

## REVIEW ARTICLE

# How to reintroduce cow's milk?

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**Abstract**

In a child that is allergic to milk, the natural next step, following the elimination diet, is the reintroduction of cow's milk. Several questions may arise. When feasible, this reintroduction has many benefits for the child and his family. However, the disease needs to be well defined by physicians and explained to parents. They need to understand that there are different types of allergy to cow's milk, specifically IgE- and non-IgE-mediated, and each of these may exhibit both a variable duration and frequently an incomplete recovery. Deciding where to first reintroduce cow's milk to a child who has previously followed a milk-free diet, whether it be at home or in a hospital, also frequently presents an issue. Following this first reintroduction, the progressive increase of milk into the diet needs to be managed properly, as not all children will go back to a normal dairy products intake. Recent studies show that most children with milk allergy tolerate products containing baked milk and that their consumption might speed up recovery. Hence, the purpose of the milk challenge in a child on a milk-free diet is becoming, even in a child still reactive to milk, the first step of gradual and individually adapted reintroduction of milk or dairy products. When reintroduction of cow's milk does not work, immunotherapy becomes an option, and this is carried out in specialized centers.

Several reviews have handled the specific problem of treating cow's milk allergy in children in the past years (1–7), focusing on clinical presentation, diagnosis, milk replacement formulas, and elimination diets. Cows' milk proteins (CMP) need to be removed from the child's diet during CMP allergy (CMPA), but most of the time, even though at least partially related to the onset of long-lasting allergic diseases, like asthma (8), CMPA disappears spontaneously, and milk and dairy products are reintroduced. 'How to reintroduce milk' in the diet of a milk allergic child is really a practical issue, open to review, as it is not specifically addressed in the only GRADED guidelines (5). Classically, the milk challenge is done in the hospital to test whether the child is still allergic to cow's milk or not. New options now prevail, based on a better knowledge of the disease and of its spontaneous evolution (9). Tolerance to milk develops with time and the process may be helped by a progressive reintroduction of milk into the diet of a child who still does not tolerate it well, especially using products containing small amounts of milk (9) or products containing baked milk (10). Milk challenges are thus transforming into an analysis of the clinical reactivity to milk meant to be the first step of a progressive reintroduction of milk or dairy products.

**Reintroducing cow's milk: what benefit for the child and his family?**

The elimination diet prevents the deleterious effects of allergic inflammation but may impair the adequate intake of essential nutrients: Undernutrition may be the consequence of an uncontrolled elimination diet (11–14). This is all the more important in the case of multiple food allergies when exclusion of foods such as wheat or egg renders the child's menu very difficult to settle and nutritional and growth deficiencies more likely to occur (14–16). Returning to a normal diet containing milk and dairy products is desirable for the child's health, to improve the quality of life of both children and parents in these situations (17–19), to favor an appropriate social integration of the child (17) and to avoid unnecessary medical follow-up. Briefly, elimination diets may impair proper nutrient intake and socialization.

**What do we already know about the child's disease?**

What clinical pattern of food allergy is this child suffering from? All clinical conditions encountered in food allergy have been described, especially for milk (4). There are IgE-mediated

and non-IgE-mediated CMP-induced reactions, including conditions which occur very frequently and which are more difficult to classify, such as gastro-esophageal reflux, diarrhea, and constipation, that du Toit et al. labeled 'allergic dysmotility' and that are shared by many IgE and non-IgE CMP-induced disorders.

