S.G. Makarova[1, 2], L.S. Namazova-Baranova[1, 2, 3], G.A. Novik[4], E.A. Vishneva[1], M.I. Petrovskaya[1, 2], S.G. Gribakin[5]
[1] Scientific Center of Children's Health, Moscow, Russian Federation
[2] Sechenov First Moscow State Medical University, Russian Federation
[3] Pirogov Russian National Medical Research University, Moscow, Russian Federation
[4] Saint Petersburg State Pediatric Medical University, Saint Petersburg, Russian Federation
[5] Russian Medical Academy of Postgraduate Education, Moscow, Russian Federation

Concerning Diet Duration at Cow's Milk Protein Allergy. How and When Should Dairy Products Be Introduced Again?

Author affiliation:
Svetlana Gennadyevna Makarova, PhD, Professor at the department of allergology and clinical immunology of the faculty of pediatrics at the State Budgetary Educational Institution (SBEI) of Higher Professional Education (HPE) "Sechenov First Moscow State Medical University", dietician, leading research fellow at the department of clinical studies of the Federal State Budgetary Research Institution (FSBRI) "Scientific Center of Children's Health" (SCCH),
Address: 2 Lomonosovskiy Av., Moscow, 199991; **tel.:** +7 (495) 967-14-21; **e-mail:** Sm27@yandex.ru

Article received: 09.02.2015. Accepted for publication: 05.05.2015.

Cow milk proteins (CMP) are the most frequent cause of allergy in infants. Despite significant progress in the sphere of laboratory diagnosis, including diagnosis of various allergic diseases in children, food allergy remains a stumbling block in many cases. Success of treating children with a CMP allergy largely depends on early diagnosis and timely prescription of adequate elimination diet and is determined by coordinated actions not only of niche specialists (allergists and dieticians), but also of the primary care physicians. The minimum efficient diet duration is determined by evidence-based studies and defined in consensus documents on managing children with a CMP allergy. Further, the diet duration is determined on the individual basis. Diet continuation should be justified, which is why the need in eliminating specific foodstuffs from a child's diet is assessed every 6-12 months. However, there are no clear predictors of the tolerance development term and duration of a strict elimination diet in children with a CMP allergy. Until recently it had been believed that up to 80-90% of children with a CMP allergy develop tolerance within the first 3-5 years of life; however, according to the latest data, the body's adaptation is observed at an older age. Overall, the studies show that persistent CMP allergy is characterized by a significantly complicated family anamnesis of atopic diseases, longer period of time between the beginning of CMP intake and onset of the first symptoms of allergy, higher frequency of multiple reactions to food and development of other allergic diseases. Partial CMP tolerance may develop with age; in that case, dairy foodstuffs should be introduced to the diet in a limited amount. In such cases specialists recommend introducing milk proteins to the diet step by step in tolerable doses (mainly as components of other foodstuffs); according to the findings, this may promote tolerance development without altering the diagnosis.
Keywords: *food allergy, children, tolerance, elimination diet, diagnostic introduction of foodstuffs.*
(**For citing:** Makarova S.G., Namazova-Baranova L.S., Novik G.A., Vishneva E.A., Petrovskaya M.I., Gribakin S.G. Concerning diet duration at cow's milk protein allergy. How

and when should dairy products be introduced again? *Pediatricheskaya farmakologiya = Pediatric pharmacology*. 2015; 12 (3): 345–353. doi: 10.15690/pf.v12i3.1364)

INTRODUCTION

A necessary condition of successful allergy treatment is elimination of a causative allergen; in terms of food allergy this stipulates withdrawal of a causative food from the diet. Cow milk protein (CMP) allergy is especially widespread in infants. According to the European Society of Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN), the allergy rate is 2-3% among infants (ESPGHAN Guidelines, 2012). By 5 years of age approximately 80% of the patients develop tolerance; therefore, by the age of 6 years the incidence rate declines to below 1% [1].

According to the latest meta-analysis conducted by the European Academy of Allergy and Clinical Immunology (EAACI) [2], the rate of allergic reactions to cow milk is considerably higher. Thus, according to survey "Self-reported lifetime prevalence", it reaches 6% (95% confidence interval [CI] – 5.7-6.4) in the population. According to the survey and skin testing results, the CMP allergy prevalence is 2.3% (95% CI – 2.1-2.5); according to the survey and specific immunoglobulin (sIg) E level appraisal – 4.7% (95% CI – 4.2-5.1); positive provocative test occurred in 0.6% of the cases (95% CI – 0.5-0.8). Comparative analysis of CMP allergy rate in different countries demonstrated that it is more prevalent in the north of Europe than in the south.

According to the EAACI, by the time of survey "Self-reported point prevalence", the milk protein allergy in under-1 children was 4.2%, in 2-5-year-old children – 3.75%; the rates of detection of sIgE to this protein were 1.6% and 6.8%, respectively [2].

A while ago, it was considered that a child may "outgrow" CMP allergy; nowadays it is evident that termination of symptoms requires a period of strict elimination of causative milk proteins. Both CMP allergy-induced diseases and CMP tolerance formation depend both on the clinical/immunological form of food allergy (IgE-mediated or non-IgE-mediated) and adequate tactics of managing a child on early stages of the pathology development. The most common cause of unsuccessful treatment of children with CMP allergy is insufficient – partial – allergen elimination (deliberate or accidental).

