, they were instructed to decrease the dose of CM by 30% and in the case of gastroenteritis or asthma by 50%, until a complete resolution of the symptoms was seen. Once the symptoms resolved, they were free to slowly increase the daily dose over a seven days period until reaching the previous maximum tolerated dose. Patients were instructed to avoid using straws (possible nebulization effect), to skip a dose in the case of tooth extraction or cuts on the tongue, and to avoid hot showers in the two hours following CM administration. Patients who experienced significant repeated pharyngeal itching or gastric pain were advised to dilute the CM in a substantial amount of fruit juice or soy milk.

Table 2 - Home SOTI protocol

Period	CM dose
between 1° and 20° day	1 ml for five days
	1.5 ml for five days
	2 ml for five days
	3 ml for five days
between 21° and 40° day	4 ml for five days
	5 ml for five days
	6 ml for five days
	7 ml for five days
between 41° and 60° day	9 ml for five days
	11 ml for five days
	13 ml for five days
	15 ml for five days
between 61° and 80° day	19 ml for five days
	23 ml for five days
	27 ml for five days
	31 ml for five days
between 81° and 100° day	40 ml for five days
	50 ml for five days
	60 m for five days
	70 ml for five days
between 101° and 120° day	90 ml for five days
	110 ml for five days
	130 ml for five days
	150 ml for five days

The starting dose corresponded to that prior to the last tolerated dose without symptoms during the open CM challenge (examples: a child reacting to 4 ml would start with 1 ml, a child reacting to 32 ml with 8 ml)

Instructions for Parents in the treatment of adverse reactions: according to our protocol (17) at the time of discharge parents received oral and written instructions on how to deal with the various reactions associated with the home phase of SOTI (Tab. 3). Treatment scheme was adapted by modifying international guidelines for the treatment of anaphylaxis by arbitrarily introducing oral bechlometasone for gastric pain and nebulized epinephrine as a first step treatment for respiratory symptoms. They were trained in how to properly administer the automatic epinephrine injector, and how to use the nebulizer with epinephrine or beta-2 agonists. Parents were given a list of email (for non-urgent communications) and phone contacts (for urgent communications) and encouraged to call with questions or misgivings. All the contacts were doctors with SOTI experience. Each patient had a detailed discharge report to present in the case of reactions requiring hospital admission. *Administration of nebulized epinephrine:* nebulized epinephrine was administered using a nebulizer at a dose of 0.1 mg/kg (maximum dose 3 mg) diluted 2 ml of normal saline and in 2 ml of beclomethasone (800 mcg). Parents were instructed to use inhaled epinephrine as a first step to manage the onset of any respiratory reaction (dysphonia, inspiratory and/or expiratory shortness of breath, wheezing and coughing). *Documentation of in-home reactions:* all the parents of the children enrolled for home SOTI were instructed to report adverse events by phone or email, and were followed-up via email or phone call by one of the doctors responsible for SOTI. Eventual emergency room admission or hospital re-admission at the Burlo Garofolo hospital was also recorded.

Collection of data

Outcome of SOTI, adverse reactions and parents satisfaction were investigated by mean of a phone interview. From the beginning of the study, all the data regarding the reactions reported by parents during the home phase were also recorded. The type and number of reactions, the possible triggers provoking the reactions, Emergency Department admissions, were all recorded. Measures of outcome.

The aim of our study was to evaluate in patients with a positive challenge for more than 2 ml of pure CM the efficacy and safety of a home SOTI protocol. Among subjects who underwent home SOTI the goal was to assess: - percentages of subjects in an unrestricted diet at one year (tolerated dose