IgE-mediated reactions may be dangerous and need recognition before any reintroduction of CMP because of the risk of anaphylaxis (1). Milk-specific (s)IgE levels providing 95% certainty of reactivity to milk have been published (4), above 5 kU/l for infants below 2 yr of age and 15 kU/l in all children. For wheal size during skin prick tests (SPT), predictive figures were, respectively, above 6 mm and above 8 mm. Several authors also recently described IgE and/or SPT threshold values serving as a prognostic marker for IgE-mediated CMPA resolution (20–22). For Vassilopoulou et al. (20) analyzing 24/116 positive CMP challenges, a negative outcome is predicted, in order of performance, by sIgE <3.94 kU/l, the combination of SPT and sIgE or an SPT wheal <4 mm, whereas SPT wheal >7.5 mm or sIgE >25.4 kU/l, or their combination predicts a positive outcome. Yavuz et al. (21) analyzing 42/94 positive CMP challenges, a negative outcome is predicted by sIgE <2.8 kU/l for <1 yr, <11.1 for <2 yr, <11.7 for <4 yr, and <13.7 for <6 yr. IgG4 and their protective effect have been investigated more recently (23).

It is likely that in the future, different phenotypes of children with CMPA will be distinguished by biologic traits, such as described for casein and milk sIgE levels, milk-specific basophil reactivity, and milk SPT wheal diameters (24).

For non-IgE-mediated CMPA, biologic tests remain less specific (25, 26). The atopy patch test was shown to be potentially helpful in predicting the evolution (27), but this remains controversial (28–30). CMP-induced reactions are typically delayed and less dangerous, except for the food protein-induced enterocolitis syndrome (FPIES), an acute, assumed to be a cell-mediated, GI food hypersensitivity characterized by severe vomiting and fluid maldistribution resulting in profuse diarrhea, pallor, and hypotonia. Symptoms usually appear between 1 and 4 h after ingestion and may progress to a state of dehydration with hypovolemic shock requiring parenteral rehydration (31, 32). This situation is currently largely under-recognized especially in emergency departments, where acute reactions to milk are still believed to be associated with high CMP sIgE levels.

Briefly, (i) milk-specific IgE and wheal size provide some indication as to the potential reactivity in case of IgE-mediated reactions; (ii) during IgE-mediated CMPA, anaphylaxis will occur during the provocation procedure itself whereas for FPIES, dehydration leading to shock may occur later, when the child is going back home.

#### **What can be expected in a condition with a variable duration and frequently incomplete recovery?**

When treated with an elimination diet, CMPA usually tends toward spontaneous remission, more or less in parallel with the evolution of biologic tests, albeit sometimes slowly and incompletely as previously reviewed (6). Studies show that

persistent cases of CMPA are characterized by the intensity of the familial atopic disease, a longer period between the consumption of the CMP and the onset of symptoms, a high frequency of multiple food allergy and allergic diseases, allergy to casein more than to soluble proteins (33–35), cosensitization to inhalant allergens, to 'less prevalent' food allergens, and to beef and reactivity to lower doses of milk (36). In the last cohort of infants with IgE-mediated CMPA, one half had resolved over 66 months of follow-up, with baseline milk sIgE level, SPT wheal size, and atopic dermatitis severity being all important predictors of the likelihood of resolution (37). CMPA with early gastrointestinal symptoms has a better prognosis (34, 38).

The mode of feeding during the elimination diet might affect the natural evolution and prognosis. Because high temperature largely destroys conformational epitopes to which IgE antibodies are primarily directed, the team at Mount Sinai hypothesized that some children with CMPA would tolerate extensively heated (baked) milk products and showed that the majority (75%) of these children did indeed tolerate such products (39). Interestingly, the addition of baked milk into the diet of children tolerating such foods was shown to accelerate the development of unheated milk tolerance compared with strict avoidance (10). Also, a study showed that LGG supplementation of an eHF hastened resolution of CMPA (40).

Even if it is common for a CMPA to resolve over time, this resolution is not always complete and some children considered to be free of CMPA may retain a 'residual disease', thus being unable to tolerate a 'normal' intake of milk and dairy products later in life (41). 'Incomplete recovery' encompasses cases where the disappearance of symptoms is accompanied by persistent sensitization, which may explain some intriguing issues such as recurrence of symptoms during intercurrent illnesses or during pregnancy and lactation (6). It is the author's experience that these situations may be seen in parents of children being treated for CMPA, albeit with no studied frequency at the moment.