CONTEMPORARY RECOMMENDATIONS ON MANAGING CHILDREN WITH CMP ALLERGY

The main principles of diagnosis and tactics of managing children with CMP allergy are described in the recently published international consensus documents. These guidelines are a foodstuff of hard work of a range of experts, who analyzed effectiveness of various diagnostic and therapeutic approaches to food allergy, on the basis whereof instructions for practicing physicians are published. Such documents for pediatricians are "Diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines" issued by the World Allergy Organization (WAO) in 2010 [3]; ESPGHAN recommendations "Diagnostic Approach and Management of Cow's-Milk Protein Allergy in Infants and Children" (2012) [1]; and the most complete document – "Food Allergy and Anaphylaxis Guidelines" issued by the EAACI [2]. The value of these documents is that they summarize the vast international clinical experience and evidence basis and provide specific recommendations for practicing physicians. Russian specialists published national documents "Food allergy: guidelines for physicians" [4] and recommendations "Diagnosis and treatment of cow milk protein allergy in infants and young children: practical recommendations" [5] approved at the XVII Congress of Pediatricians of Russia in 2014 and based on the aforementioned documents, personal experience and results of scientific studies. All the aforelisted documents are aimed at helping a practicing physician to

avoid faulty diagnosis and management of children with food allergies and, therefore, to improve quality of medical care, as well as prognosis in this category of patients.
A completely milk-free diet excluding all CMP- and beef-containing foodstuffs should be designed in the event of acute or subacute CMP allergy. Physician should warn parents (and patients) of the risk of cross-reactions (e.g. with goat milk, sheep milk or buffalo milk) and tune the children's parents to compulsory and strict observation of the diet [2]. In order to achieve compliance, it is important to describe the general plan of the child's management to the parents, specify the approximate duration of the diet and time of the follow-up examination. Such information (even approximate) helps parents to observe the elimination diet tactics.
However, the question of **when and how** to reintroduce the previously excluded CMP is one of the most complicated practical issues of managing children with this pathology. On the one hand, the diet should be sufficiently long-lasting in order to completely terminate symptoms and form tolerance. On the other hand, an unreasonably protracted diet may negatively affect a child's nutritive status and food behavior formation; this will become an unreasonable psychological burden for a child and all members of his/her family just as well [2].

MINIMAL ELIMINATION DIET DURATION

According to contemporary recommendations [1, 2, 5], if diagnosis of CMP allergy has been proven, an under-1 child should remain on a milk-free diet until the age of at least 6 months or even 12 months. If breastmilk is available, natural feeding should be maintained, and the mother should observe a milk-free hypoallergenic diet (it is important to exclude all milk protein-, beef- and veal-containing foodstuffs). If breastmilk is not available, a child should be fed with a therapeutic formula based on extensively hydrolyzed milk protein or amino acids. Step-by-step CMP allergy diet therapy algorithms are described in our previous publications and national guidelines [4, 5].
If treatment of children with IgE-mediated food allergy yield positive results, it is reasonable to reintroduce a previously excluded foodstuff after monitoring the blood level of specific IgE-antibodies at least 6 months after the introduction of the elimination diet. Infants with severe and immediate IgE-mediated reactions may remain on the elimination diet until the age of 12-18 months, when they undergo a follow-up specific IgE assay.
As unreasonably protracted exclusion of CMP-containing foodstuffs is also considered unfavorable for children [2], the maximum duration of an elimination diet without a follow-up examination should not exceed 12 months (in case of extremely severe and anaphylactic reactions – 18 months) even in children with pronounced symptoms of allergy and high level of sIgE to CMP. After that a follow-up examination should be conducted in order to avoid unreasonable continuation of an elimination diet. Persisting IgE sensitization in children is a cause for elimination diet prolongation.
Open provocative test may be performed in children with non-IgE-mediated CMP allergy and absence of allergic reactions in the anamnesis, on the basis whereof a conclusion is made, whether CMP-containing foodstuffs may be introduced to the diet [1, 2, 5].

TERM OF TOLERANCE FORMATION IN CHILDREN WITH CMP ALLERGY

In order to avoid term confusion, we will define the type of tolerance analyzed in this article. Tolerance is widely discussed in the following two aspects.
1. Formation of food protein tolerance in the process of development of such an immunological phenomenon as "oral tolerance", when a child's immune system "learns" not to react actively to a broad spectrum of enterally entering proteins. This process begins intrauterine, when extremely small amounts of food proteins contained in the mother's blood enter the fetus transplacentally, and actively continues throughout the first months of life and infancy. It has been recognized that the most significant events affecting a human's immune system and health occur in the first

“1,000 days” of life; the count begins at conception. The possibility of affecting mechanisms of formation of such a “primary” tolerance is the basis of contemporary approaches to prevention of food allergies.
2. The children allergic to food proteins may form tolerance to these proteins with time. The rate of such adaptation varies depending on the type of proteins: it is especially high for cow milk and chicken egg proteins. Tolerance to peanut, fish and most other allergens develops far less often. This review is dedicated to this “secondary” tolerance in the children suffering from food allergies.

Term of tolerance formation in these patients and, therefore, duration of elimination measures at CMP allergy vary on an individual basis. Apart from tolerance formation as a result of observation of an elimination diet (natural tolerance), food protein tolerance may be achieved by means of allergen-specific immunotherapy (induced desensitization). The latter process is different from tolerance formation; it is called desensitization, which is not a complete synonym of tolerance. As this a large separate matter and specific immunotherapy with food allergens is not certified and not conducted in the Russian Federation, this article will feature only formation of tolerance to CMP as a result of an elimination diet.
As the table shows, the milk protein tolerance formation rate in children with non-IgE-mediated CMP allergy who suffered from the allergy in the first year of life may reach 100% by the age of 5 years [13], whereas in children with IgE-mediated form these figures and far lower. Thus, according to K.M. Saarinen et al. [7], CMP tolerance develops in 74% and 85% of the children with IgE-mediated allergy by the age of 5 years and 8-9 years, respectively. According to A. Elizur et al. [11], this occurs in 41% of the children by the age of 2 years and in 57% of the children by the age of 4 years. The least optimistic prognosis is given by J.M. Skripak et al. [12], who analyzed the largest number of clinical studies (807 patients): 19% - by the age of 4 years, 64% - by the age of 12 years, 79% - by the age of 16 years. This means that every fifth child with IgE-mediated CMP allergy, which set on in infancy, remains sensitive to milk even at the age of 16 years.