Table 3 - Scheme for treatment of adverse reactions

Symptoms	Treatment
Throat and/or tongue transient itching Perioral urticaria	No treatment
Throat and/or tongue persistent itching Rhinitis and/or conjunctivitis Generalized urticaria	Antihistaminic per os (cetirizine)
Abdominal pain	Oral beclomethasone 800 mcg
Laryngospasm or hoarse voice, inspiratory dyspnoea, asthma	Nebulized epinephrine (1 ml/10 Kg of adrenaline in 2 ml of saline solution or in 800 mcg beclomethasone) in association with one or more of the following drugs: Nebulized epinephrine repeated Nebulized salbutamol (0,05-0,15 mg/kg) Steroids per os (bethametasone 0,2 mg/kg or prednisone 2 mg/kg) Antihistaminic per os (cetirizine)
Reaction perceived immediately as severe and systemic (severe dyspnoea, cyanosis, loss of consciousness, collapse), all the symptoms that fail to respond to previous treatment	Intramuscular epinephrine with automatic injector (Fastjekt junior 0.165 mg < 30 kg, Fastjekt 0.330 mg ≥ 30 kg)

> 150 ml) - percentage of patients able to tolerate significant amounts of CM (> 5 ml and < 150 ml) - percentage of patients in an exclusion diet who abandoned SOTI - incidence and type of adverse effects, triggers of side effects, treatments required and need of hospital admission - level of parents' satisfaction.

Statistical analysis

For categorical variables data are presented as numbers and percentages; for continuous variables, data are presented as means and ranges. Data presented are mainly descriptive. Analysis was performed using SPSS 11 for windows.

Results

In the study period 245 patients were enrolled for CM challenge. Baseline characteristics are reported in Table 4. Among the 245 patients who underwent CM challenge 175 were positive, 35 negative (tolerant) and 35 were suspended.. Among subjects with positive results the mean trigger dose was 10.2 ml (1 drop to 32 ml). Fifty patients did not tolerated a dose equal or inferior to 2 ml and were either enrolled for intra-hospital SOTI or repeated the challenge a year later (Tab. 5 and Fig. 1). Of the 125 subjects with a positive challenge and able to tolerate a minimum dose of 2 ml, 122 were enrolled for home SOTI; 3 parents refused to enter the study. At one year follow up 4 patients could not

Table 4 - Baseline characteristics

Age mean (range)	4,55 years (1,58-13,08)
Age median	4,00 years
F:M ratio	1:2,26
Specific IgE mean (range)	17,72 KU/l (0,30-100,00)*
Skin prick test mean (range)	9 mm (4-30)

** Our lab does not determine IgE values higher than 100 KU/l, so 100 was the highest possible value.*

Table 5 - Challenge results

Tolerated dose (drops or ml)	Patients (%)
< 2 drops	10 (4,8%)
4 drops	5 (2,4%)
8 drops	10 (4,8%)
16 drops	25 (11,9%)
2 ml	30 (14,3%)
4 ml	40 (19,0%)
8 ml	40 (19,0%)
16 ml	10 (4,8%)
32 ml	5 (2,4%)
150 ml	35 (16,6%)
	210 (100%)

be contacted. Among 118 subjects who completed the study 89 (75.4%) patients were in an unrestricted diet, 19 (16.1%) ("partially tolerant") were able to tolerate significant amounts of milk (between 5 and 150 ml) and 10 (8.5%) had suspended the protocol because of recurrent minor adverse effects or refused of child or parents to continue. Eighty-two (69.5%) children were aged five years or less; among this patients 61 (74.4%) were in unrestricted diet and 13 (15.8%) were partially tolerant at follow-up. Thirty-six patients (30.5%) were older than five years; in this group 28 (77.8%) were in unrestricted diet and 6 (16.7%) were partially tolerant at follow-up. No statistically significant differences emerged between the two age groups.

During the home phase 36 (30.5%) subjects presented some adverse effects (table 6). An admission to the local emergency department was required for 5 (4.2%) patients. No patient was hospitalized. No child was treated with intramuscular epinephrine. Factors triggering reactions are shown in table 7. The degree of satisfaction of parents was evaluated with a telephone follow-up at one year. Approximately 87% of parents were satisfied or very satisfied with the SOTI. 8% of parents were partially satisfied because they felt the shelter of severe reactions to accidental contact but hoped for a better outcome. 5% of parents were unsatisfied due to the lack of complete liberalization of the diet or because of the repeated occurrence of adverse effects, although not severe.

