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Practice guidelines

Nutritional management of cow's milk allergy in children: An update

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ABSTRACT

Cow's milk is one of the most common foods responsible for allergic reactions in children. Cow's milk allergy (CMA) involves immunoglobulin E (IgE)- and non-IgE-mediated reactions, the latter being both variable and nonspecific. Guidelines thus emphasize the need for physicians to recognize the specific syndromes of CMA and to respect strict diagnostic modalities. Whatever the clinical pattern of CMA, the mainstay of treatment is the elimination from the diet of cow's milk proteins. The challenge is that both the disease and the elimination diet may result in insufficient height and weight gain and bone mineralization. If, during CMA, the mother is not able or willing to breastfeed, the child must be fed a formula adapted to CMA dietary management, during infancy and later, if the disease persists. This type of formula must be adequate in terms of allergic efficacy and nutritional safety. In older children, when CMA persists, the use of cow's milk baked or heated at a sufficient temperature, frequently tolerated by children with CMA, may help alleviate the stringency of the elimination diet. Guidance on the implementation of the elimination diet by qualified healthcare professionals is always necessary. This guidance should also include advice to ensure adequate bone growth, especially relating to calcium intake. Specific attention should be given to children presenting with several risk factors for weak bone mineral density, i.e., multiple food allergies, vitamin D deficiency, poor sun exposure, steroid use, or severe eczema. When CMA is outgrown, a prolonged elimination diet may negatively impact the quality of the diet over the long term.

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1. Introduction

Breastfeeding is the optimal way of infant feeding, exclusively until 6 months of age and partially until 2 years according to the World Health Organization (WHO) [1]. Non-breastfed infants must be fed with infant formulas complying with the European regulations (Commission Directive 2006/141/EC on infant formulae and follow-on formulae, which will be replaced by the

Delegated Regulation No. 2016/127), containing proteins generally obtained from cow's milk. Cow's milk allergy (CMA) is the most commonly reported childhood food allergy, even though community-based incidence and prevalence estimates vary widely, due to possible misinterpretations of presumed reactions to cow's milk and to differences in diagnostic criteria [2]. In children up to age 2 years of age from the EuroPrevall birth cohort (nine European countries), 0.54% had confirmed CMA, proven by Double-Blind Placebo-Controlled Food Challenge (DBPCFC) to milk, with variations from 1% in the Netherlands and the United Kingdom (UK) to less than 0.3% in Lithuania, Germany, and Greece [3]. CMA has multiple clinical manifestations; its management requires

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elimination of cow's milk protein (CMP)-containing products. This elimination diet may, among other factors, have a negative impact on the nutritional status of affected children. The purpose of this paper is to describe the different clinical situations and their impact on the nutritional status, the available substitution products, and the main points to consider for following an appropriate CMP elimination diet.

2. The nutritional risk in CMA

Scientific bodies increasingly highlight the importance of the assessment of physical growth in children with CMA [4–6].

2.1. Height and weight patterns of children with CMA

The growth deficit in children with proven CMA was identified in the early 1990s [4]. Growth may be affected by CMA before its recognition and treatment, and also during the elimination diet. In a Finnish nested case-control study, children on a milk elimination diet for at least 1 year had slower growth than healthy controls, with no catch-up growth by the age of 5 years [7]. Among Norwegian infants having followed a CMP-free diet for a median of 17 weeks, 10.5% had a weight z-score below -2.0 (Norwegian reference) and the same proportion had a Body Mass Index (BMI) z-score below -2.0 [8]. Finnish children with food allergy (FA) avoiding cow's milk alone or cow's milk and wheat were smaller, albeit not significantly, than their peers [9]. In the American National Health and Nutrition Examination Survey (NHANES), involving 6189 children aged 2–17 years, mean weight, height, and BMI percentiles were significantly lower in those with CMA [10]. Also in a large observational study conducted in the United States, children avoiding any form of cow's milk were smaller and lighter than healthy controls [11]. In 91 Italian children younger than 3 years with FA, 80 having CMA, 23% had a weight-for-length (WFL) z-score ≤ 2 versus 3% in healthy-matched children [12]; they also had significantly lower weight-for-age (WFA), length-for-age (LFA), and head circumference-for-age (HCA) z-scores. In Brazilian infants with a high suspicion of CMA, 16.5% were underweight, 27.8% stunted, and 13.9% wasted [13]. The impact of CMA on growth can also be seen in studies where the effect of CMA-adapted formula feeding was assessed [14]. Before starting feeding with an adapted formula, Italian infants with CMA had lower WFA z-scores than healthy controls [15]. In a large Dutch cohort of 119 children with CMA, 22.1% were underweight, 31.7% stunted, and 3.0% wasted [14]. In addition, between birth and enrollment at the age of $4.2 (\pm 1.4)$ months, the mean WFA z-score (based on WHO standards) significantly decreased from $0.3 (\pm 1.1)$ to $-1.2 (\pm 1.2)$ [14]. Similarly, in 30 infants with CMA, mean WFA and LFA z-scores significantly decreased by $0.7 (\pm 1.0)$ and $0.6 (\pm 1.1)$, respectively, between birth and recruitment at a mean age of $4.8 (\pm 3.0)$ months [16]. Among the risk factors associated with poor growth (Table 1), the early onset of symptoms, before 6 months, might prevent the parents from increasing the amount of solid foods