Table. ***Rate (%) of tolerance formation in children with CMP allergy depending on the form of allergy (according to various studies)***

Source	**Rate of CMP tolerance formation (%)**									
	Age (years)									
	1	**2**	**3**	**4**	**5**	**8**	**9**	**10**	**12**	**16**
IgE- and non-IgE-mediated forms										
Host A., Halken S. [6]	56	77	87							
Saarinen K.M. [7]		51								
Vanto T. [8]		44	69	77						
Garcia-Ara M.C. [9]				68						
Wood R.A. [10]					53					
IgE-mediated form										
Elizur A. [11]		41		57						
Skripak J.M. [12]				19		42		52	64	79
Saarinen K.M. [7]					74		85			
non-IgE-mediated form										
Saarinen K.M. [7]					100					

FACTORS AFFECTING THE TERM OF CMP TOLERANCE FORMATION AND ELIMINATION DIET DURATION

Normally, CMP lymphocyte priming should being prenatally [14]. Later, pronounced immune response to CMP and other food proteins is observed in the first months of life. Increase in the level of IgG, including subclass IgG1, is a physiological reaction to introduction of a foreign protein [15, 16]. The level of specific IgG-antibodies continues to increase throughout several weeks after introduction to milk formulas fed to the child and reaches its peak after 3-4 months [15, 16]. Small amounts of specific IgE are also a part of the physiological reaction to foreign cow milk proteins [17]. However, as has been mentioned previously, high production of specific IgE to CMP in combination with clinical manifestations is a diagnostic criterion of an IgE-mediated milk protein allergy [1, 2, 5] and a predictor of its persistence [7, 12, 18]. At the same time, periodic examination including monitoring of the level of specific IgE allows predicting tolerance development [2, 19, 20].

Apart from the allergy form (IgE- or non-IgE-mediated), tolerance formation in children with CMP allergy depends on a range of obscure factors. There are findings, according whereto a profile of the CMP epitopes, wherewith specific IgE bind, is important for tolerance development. Thus, persistent CMP allergies are characterized by development of IgE to a broader spectrum of antigen determinants [21-23], as well as higher avidity (binding capacity) of antibodies [24].

Specific IgG4 response to food proteins is seen as physiological [25]; it has been proven to be more pronounced when milk proteins are introduced early on [26, 27]. Later, specific IgG4 are, apparently, involved in food protein tolerance formation [28]. Thus, examination of the 8-9-year-old children who “outgrew” allergy to CMP observed at a younger age revealed a higher level of specific IgG4 to this protein [19, 29]. Interestingly, blood serum IgG4-antibodies in the CMP-tolerant children were characterized by higher capacity of binding to a considerably broader spectrum of epitopes than in the children with persistent CMP allergy [24, 29]. It has also been demonstrated that children with CMP allergy and low level of IgG4 to β-lactoglobulin require a longer lasting elimination diet [30].

Apparently, balance of IgE and IgG4 to CMP affects tolerance development. It has been assumed that the ratio of IgE/IgG4 antibodies reflects the cytokine status and the balance of T-cell subclasses. In particular, interleukin (IL) 4 induces production of both IgE and IgG4 by B-cells, while IL 10 promotes production of IgG4 and inhibits production of IgE [31, 32].

Impact of polymorphism of gene rs324015, which is responsible for the production of transcription factor STAT 6 and takes part in Th2 differentiation, on the CMP tolerance development prognosis has been revealed [10].

In practice, results of provocative and skin tests may serve as tolerance predictors. It has been shown that the reaction to minimal amounts of cow milk (10 ml and less) in case of a provocative test and large papule size after a skin prick test are predictors of CMP allergy persistence [1], as well as of severe course of atopic dermatitis [33]. Small papule size and low level of specific IgE to CMP allow predicting a rather rapid development of tolerance [7, 8, 34].

A multicenter study demonstrated how the choice of therapeutic formula affects CMP tolerance development in children with milk protein allergy [35]. Results of a provocative test performed 12 months after elimination diet demonstrated that the use of casein hydrolysates yields a higher percentage of CMP tolerance development in comparison with the use of amino acid formulas, soy diet or rice hydrolysates. Food enrichment with lactic bacilli (LGG) enhances the formula’s tolerogenic effect.

Remission to a greater or lesser extent usually occurs simultaneously with changes in the results of laboratory tests in the setting of adequate elimination therapy, which is why a provocative test is required to solve the question of diet expansion. In order to avoid unreasonable early testing and reduce the rate of adverse reactions when performing a provocative test, predictive criteria of positive and negative provocative tests are being developed.

Thus, a reaction to milk protein introduction (or provocative test results) might be predicted in case of IgE-mediated allergy on the basis of the level of specific IgE to CMP and/or results of prick tests. Positive reaction predictors when performing a provocative test are the level of specific IgE to milk over 5 kU/l in under-2 children and 15 kU/l in children of any age [36]. According to S.T. Yavuz et al., analysis of 94 provocative CMP tests demonstrated the following predictive threshold of a negative provocative test: sIgE level < 2.8 kU/l – in under-1 children; < 11.1 kU/l – in under-2 children; < 11.7 kU/l – in under-4 children; < 13.7 kU/l – in under-6 children [33]. The predictive factor of skin prick tests is the papule size over 6 mm and 8 mm, respectively.

Vassilopoulou et al. [37] analyzed 116 provocative CMP tests and determined the negative predictive threshold: sIgE level < 3.94 kU/l and papule size at prick tests < 4 mm. On the contrary, papule size > 7.5 mm and/or sIgE level > 25.4 kU/l are predictors of positive result of a provocative test. Therefore, in such cases it is recommended to postpone a provocative test (or foodstuff introduction). However, it has been shown that the level of specific IgE to CMP in 52.6% of the patients with positive results of provocative milk tests was < 0.35 kU/l [38].

No laboratory predictors have been developed for non-IgE-mediated CMP allergies, which is why physicians have to rely only on the anamnestic data and provocative test (diagnostic foodstuff introduction) results [39].