Figure 1 - Tolerated dose distribution during CM challenge. Initial doses are given in drops, the followings in millilitres. Above the columns is shown the absolute number of patients able to tolerate each dose.

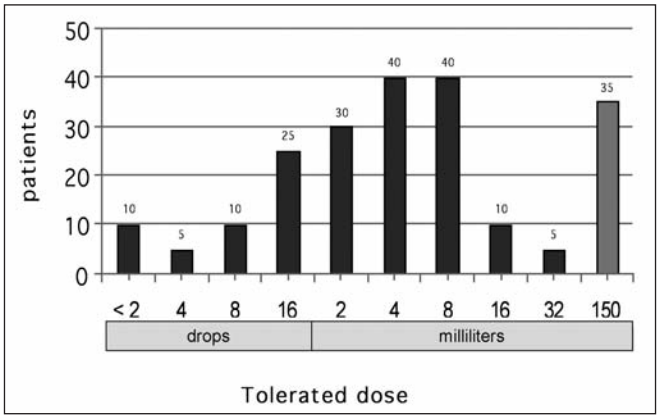

Table 6 - Adverse effects

Number of patients (%)*	36 (30.5%)
Hospital admission (%)	5 (4.2%)
Minor adverse effects (throat and/or tongue itching, mild rhinitis and/or conjunctivitis, urticaria, abdominal pain)	25 (21.2%)
Major adverse effects (respiratory symptoms)	11 (9.3%)

no patient experienced more than 10 reaction during the SOTI period (range 1-10)

Table 7 - Factors triggering reactions

Factors:	Total Reactions (%)
Unknown causes	31.2
Increase in CM dose	26.6
Physical Activity	20.3
Infection	16.5
Other causes (pollen season in allergic patients, continuous use of dairy products instead of CM, hot shower, vomiting)	5.4

Discussion

In these series the majority of patients who experienced a systemic reaction to CM was still not tolerant at a mean age of 4 years. According to standard guidelines all these subjects should have received the prescription of continuing an exclusion diet for at least one year or two before being re-challenged. In our experience these children (excluding those which tolerated less than 2 ml) restarted to assume CM the day after the challenge. In this way more than 70% of this population resulted tolerant at one year. Those who could assume only limited amounts of CM reported a significant improvement in their perceived quality of life. At the challenge the majority of these patients tolerated a limited amount of CM (partially tolerant), while 23.9% reacted to a dose below 2 ml. These data show that these "partially tolerant" children can be successfully treated by the very day of the challenge with a home SOTI protocol, with high efficacy and limited side effects. At the moment the recommended treatment for these "partially tolerant" patients is to continue absolute milk avoidance and retest in one or two years time (2,4). This approach has some limits: the nutritional and the psychological burden of exclusion diet is maintained while the risk of adverse reaction for an accidental contact with the antigen is still present. On the other hand the fact of assuming milk (even in limi-

ted amounts) and an earlier acquisition of tolerance are perceived by the families as a relevant improvement in their quality of life. Data about the cost benefit ratio of SOTI are still limited in the literature but available evidence allows to distinguish between two definite subsets of patients. In our experience one group is made of patients at high risk of adverse reactions and poor outcome in a significant percentage of cases . These are the patients which tolerate only limited amounts of pure CM (less than 5 ml at the end of the in hospital phase of SOTI) with high specific IgE levels (higher than 50 KU/L) (17, 25). The other group is made of patients with low risk of adverse reactions and a good outcome in a high percentage of cases. These are the patients that tolerate higher amounts of CM at the challenge (or at the end of the in hospital phase of SOTI) and have lower specific IgE levels. As a matter of fact strikingly similar data have been reported by different groups, which showed that SOTI has high efficacy and very limited side effects (no need of intramuscular epinephrine) in series of children with lower IgE levels (5-9, 11, 14). On the other hand a poorer outcome with more severe side effects (need of im epinephrine) was reported in series with children with higher specific IgE levels (10, 12, 13, 17, 18, 25). These data show that a slowly performed challenge allows to detect a safety threshold which can be used as a starting point for SOTI. The advantage of this approach is represented by the earlier acquisition of an unrestricted diet . The main drawbacks to balance are the risk of adverse events and the engagement for the families. As far as the first issue is concerned we believe that the safety record of this series and of the others published reports (5-9, 11, 14), dealing with children with mild allergy, justifies this approach. As far as families engagement is concerned this was considered worthwhile by the great majority of parents.