The required duration of the strict elimination diet and, hence, the schedule of the reintroduction of CMP into the diet cannot be clearly established for a given individual. In practice, however, early CMPA, non-IgE-mediated, with predominantly digestive manifestations, may only last for a short period of time, and may warrant considering reintroducing milk from the age of 9 months. In contrast, in cases of CMPA with later onset, IgE-mediated, with skin manifestations among others, CMPA might be persistent and should not require further allergic evaluation before the age of 1 yr. These infants still require surveillance in terms of evaluating dietary sufficiency, and their family need assistance with weaning. Also, severe cases of CMPA, either non-IgE-mediated or with high milk sIgE, can persist in children who will never be able to outgrow it.

Briefly, (i) in infants, non-IgE-mediated milk allergy will last less than the IgE-mediated form; (ii) in both conditions, some cases seem difficult to outgrow; (iii) recovery may be partial so that children may tolerate a limited amount of milk and dairy products.

### **Customizing of the milk challenge: small amounts, cooked, fermented milk?**

When the physician considers discontinuing the elimination diet, he usually begins with an oral milk challenge or provocation test, typically performed in the hospital day care unit, and followed by the gradual reintroduction of milk and dairy products at home (9).

A complete milk challenge usually goes up to approximately 200 ml, that is one bottle, and when this amount is tolerated, a tolerance can be said to have been achieved, at least in most cases.

A negative milk challenge in patients previously diagnosed with CMPA is logically followed by a normal diet, stopping an elimination that has become unnecessary (17–19). However, tolerance is not always achieved despite a normal milk challenge (19), indicating a late reaction and some families continue milk avoidance (17).

If the child is not able to tolerate a large amount of milk, the physician may be willing to reintroduce small amounts, in an attempt not only to facilitate the family cooking, but also in an attempt to 'force' tolerance, in what may actually be labeled an 'oral immunotherapy', previously referred to as an 'induction of tolerance'. Milk challenges with low doses have been suggested and seem efficacious (42). This is all the more important as food allergy is no longer a matter of 'yes' or 'no' but a matter of 'how much is tolerated'. A child reacting with 30 ml of milk is still considered allergic to milk but nowadays also as being able to tolerate lower amounts of milk: He can be fed daily with minute amounts of CMP, progressively increasing thereafter. Some authors now suggest a progressive reintroduction of milk into the diet based on this first evaluation of the tolerated level (9).

Actually, the recent evidence that the majority of children with CMPA tolerate baked milk (39) changes the purpose of milk challenges and the way they are conducted: The physician now wants to know whether the child tolerates baked milk and in what quantities, so that he may introduce products containing baked milk into the diet of the child, both alleviating the family burden of the elimination diet and, hopefully, speeding up the recovery process. Recently, a fully matured cheese (Parmigiano-Reggiano) was tolerated by 58% of CMPA children, in correlation with the absence of IgE toward beta-lactoglobulin (43), opening new prospects for the role of transformed milk in the reintroduction process.

Milk oral challenges are thus changing, evolving from a reintroduction of a bottle of milk in the hospital to more personalized procedures where according to age, clinical presentation and past tests on the child, milk may be offered in higher or lower amounts, in more or less baked and/or fermented products or not, sometimes first baked and then raw, consecutively during the same day. However, it is not possible at the moment to really predict who is able and who is unable to pass a complete milk challenge and which form seems the most adapted. Biologic tests may help. It was shown that casein and milk sIgE level, milk-specific basophil reactivity, and milk SPT wheal diameter are all significantly greater among patients with CMPA who react to baked milk than

among those who tolerate it (24). Also, combined with clinical history and the expertise of the physician, the use of cutoff decision points for sIgE levels to casein could identify the optimal candidates for baked milk oral challenges and improve the management of children with suspected CMA (44). Following this introduction of baked milk, it might prove interesting to try using less baked milk products and to try more raw ones, as several factors in bovine milk have been described that might explain how raw cow's milk consumption can decrease the risk of allergies early in life (45).