DIAGNOSTIC FOODSTUFF INTRODUCTION

As classic provocative tests are not certified in the Russian Federation, introduction of a foodstuff is basically a diagnostic measure. That is why we have previously proposed term **“diagnostic foodstuff introduction”** (L.S. Namazova-Baranova, S.G. Makarova) [40]. Amount of CMP-containing foodstuff for the first trial introduction is determined on the basis of the anamnestic data (amount of foodstuff required to induce a reaction, intensity of the reaction to this amount). Diagnostic foodstuff introduction is started with a considerably lower dose than the one that induced the reaction. Duration of waiting for the response after diagnostic foodstuff introduction also depends on the nature of previous reactions to this foodstuff and may vary from 2 hours to 2 days depending on the type of reaction registered in the anamnesis (immediate or deferred [delayed], respectively). If the first diagnostic foodstuff introduction does not yield a negative response, the foodstuff is introduced to the diet in gradually increasing amounts with compulsory registration of all the symptoms: skin, gastrointestinal and respiratory manifestations of allergies should be checked [40]. In case of a deferred reaction it is reasonable to keep a diet diary for some time.

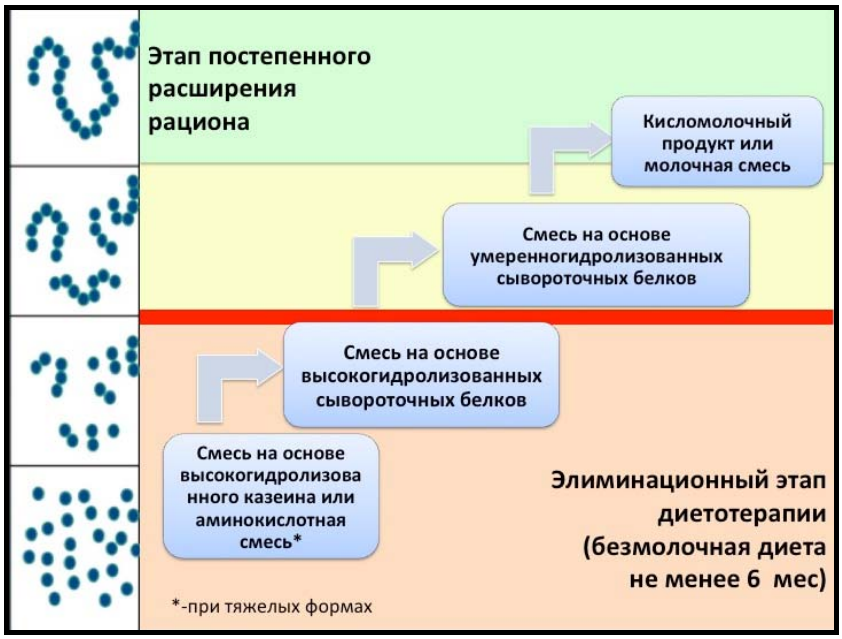
If negative symptoms after diagnostic introduction of milk protein are absent, the physician is to provide recommendations on expanding the diet. However, it has been demonstrated that even if no reaction to a single test is observed, long-term tolerance to dairy products may not be present; apparently, this might be connected with deferred reactions [41]. Moreover, some patients develop partial tolerance to dairy products. Thus, in some cases tolerance to a small amount of milk protein [41] or only to heat-treated dairy products, e.g. to powdered milk as a component of pastry, is observed [42, 43].

NEW QUESTION: “HOW MUCH IS TOLERATED?”

One of the crucial questions on the diet expansion stage is in what amount and within what products to introduce milk proteins.

If a child does not tolerate considerable CMP amount, but tolerates small doses, many food allergy specialists recommend introducing tolerable amounts of milk or dairy product to the child’s diet. On the one hand, these recommendations are aimed at making food preparation in family conditions easier, on the other hand and more importantly, it is an attempt to naturally induce tolerance, as it has demonstrated clinical effectiveness [37]. Thus, formerly, a food

allergy would raise a yes/no question whether the foodstuff should be excluded; now, the question raised when designing a diet on the diet expansion stage is as follows: **"how much is tolerated?"** [43, 44].
Thus, if a child tolerates only 30 ml of milk or milk formula, CMP allergy diagnosis remains unchanged, but it is recommended to gradually increase the amount of milk proteins in the diet starting from the minimal tolerable amounts determined by means of a provocative test (or diagnostic foodstuff introduction) [36, 37].
Given the aforementioned, an step-by step diet therapy algorithm for infants with CMP allergy we develop appears absolutely reasonable to use, when on the stage of diet expansion (after the period of strict CMP elimination) a child is transferred from extensively hydrolyzed formulas (in that case – formulas Friso Pep AC and Friso Pep) to feeding with hypoallergenic formulas based on moderately hydrolyzed milk protein (Frisolac GA 1 or 2) while being monitored for tolerance and only then, after diagnostic foodstuff introduction, being monitored for tolerance, he/she is transferred to a foodstuff containing undegraded milk proteins [4, 46] (pic.). This approach has completely proved itself well in practice and was the most effective when using such a method as determination of the level of specific IgE to peptide components of therapeutic and preventive formulas by means of IFA-Lacttest kit for formula tolerance control [46].



Pic. Step-by-step formula prescription algorithm for children with CMP allergy

Элиминационный этап диетотерапии (безмолочная диета не менее 6 мес)	*Elimination stage of diet therapy (milk-free diet for at least 6 months)*
Смесь на основе высокогидролизованного казеина или аминокислотная смесь при тяжелых формах	*Extensively hydrolyzed casein formula or amino acid formula For severe forms*
Смесь на основе высокогидролизованных сывороточных белков	*Extensively hydrolyzed serum protein-based formula*
Смесь на основе умеренногидролизованных сывороточных белков	*Moderately hydrolyzed serum protein-based formula*
Этап постепенного расширения рациона	*Gradual diet expansion stage*
Кисломолочный продукт или молочная смесь	*Fermented dairy product or milk formula*

Follow-up observation of CMP tolerance formation demonstrated that many children with milk allergy may eventually tolerate heat-treated milk proteins [2, 41, 47]. Thus, it has been

demonstrated that up to 75% of the children with CMP allergy start to tolerate boiled or otherwise heat-treated cow milk, including such milk as a pastry component, with time [47]. Analysis of peculiarities of immune response in the patients who eventually started to tolerate boiled milk preserving reactions to raw milk demonstrated that they are characterized by higher level of IgG4 to casein in comparison with the children reacting to all dairy products [42]. Those children who do not tolerate neither raw nor heat-treated milk feature an increased level of sIgE to CMP and casein, as well as the basophil activation indicator; they also have a larger blister when completing a skin test [48].