This experience reveals that nebulized epinephrine can play a pivotal role in the management of these patients. In the International Guidelines (19-20), nebulized epinephrine has only recently been introduced as a second line treatment, following IM injection for persistent respiratory symptoms. However, it is well known that respiratory symptoms during anaphylaxis are more prevalent in children than systemic symptoms, such as hypotension that is typical of adults (21). Therefore, it is reasonable to hypothesize that, even with a low level of epinephrine in the blood, the local anti-edema action and the alfa 1-adrenergic effect provided by nebulization plays a major role in the control of symptoms and may arrest the negative chain of respiratory events. The positive effects of nebulized epinephrine were outlined by Hourihane and Warner in 1995 (22) who reported that in 20 years of practice the use of IM epinephrine was replaced by nebulized epinephrine. In their study Simons and Estelle (23-24) have shown that most children are unable to inhale epinephrine from a pre-measured dosage nebulizer. However, a thorough search of the literature has not revealed evidence comparing continuous nebulization to pre-measured dosages. The data presented in this article requires cautious interpretation and should not be transferred to any other study or taken out of context. Actually all the reactions occurred at home and were managed by trained parents . Nebulized epinephrine should only be used in cases of provoked anaphylaxis, as the event is expected and the epinephrine is ready to be used. Nebulized epinephrine should not be used to replace IM epinephrine in the case of spontaneous anaphylaxis.

This study has some limits. One is the absence of a control group. Even though the percentage of children acquiring spontaneously tolerance for milk each year is well known in literature, about 20% (3). Quite surprisingly there was no difference in the percentage of children acquiring tolerance between younger (less than 5 years) and older patients. This may be due to the reduced number of older children (30%) not allowing to detect a difference. On the other hand in our experience in children with severe allergy requiring a first in hospital phase of SOTI younger age was not a predictive factor of success (17). It is conceivable to hypothesize that SOTI can be easier to perform in older children due to a reduced number of undercurrent infections (which are a well known trigger of adverse reactions) and to a higher compliance and motivation of more grown up patients.

In any case the difference in the percentage of children acquiring tolerance between our series (76%) and the average rate of spontaneously acquired tolerance (20%) can be considered as relevant. Furthermore it is important to note that the literature shows that children with IgE levels greater than 20 Ku/ml are intended to capture spontaneous tolerance only in many years (3). For these reasons we believe that guidelines should be reviewed and that partially tolerant children should not straightforwardly undergo through an exclusion diet, especially children with lower specific IgE levels tolerating significant milk amounts. Strong and repeated evidence from the most recent literature (15-16) suggests that the prerequisite for the development of tolerance is repeated exposure to antigen and that contact with antigen induces tolerance. On the other hand it is now strongly suggested that in the proper development of tolerance food avoidance can even be deleterious and prevent the development of normal regulatory mechanism and that in many

children the partial tolerance could be broken when the child is put on an elimination diet (15, 26). We suggest that maintaining on an exclusion diet a child partially tolerant to significant amounts of CM should be considered at least debatable at this point. Actually we now believe non ethical to restart an exclusion diet in a child who has tolerated a significant amount of milk. Acknowledgements: The authors wish to thank doctor Javier Bonè (Zaragoza, Spain) for sharing many ideas.

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