Briefly, (i) consider reintroducing small amounts, even in the hospital ward, to test the potential reintroduction of limited amounts at home; (ii) consider a provocation test with baked forms of milk; (iii) milk allergic children might now be classified as baked milk-tolerant vs. baked milk-intolerant.

### **Where to challenge children with milk, at hospital or at home?**

Several working parties have set up rules for oral food challenges (46–48), which are very useful from a practical and legal point of view, indicating, among other recommendations, that the milk challenge must be carried out in an area equipped for severe reactions, close to an intensive care unit, by a medical personnel and paramedics in the habit of performing these tests and present on site to detect adverse reactions, with informed consent from patients and their families. These recommendations also include the schedule of the test and the doses of the food to be used. Duration of monitoring depends on the clinical circumstances: Children with IgE-mediated CMA usually react within 1–2 h (48), whereas in children with FPIES, a delayed reaction takes place, usually appearing within 4 h (49).

From a practical point of view, however, this admission to the hospital, even for only one day, is a limiting factor, at least in Europe where healthcare systems are reluctant to spend money. Alternative pathways need to be sought, taking into account the ethical and legal issue of food challenges in allergic children outside the hospital. If a child had inadvertent milk challenge (e.g., a glass of milk at a friend's house) and it is clear from the history that no reaction occurred, admitting him to hospital for a similar challenge is not worthwhile. Most children with non-IgE-mediated CMPA do not need day care admission, as they are not at risk of anaphylactic shock, except those recognized as having FPIES, which puts them at risk of dehydration following the end of the milk challenge.

Briefly, (i) milk challenges are mostly done in the hospital in case of IgE-mediated CMPA and at home in case of non-IgE-mediated milk allergy; (ii) FPIES, a non-IgE-mediated disease, nonetheless merits a hospital challenge, with a follow-up several hours thereafter.

### **At home, managing the progressive increase of milk into the diet**

Following the initial oral milk challenge, the progressive reintroduction of CMP continues at home. The clinical response of a durable exposure to CMP in a child who was on elimination diet is also difficult to predict. Reactions may

occur, especially in the case of non-IgE-mediated CMA, days or weeks after starting the reintroduction process. A gradual increase of the milk and dairy product intake at home is thus desirable. This progressive reintroduction at home allows determining the CMP dose that the child is able to tolerate. This dose may correspond to the usual intake of milk and dairy foods in a Western diet or be more limited in children who continue to suffer from the 'residual disease' mentioned above (41). The current state of research does not allow us to say what percentage of children who are able to tolerate one bottle will actually exhibit a limited long-term tolerance to dairy products. The persistence of clinical symptoms suggestive of the recurrence of a CMPA during the gradual increase of CMP intake at home does not ipso facto warrant a return to the strict exclusion of CMP. Indeed, several recent studies indicate that the continued presence of CMP in the diet at a tolerated dose facilitates the acquisition of a long-term tolerance (50, 51). The increase in food diversity allowed into the diet also makes social life easier. Such a management requires a full education and the active participation of parents and is not always feasible. It is facilitated by the knowledge of the protein concentrations in the dairy products available (6).

Briefly, (i) back home, the clinical reaction to milk may be delayed: wait at least another day before giving milk back home (never give milk during dinner the day of the challenge); (ii) tolerance of milk in a one day oral challenge does not always mean that daily iterative ingestions will be tolerated.

### When reintroduction of cow's milk does not work

Feeding older children still allergic to milk may be problematic, for different reasons. First, milk is so prevalent in children's food and in food processing that milk avoidance leads to constraints which could potentially limit the socialization of children. Second, in the regular children's diet, there is a potential risk of inappropriate calcium intake, in the absence of approximately two sufficient amounts of milk or dairy products every day. Third, in the general view of most parents, prohibiting the intake of dairy products prevents the child from having a 'normal' breakfast, with some liquid to drink.

The child may be kept on regular feeding with adapted formulas (protein hydrolysates or amino-acids), if the child still accepts, but this represents a non-negligible cost, often unbearable in the absence of reimbursement.