Formation of such tolerance depends not only on sensitization to thermolabile or thermostable cow milk proteins, but also on the nature of antigen epitopes, whereto antibodies have been formed. As high temperature largely destructs conformational parts of antigen macromolecules, children with IgE to these epitopes may tolerate boiled milk. If IgE is binded by non-conformational antigen determinants, tolerance to boiled milk does not form [48].

In a study by I. Devenney [44], heat-treated milk (in tolerable doses, as a pastry component) was introduced to diets of the children tolerating such milk. After 3 months of observation it was discovered that the mean skin test papule size decreased significantly; at the same time, the level of IgG4 to casein increased in comparison with the initial level. Other immunological parameters, such as intestinal permeability, did not differ.

A study (70 children aged from 6 months to 16 years, average age – 3 years) conducted in Italy demonstrated that 58% of the children with CMP allergy tolerate ripened cheese (in that case – Parmesan); tolerance was observed in children lacking IgE to β-lactoglobulin [49]. There are findings demonstrating that 86% of the children with positive provocative milk tests (25 ml of boiled milk) do not react to butter (10 ml of butter, which is equivalent to 2.9 ml of milk in terms of proteins) [50]. In the cited study, the level of specific IgE to CMP < 17.8 kU/l served as the predictive factor of the negative provocative butter test [50].

Such studies help to discover new approaches to tactics of managing children to CMP allergy and allow a more personalized approach on the diet expansion stage, when milk in a greater or lesser amount and more or less hydrolyzed or heat-treated and/or fermented foodstuffs may be introduced to the diet [43]. It is no wonder that the EAACI “Food Allergy and Anaphylaxis Guidelines”(2014; section 7) include the study of “efficacy of heat-treated, dried or fermented food allergens (including allergens as parts of dairy products) to accelerate the development of tolerance” among the new promising lines of research in the sphere of tactics of managing children with food allergies [2].

TACTICS OF MANAGING CHILDREN WHEN DAIRY PRODUCTS CANNOT BE INTRODUCED TO THE DIET

When reactions to diagnostic introduction even of the minimal amounts of milk proteins are observed and expansion of the diet with dairy products is infeasible, the patient should continue receiving therapeutic formulas (based on extensively hydrolyzed milk proteins or amino acids); in this setting, the range of supplemental feeding products should gradually expand. Nutrient composition of therapeutic formulas is adapted to infant needs, which is why a child may continue receiving therapeutic formulas (based on extensively hydrolyzed milk proteins or amino acids) as long as necessary if a long-term observation of milk-free diet is required. In children over 6 months of age the hydrolysate may be replaced with a soy formula while the children are being monitored for tolerance in the period of remission of allergy symptoms; this eases the financial burden the family endures due to the need in purchasing therapeutic products.

Soy-, rice-, almond-, coconut or chestnut-based drinks often branded milk and sold mostly at health food stores do not fulfill the infants’ needs and may not serve as a replacement of adapted formulas [1, 2]. However, they may be recommended to older children if they remain allergic to milk protein-containing foodstuffs. These drinks do not fulfill demand of many nutrients in older children as well [51-53]; however, they may be used to make breakfast or brunch for a child, as

supplemental feeding, though only if a child receives a sufficient amount of calcium and features a completely balanced diet.
Goat milk and sheep milk, both fermented and non-fermented, as well as cheeses, may serve as an additional source of nutrients, including calcium, in children over 1 year of age. However, use of these foodstuffs on the elimination stage of diet therapy in children with CMP allergy is absolutely prohibited. Their use is extremely restricted on the diet expansion stage as well due to high rate of allergic cross-reactions [1, 2, 54].
Any way, if a strict elimination diet is required, a child should be observed not only by an allergist, but also by a dietician in order to carefully compensate all the nutrient deficits as needed [4, 52, 53]. It has been demonstrated that parameters of physical development of the children with food allergies undergoing an elimination diet (milk-free and gluten-free) do not differ from the population norm if the diet is completely balanced [55]. Specific attention when observing a long-lasting milk-free diet should be given to adequate consumption of calcium; otherwise the risk of osteoporosis development in puberty is very high [56, 57]. Approaches to the diet for older children with food allergies are described in the national guidelines in detail [4].

CONCLUSION

The process of formation of tolerance to food proteins depends on many factors [58]. According to specialists, there are no clear predictors of the term of tolerance development in children with CMP allergy, as well as of strict elimination diet duration. In practice, dairy products may be introduced to some children characterized by early manifestation of CMP allergy, especially if the allergy is gastrointestinal and non-IgE-mediated, at the age of ~ 9 months. On the contrary, diseases with late onset of symptoms, skin manifestations and IgE-mediated forms tend to persist and require a follow-up evaluation of the level of specific IgE at the age of ~ 1 year [43]. At the same time, severe cases of CMP allergy, both IgE-mediated and non-IgE-mediated, persist for a long time, and children may never “outgrow” them [10, 43]. In general, studies demonstrate that persistent CMP allergy is characterized by a significantly burdened family anamnesis in terms of atopic diseases, longer time between the beginning of CMP consumption and manifestation of the first symptoms of allergy, higher incidence of multiple reactions to food and presence of other allergic diseases. Persistent forms are also characterized by sensitization to casein, not to milk’s serum fraction proteins; reactions to low doses of milk proteins; cross-reactions to beef; accompanying sensitization to air allergens [59, 60].
Partial CMP tolerance may develop with time; then dairy products may be introduced to the diet in limited amounts. In such cases specialists recommend keeping diagnosis of CMP allergy and gradually introducing milk proteins to the diet in tolerable doses (primarily as components of other products), as this has been shown to be capable of promoting tolerance formation [43, 44, 48].
It has been considered until recently that up to 80-90% of children with CMP allergy form tolerance in the first 3-5 years of life [1, 10, 61]. However, according to the latest data, tolerance formation occurs at an older age [7, 33]. Nevertheless, the significance of milk allergy in older children is sometimes underestimated. Thus, CMP allergy may unobviously persist at school age and be associated with such allergy manifestations as rhinoconjunctivitis, atopic dermatitis or bronchial asthma [62], as well as be a cause of recurrent episodes of abdominal pain [63]. Therefore, the real rate of tolerance formation in children with CMP allergy may be even lower than recognized at the moment [59, 64].
Change of question on the diet expansion stage from a yes/no question to “how much is tolerated?” leads to a different medical approach: provocation of exacerbation for a diagnostic purpose is replaced by introduction of a foodstuff in a tolerable dose and tolerance formation. Therefore, introduction of CMP-containing foodstuffs to children with CMP allergy is characterized by slow increase in the dose and tolerance monitoring. However, occurrence of any