in the diet [17]. The frequent delay in CMA diagnosis increases the risk for undernutrition [18]. Improper food substitutions, such as the use of an extensively hydrolyzed protein-based formula (eHF) in an eHF-intolerant child results in continued low-grade antigen challenge and inflammation, a situation probably more frequent in children with multiple FAs [17,19]. As the number of weeks on a CMP-free diet was positively correlated with nutritional status [8], poor growth in CMA children could be due to persistent intestinal inflammation through reduction of nutrient absorption and/or increased requirements [20]. Despite nutrient intakes equivalent to those of the control population, French children with at least one FA, including CMA, still had growth retardation [21]. In children with CMA in the NHANE Survey, growth measurements remained low after adjustment for energy and nutrient intakes [10], and weight and BMI percentiles were lower than in healthy children who were not drinking milk.

2.2. Height and weight patterns of children with multiple FAs

Several studies suggested an increased deleterious effect on growth as the number of FAs increased. In the United States, allergy to two or more foods resulted in a lower HFA percentile than allergy to one food in 1-month- to 10-year-old children [22]. In 245 children aged 4.1 ± 2.9 years with real or perceived FA (peanut, hen's egg, then cow's milk), allergy to more than two foods was associated with lower weight and height percentiles than allergy to one or two foods [23]. In the UK, children with FAs aged 27 (0.5–149) months, the elimination of three or more foods was associated with a lower WFA z-score [24]. In Korean children with atopic dermatitis (AD), a higher number of FAs had a negative effect on growth [25]. In French children aged 4.7 ± 2.6 years with at least one FA (peanut, eggs then cow's milk) [21], allergy to three or more foods resulted in WFA and HFA z-scores ≤ 2 more frequently (14.5 and 12.1%) than in those with allergy to one or two foods (1.8 and 3.6%). These high figures in tertiary reference centers might relate to the more severe atopic population, since no effect was seen on height or weight in children avoiding more than one food in a general pediatric population [11].

2.3. Height and weight patterns of children with CMA compared to other FAs

CMA might be deleterious in itself. Weight and height deficits observed in children with CMA were not observed for other food allergies [11]. In the American cohort of children with real or perceived FA [23], cow's milk avoidance resulted in lower weight percentiles than avoidance of other foods. In the NHANE survey, mean weight, height, and BMI percentiles were lower in children with CMA but not in children with other FAs [10]. Recently, decelerated growth within the 1st year on the diet in children eliminating cow's milk was not observed in children eliminating wheat, barley, or rye [7]. In Japan, anthropometric indices were assessed at school age (7–15 years) in 11,473 children, among whom 3.6% had avoided food in the past due to allergic symptoms

Table 1
Risks factors associated with impaired growth in children with food allergy (issued from [18]).

(i)	Delayed diagnosis
(ii)	Onset of disease at an early age
(iii)	Multiple food allergies
(iv)	Active disease
(v)	Persistent (subclinical) inflammation of the gut resulting in increased requirements and/or losses and poor utilization of nutrients
(vi)	Inadequate food intake due to poor appetite, regulation of gastrointestinal symptoms by modifying diet
(vii)	Elimination of staple, nutritionally central foods from diet (milk, cereals)
(ix)	Poor compliance in dietary management (unwillingness to broaden diet variety)
(x)	Extreme self-restriction of foods

[26]. In those with a persistent allergy at 3 years, avoidance of cow's milk, but not avoidance of wheat and eggs, resulted in a lower HFA z-score.

2.4. Nutritional risk in CMA according to the clinical pattern

The nutritional risk may vary according to the type of clinical manifestations of FAs. Co-morbid disorders such as AD and feeding difficulties may adversely impact nutrient intakes [27,28]. AD increases skin turnover and metabolic requirements, in relation with the disease extent and protein exudation [29–31], as well as agitation and sleep disturbances [32]. AD is characterized by periods of flares and remission, and multiple foods may be unnecessarily eliminated by caregivers when complementary feeding has started and the offending allergen not yet clearly determined [28]. The association between feeding problems and reduced growth is not consistent across studies. In Norwegian infants with CMA, the occurrence of food refusal was associated with lower weight and BMI z-scores [8]. In a UK tertiary referral center, 30–40% of children with digestive manifestations of FA and eliminating at least cow's milk had feeding difficulties, with faltering growth being more frequent in those with feeding problems (67.6% vs 45.8%) [33]. In contrast, in another study, young children eliminating cow's milk had more feeding difficulties and fussy eating than those on an unrestricted diet, but feeding problems were not correlated with growth [34]. Infants with milk or soy food protein-induced enterocolitis syndrome (FPIES) might have a greater risk of developing FPIES to solid foods (rice and other grains, poultry or legumes) [35]. The occurrence of milk and/or soy FPIES before complementary feeding may thus lead to a delayed introduction of these solids, further limiting the diet [36]. During eosinophilic esophagitis (EoE), poor dietary intake related to chronic emesis, feeding difficulties, food refusal, abdominal pain, poor appetite, or other maladaptive feeding behaviors could induce a higher risk for nutritional deficiencies [37]. Milk, eggs, wheat, and soy, the most commonly implicated foods in EoE, are often eliminated in the initial dietary therapy, further increasing the risk for nutrient deficiencies and feeding difficulties [37,38]. Iron-deficiency anemia (IDA) can appear during CMA, associated with overt or unapparent mucosal bleeding, inflammation, or malabsorption. The incidence of IDA in children with CMA are similar to the incidence of IDA in the general population of infants and children reported in resource-rich countries, so that iron should only be administered for repletion, based on measurements of iron deficiency such as reduced hemoglobin, red blood cell indices, or ferritin level [39].