Replacement foods may be needed. After 6 months of age, and also subject to prior verification of clinical tolerance, soy protein follow-on formulas may be used. Vegetable juices made of soy, rice, almond, coconut, or chestnut, often labeled 'milks', mostly sold in organic outlets, do not meet the nutritional needs of an infant (52–54). In older children, they can occasionally be used provided that they are ready-fortified with Ca, and as long as there is a trained dietician involved. If parents are in need of liquid food, for breakfast for instance, vegetable juices can thus be part of complementary feeding, provided that the diets of such children are correctly balanced.

There tends to be some confusion regarding the appropriateness of milk from mammals other than cow. The composition (i.e., the protein, fat, folic acid, and mineral content) of milk from

goat, sheep, donkey, horses, and camel makes them nutritionally absolutely unsuitable for infants, whether they are allergic or not. After infancy, if a tolerance to cows' milk has not been acquired, goat's and ewe's milk, fermented or not, and cheeses might provide a real benefit, including for Ca intake (6). However, goat's and ewe's milk proteins may cross-react with CMP in patients with CMPA: Their potential use depends on individual susceptibility (55–57), being probably lower than 25% for goat's milk (58), but seemingly improving in children treated with oral immunotherapy (59). Their tolerance has to be demonstrated, at in-hospital challenges, at least for IgE-mediated CMA.

Children allergic to milk are allergic to bovine meat in 13–20% of cases (60), which means that most of the time, they may be fed beef and veal, if clinically tolerated.

Briefly, (i) vegetable juices can occasionally be used if ready-fortified with Ca, and under a trained dietician surveillance; (ii) ewe and goat milks and dairy products can be part of complementary feeding after 1 yr of age, but tolerance has to be tested first.

### Forcing tolerance in case of 'resistance'

Cases where the acquisition of a tolerance is lagging behind are responsible for attempts at 'forcing' it using 'immunotherapy', that is, various amounts of milk given orally, either in increasing amounts to be swallowed or limited amounts to be placed sublingually (61). These techniques are intended to produce either a 'tolerance', a final state of non-reactivity to the allergen independent of its regular use, or only 'desensitization' with a mere increase in the threshold in reactivity to milk. For milk oral immunotherapy, the quality of trials has increased with time, but a Cochrane review (62) showed that studies to date have involved small numbers of patients, with the quality of evidence generally low. Milk oral immunotherapy can lead to desensitization in the majority of individuals with IgE-mediated CMPA, but the development of long-term tolerance has not been established (63). To that end, different diets are being studied (64). A major drawback is the frequency of adverse effects, even though most are mild and self-limited and the use of parenteral epinephrine not infrequent (65). There are no standardized protocols, and authors suggest generating guidelines prior to incorporating desensitization into clinical practice (62). Sublingual immunotherapy has also been attempted (66) alone or combined with milk oral immunotherapy (67), showing that the oral route was more efficacious for desensitization than the sublingual one alone but accompanied by more systemic side effects, with clinical desensitization being lost in some cases within 1 wk off therapy.

Briefly, (i) milk immunotherapy is still in a research phase; (ii) obtaining tolerance might be a long process, requiring years.

### Accompanying parents in the reintroduction process

Reintroducing milk in a child always told about the potential lethal effect of this food may be very troublesome for the child. A personal study showed that the prevalence of food neophobia, *that is*, the refusal by children to eat new food, known to be a normal phenomenon between 2 and 10 yr of age, seems to be more common or pronounced when an elimination diet has been imposed by a food allergy (68).

## Conclusion

Allergy to milk is evolving. Elimination diet and clinical observation were the mainstays of treatment. Children are now being taken care of more actively, using milk and dairy products both in increasing amounts and with transformed proteins, especially

baked, in an attempt to speed up the acquisition of a tolerance. Creating a tolerance to milk in children for whom such an evolution could not be expected before has also become a goal. Some caution should still be taken, as this approach is new and largely in the research phase.

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