persistent symptoms must be analyzed by the physician in terms of potential insufficient CMP tolerance and the child should be transferred back to a milk-free diet with periodic evaluation of the effectiveness thereof.

Apparently, different phenotypes of allergies to CMP to casein and milk's serum fraction in children will be discovered, as well as of specific basophil activation depending on the sIgE level (and, potentially, on the IgG4 level) and the intensity of reactions at skin prick tests (papule diameter); genetic markers of tolerance formation may also be proposed in the future [34, 65]. Therefore, the studies that will allow determining CMP tolerance formation predictors, tolerance markers and tolerable milk protein dose criteria on the diet expansion stage more clearly are required.

CONFLICT OF INTEREST

The authors of this article have declared absence of reportable financial support / conflict of interest.

REFERENCES

1. Diagnostic approach and management of cow's milk protein allergy in infants and children: ESPGHAN GI committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012; 55 (2): 221–229.
2. Muraro A., Roberts G., Worm M., Bilo M.B., Brockow K., Fernandez Rivas M., Santos A.F., Zolkipli Z.Q., Bellou A., Beyer K., Bindslev-Jensen C., Cardona V., Clark A.T., Demoly P., Dubois A.E., Dunn Galvin A., Eigenmann P., Halken S., Harada L., Lack G., Jutel M., Niggemann B., Ruëff F., Timmermans F., Vlieg-Boerstra B.J., Werfel T., Dhami S., Panesar S., Akdis C.A., Sheikh A. Food Allergy and Anaphylaxis Guidelines. *Allergy*. 2014; 69: 1026–1045.
3. Diagnosis and rationale for action against cow's milk allergy (DRACMA) guidelines. World Allergy Organization. *Pediatr Allergy Immunol*. 2010; 21: 1–125.
4. A.A. Baranov, L.S. Namazova-Baranova, T.E. Borovik, S.G. Makarova, I.N. Pampura, I.N. Zakharova et al. Food allergy. Ed. by A.A. Baranov, L.S. Namazova-Baranova, T.E. Borovik, S.G. Makarova. Series "Pediatric diseases from A to Z". *Moscow.* 2013. 160 p.
5. Diagnosis and treatment of cow milk protein allergy in infants and young children: practical recommendations. Ed. by A.A. Baranov, L.S. Namazova-Baranova, T.E. Borovik, S.G. Makarova. *Moscow: Pediyatr.* 2014. 48 p.
6. Host A., Halken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy*. 1990; 45: 587–96.
7. Saarinen K.M., Pelkonen A.S., Makela M.J., Savilahti E. Clinical course and prognosis of cow's milk allergy are dependent on milk-specific IgE status. *J Allergy Clin Immunol*. 2005; 116: 869–75.
8. Vanto T., Helppila S., Juntunen-Backman K. et al. Prediction of the development of tolerance to milk in children with cow's milk hypersensitivity. *J Pediatr*. 2004; 144: 218–22.
9. Garcia-Ara M.C., Boyano-Martinez M.T., Diaz-Pena J.M., Martin-Munoz M.F., Martin-Esteban M. Cow's milkspecific immunoglobulin E levels as predictors of clinical reactivity in the follow-up of the cow's milk allergy infants. *Clin Exp Allergy*. 2004; 34: 866–70.
10. Wood R.A., Sicherer S.H., Vickery B.P., Jones S.M., Liu A.H., Fleischer D.M., Henning A.K., Mayer L., Burks A.W., Grishin A., Stablein D., Sampson H.A. The natural history of

milk allergy in an observational cohort. *J Allergy Clin Immunol*. 2013 Mar; 131 (3): 805–12.
11. Elizur A., Rajuan N., Goldberg M.R., Leshno M., Cohen A., Katz Y. Natural course and risk factors for persistence of IgE-mediated cow's milk allergy. *J Pediatr*. 2012; Sep; 161 (3): 482–487.
12. Skripak J.M., Matsui E.C., Mudd K., Wood R.A. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol*. 2007; 120: 1172–7.
13. Savilahti E.M., Savilahti E. Development of natural tolerance and induced desensitization in cow's milk allergy. *Pediatr Allergy Immunol*. 2013; 24: 114–121.
14. Westerholm-Ormio M., Vaarala O., Tiittanen M., Savilahti E. Infiltration of Foxp3- and Toll-like receptor-4-positive cells in the intestines of children with food allergy. *J Pediatr Gastroenterol Nutr*. 2010; 50: 367–76.
15. Kemeny D.M., Price J.F., Richardson V., Richards D., Lessof M.H. The IgE and IgG subclass antibody response to foods in babies during the first year of life and their relationship to feeding regimen and the development of food allergy. *J Allergy Clin Immunol*. 1991; 87: 920–9.
16. Vaarala O., Saukkonen T., Savilahti E., Klemola T., Akerblom H.K. Development of immune response to cow's milk proteins in infants receiving cow's milk or hydrolyzed formula. *J Allergy Clin Immunol*. 1995; 96: 917–23.
17. Hattevig G., Kjellman B., Bjorksten B. Appearance of IgE antibodies to ingested and inhaled allergens during the first 12 years of life in atopic and non-atopic children. *Pediatr Allergy Immunol*. 1993; 4: 182–6.
18. Fiocchi A., Terracciano L., Bouygue G.R. et al. Incremental prognostic factors associated with cow's milk allergy outcomes in infant and child referrals: the Milan Cow's Milk Allergy Cohort study. *Ann Allergy Asthma Immunol*. 2008; 101: 166–73.
19. Savilahti E.M., Saarinen K.M., Savilahti E. Duration of clinical reactivity in cow's milk allergy is associated with levels of specific immunoglobulin G4 and immunoglobulin A antibodies to beta-lactoglobulin. *Clin Exp Allergy*. 2010; 40: 251–6.
20. Shek L.P., Soderstrom L., Ahlstedt S., Beyer K., Sampson H.A. Determination of food specific IgE levels over time can predict the development of tolerance in cow's milk and hen's egg allergy. *J Allergy Clin Immunol*. 2004; 114: 387–91.
21. Vila L., Beyer K., Jarvinen K.M., Chatchatee P., Bardina L., Sampson H.A. Role of confor- mational and linear epitopes in the achieve ment of tolerance in cow's milk allergy. *Clin Exp Allergy*. 2001; 31: 1599–606.
22. Cerecedo I., Zamora J., Shreffler W.G. et al. Mapping of the IgE and IgG4 sequential epitopes of milk allergens with a peptide microarray-based immunoassay. *J Allergy Clin Immunol*. 2008; 122: 589–94.
23. Wang J., Lin J., Bardina L. et al. Correlation of IgE/IgG4 milk epitopes and affinity of milk-specific IgE antibodies with different phenotypes of clinical milk allergy. *J Allergy Clin Immunol*. 2010; 125: 695–702.
24. Wang J., Lin J., Bardina L. et al. Correlation of IgE/IgG4 milk epitopes and affinity of milk-specific IgE antibodies with different phenotypes of clinical milk allergy. *J Allergy Clin Immunol*. 2010; 125: 695–702.
25. Stapel S.O., Asero R., Ballmer-Weber B.K. et al. Testing for IgG4 against foods is not rec-ommended as a diagnostic tool: EAACI Task Force Report. *Allergy*. 2008; 63: 793–6.
26. Jenmalm M.C., Bjorksten B. Exposure to cow's milk during the first 3 months of life is associated with increased levels of IgG subclass antibodies to beta-lactoglobulin to 8 years. *J*

Allergy Clin Immunol. 1998; 102: 671–8.
27. Juvonen P., Mansson M., Kjellman N.I., Bjorksten B., Jakobsson I. Development of immunoglobulin G and immunoglobulin E antibodies to cow's milk proteins and ovalbumin after a temporary neonatal exposure to hydrolyzed and whole cow's milk proteins. *Pediatr Allergy Immunol*. 1999; 10: 191–8.
28. Lemon-Mule H., Sampson H.A., Sicherer S.H., Shreffler W.G., Noone S., Nowak-Wegrzyn A. Immunologic changes in children with egg allergy ingesting extensively heated egg. *J Allergy Clin Immunol*. 2008; 122: 977–83.
29. Savilahti E.M., Rantanen V., Lin J.S. et al. Early recovery from cow's milk allergy is associated with decreasing IgE and increasing IgG4 binding to cow's milk epitopes. *J Allergy Clin Immunol*. 2010; 125: 1315–21. e9.
30. Tomicic S., Norrman G., Falth-Magnusson K., Jenmalm M.C., Devenney I., Bottcher M.F. High levels of IgG (4) antibodies to foods during infancy are associated with tolerance to corresponding foods later in life. *Pediatr Allergy Immunol*. 2009; 20: 35–41.
31. Satoguina J.S., Weyand E., Larbi J., Hoerauf A. T regulatory-1 cells induce IgG4 production by B cells: role of IL-10. *J Immunol*. 2005; 174: 4718–26.
32. Meiler F., Klunker S., Zimmermann M., Akdis C.A., Akdis M. Distinct regulation of IgE, IgG4 and IgA by T regulatory cells and toll-like receptors. *Allergy*. 2008; 63: 1455–63.
33. Yavuz S.T., Buyuktiryaki B., Sahiner U.M., Birben E., Tuncer A., Yakarisik S., Karabulut E., Kalayci O., Sackesen C. Factors that predict the clinical reactivity and tolerance in children with cow's milk allergy. *Ann Allergy Asthma Immunol*. 2013 Apr; 110 (4): 284–9.
34. Venter C., Brown T., Shah N., Walsh J., Fox A.T. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy — a UK primary care practical guide. *Clinical and Translational Allergy*. 2013; 3: 23.
35. Canani R.B., Nocerino R., Terrin G., Frediani T., Lucarelli S., Cosenza L., Passariello A., Leone L., Granata V., Di Costanzo M., MD, Pezzella V., Troncone R. Formula Selection for Management of Children with Cow's Milk Allergy Influences the Rate of Acquisition of Tolerance: A Prospective Multicenter Study. *Journal of Pediatrics*. 2013; 163 (Issue 3): 771–777.
36. du Toit G., Meyer R., Shah N. et al. Identifying and managing cow's milk protein allergy. *Arch Dis Child Educ Pract Ed*. 2010; 95: 134–44.
37. Vassilopoulou E., Konstantinou G., Kassimos D. et al. Reintroduction of cow's milk in milk-allergic children: safety and risk factors. *Int Arch Allergy Immunol*. 2008; 146: 156–61.
38. E.E. Varlamov, A.N. Pampura, T.S. Okuneva. Diyagnosticheskoye znacheniye peroralnykh provokatsiyonnykh prob u detey s atopicheskim dermatitom. *Rossiyskiy vestnik perinatologiyi i pediyatriyi.* 2012; 57 (6): 37-41.
39. Shek L.P., Bardina L., Castro R., Sampson H.A., Beyer K. Humoral and cellular responses to cow milk proteins in patients with milk-induced IgE-mediated and non-IgE-mediated disorders. *Allergy*. 2005; 60: 912–9.
40. S.G. Makarova, L.S. Namazova-Baranova, E.A. Vishnyova, A.K. Gevorkyan, A.A. Alexeyeva, M.I. Petrovskaya. Aktuyalniye voprosy diyagnostiki pishchevoy allergiyi v pediyatricheskoy praktike, *Vestnik RAMN.* 2015; 1: 41-46.
41. Dambacher W.M., de Kort E.H., Blom W.M., Houben G.F., de Vries E. Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses. *Nutr J*. 2013; 12: 22.

42. Kim J.S., Nowak-Wegrzyn A., Sicherer S.H., Noone S., Moshier E.L., Sampson H.A. Dietary baked milk accelerates the resolution of cow's milk allergy in children. *J Allergy Clin Immunol*. 2011; 128: 125–31.
43. Dupont C. How to reintroduce cow′s milk? *Pediatr Allergy Immunol*. 2013; 24: 627–632.
44. Devenney I., Norrman G., Oldaeus G., Stromberg L., Falth-Magnusson K. A new model for low-dose food challenge in children with allergy to milk or egg. *Acta Paediatr*. 2006; 95: 1133–1142.
45. Longo G., Berti I., Barbi E. et al. Diagnosed child, treated child: food challenge as the first step toward tolerance induction in cow's milk protein allergy. *Eur Ann Allergy Clin Immunol*. 2012; 44: 54–60.
46. T.E. Borovik, S.G. Makarova, N.N. Semyonova, S.N. Darchiya, L.V. Shumilina, S.N. Shikhov, A.P. Chekannikova. Novye podkhody v diyagnostike i diyetoterapiyi pishchevoy allergiyi u detey rannego vozrasta. *Rossiyskiy allergologicheskiy zhurnal.* 2010; 3: 30-42.
47. Nowak-Wegrzyn A., Bloom K.A., Sicherer S.H. et al. Tolerance to extensively heated milk in children with cow's milk allergy. *J Allergy Clin Immunol*. 2008; 122: 342–739.
48. Ford L.S., Bloom K.A., Nowak-Wezgrzyn A.H., Shreffler W.G., Masilamani M., Sampson H.A. Basophil reactivity, wheal size, and immunoglobulin levels distinguish degrees of cow's milk tolerance. *J Allergy Clin Immunol*. 2013; 131: 180–6.
49. Alessandri C., Sforza S., Palazzo P. et al. Tolerability of a fully maturated cheese in cow's milk allergic children: biochemical, immunochemical, and clinical aspects. *PLoS ONE*. 2012; 7: e40945.
50. Yanagida N., Minoura T., Kitaoka S. Butter Tolerance in Children Allergic to Cow's Milk. *Allergy Asthma Immunol Res*. 2015 Mar; 7 (2): 186–9.
51. Liu T., Howard R.M., Mancini A.J. et al. Kwashiorkor in the United States: fad diets, perceived and true milk allergy, and nutritional ignorance. *Arch Dermatol*. 2001; 137: 630–6.
52. Fox A.T., Du Toit G., Lang A., Lack G. Food allergy as a risk factor for nutritional rickets. *Pediatr Allergy Immunol*. 2004; 15: 566–9.
53. Yu J.W., Pekeles G., Legault L., McCusker C.T. Milk allergy and vitamin D deficiency rickets: a common disorder associated with an uncommon disease. *Ann Allergy Asthma Immunol*. 2006; 96: 615–9.
54. Carroccio A., Cavataio F., Iacono G. Cross-reactivity between milk proteins of different animals. *Clin Exp Allergy*. 1999; 29: 1014–6.
55. Berry M.J., Adams J., Voutilainen H., Feustel P.J., Celestin J., Järvinen K.M. Impact of elimination diets on growth and nutritional status in children with multiple food allergies. *Pediatr Allergy Immunol*. 2015 Jan 31.
56. Nachshon L., Goldberg M.R., Schwartz N., Sinai T., Amitzur-Levy R., Elizur A., Eisenberg E., Katz Y. Decreased bone mineral density in young adult IgE-mediated cow's milk-allergic patients. *J Allergy Clin Immunol*. 2014 Nov; 134 (5): 1108–1113.
57. Ambroszkiewicz J., Rowicka G., Chelchowska M., Gajewska J., Strucińska M., Laskowska-Klita T. Biochemical markers of bone metabolism in children with cow's milk allergy. *Arch Med Sci*. 2014 Dec 22; 10 (6): 1135–41.
58. G.A. Novik. Strategiya formirovaniya tolerantnosti u detey s pishchevoy allergiyey. *Voprosy sovremennoy pediyatriyi.* 2015; 11 (1): 70-77.
59. E.E. Varlamov, A.N. Pampura, T.S. Okuneva. Prognosticheskiye kriteriyi razvitiya tolerantnosti k produktam pitaniya u detey s pishchevoy allergiyey. *Rossiyskiy vestnik perinatologiyi i pediyatriyi.* 2008; 6: 64-69..

60. Fiocchi A., Terracciano L., Bouygue G.R. et al. Incremental prognostic factors associated with cow's milk allergy outcomes in infant and child referrals: the Milan Cow's Milk Allergy Cohort study. *Ann Allergy Asthma Immunol*. 2008; 101: 166–73.
61. Venter C., Arshad S.H. Epidemiology of food allergy. *Pediatr Clin North Am*. 2011; 58 (2): 327–349.
62. Sampaio G., Marinho S., Prates S., Morais-Almeida M., Rosado-Pinto J. Transient vs persistent cow's milk allergy and development of other allergic diseases. *Allergy*. 2005; 60 (3): 411–412.
63. Saps M., Bonilla S. Early life events: infants with pyloric stenosis have a higher risk of developing chronic abdominal pain in childhood. *J Pediatr*. 2011; 159 (4): 551–554.
64. Rona R.J., Keil T., Summers C., Gislason D., Zuidmeer L., Sodergren E. et al. The prevalence of food allergy: a meta-analysis. *J Allergy Clin Immunol*. 2007; 120 (3): 638–646.
65. Hochwallner H., Schulmeister U., Swoboda I., Spitzauer S., Valenta R. Cow's milk allergy: From allergens to new forms of diagnosis, therapy and prevention. *Methods*. 2014 March 1; 66 (1): 22–33.