2.5. Bone health in children with CMA

Small cohorts of prepubertal children and young adults documented the potential deleterious effect of CMA on bone mineral density (BMD) [40,41]. Lumbar spine BMD z-scores of 52 children with CMA aged 6.9 ± 1.9 years were lower than in healthy controls [40]. Only 39% of children with CMA had calcium intakes above the American Recommended Daily Allowance (RDA) vs 74% for controls ($P = 0.003$) and > 20% of children with CMA had a calcium intake below two-thirds of the RDA. In another cohort, the mean z-scores of BMD in hip, femoral neck, and lumbar spine of young adults aged 19.7 ± 3.1 years with IgE-mediated CMA were reduced compared to healthy controls [41]. Intake of calcium was severely reduced in CMA patients compared to controls, 335 ± 159 vs 768 ± 340 mg/day, and a significant correlation was found between calcium intakes and BMD. Patients who outgrew CMA had BMD z-scores higher than CMA patients, with BMD normal values in 66.7% vs 12.1%; subjects with outgrown CMA significantly consumed more proteins and calcium. There is a risk of increased bone resorption in

prepubertal children with CMA on a dairy-free diet for at least 1 year: an increase in receptor activator of nuclear factor κ B ligand (RANKL) level and a decrease in the osteoprotegerin/RANKL ratio suggested accelerated bone resorption [42]. A similar risk was shown in patients with EoE [43]. In children aged 2–18 years, national food consumption surveys showed that milk and other dairy products contribute to 45 and 47% of the total daily intake of calcium in the United States and Australia, respectively, and to 49% in French children aged 3–17 years [44]. Low calcium intakes are thus expected in patients with CMA following an elimination diet [7,10,12,22,45]. Human milk and infant formulas contribute more than 90% of total daily calcium intake in infants below 6 months, and to about 60% in 6- to 12-month-old children according to a US survey [46]. Children with CMA were at risk of consuming less than the recommended amount of calcium, 15 of 26 vs 12 of 39 in controls ($P < 0.05$), but 91% (10/11) of them met their dietary reference intakes (DRIs) for calcium and vitamin D when fed an adapted infant/toddler formula or a calcium-fortified soy beverage [22]. Calcium intake thus highly contributes to bone health in children with CMA, for whom mechanisms of deficient BMD are poorly understood. Low calcium intake has been associated with decreased bone remodeling, i.e., decreased bone formation, rather than with increased bone resorption [47]. In children with CMA, decreased intakes of energy and nutrients such as proteins, potassium, and zinc [12,45] might jeopardize the acquisition of the peak bone mass, thereby impacting bone health.

3. Formulas adapted to feeding children with CMA

Children with CMA need appropriate feeding with replacement formulas that must be tolerated, lead to remission of allergic symptoms, and allow proper and even catch-up growth.

3.1. Classification of formulas adapted to CMA

Breast milk is best for all infants, including those with CMA. If the child is diagnosed with CMA when breastfed, the mother should remove milk and dairy products from her own diet, and be advised on how to keep a balanced diet comprising calcium and vitamin D supplements [4,48]. For non-breastfed babies, three main categories of formulas are available (Tables 2–4): eHFs based on caseins (eHCF) or whey proteins (eHWF), amino acid-based formulas (AAFs) and non-cow's milk-based formulas based on soy or rice proteins. In eHFs, the CMP have been hydrolyzed into smaller segments less likely to cause an allergic reaction. Formulas based on soy proteins are not recommended as first-line treatment in infants younger than 6 months [49] because of an increased risk that children with CMA also react to soy proteins, ranging from 10% [50] to 14% [51] vs 0–0.5% for the general population [52], and of the unclear effects of phytoestrogens on hormonal balance [53]. Vegetable drinks based on soy, rice, almond or sweet chestnut, sometimes called vegetable milks, are not nutritionally suited to the exclusive or partial feeding of infants [54,55] and should be considered as complementary foods in an otherwise well-balanced diet. They may help in older children with persistent CMA under precise dietary surveillance. Children with CMA are at high risk of reacting to other mammalian milks [56,57], so goat's or ewe's milk-based formulas or products may be used only after testing on an individual basis.

3.2. Hypoallergenicity of formulas adapted to CMA

The American Academy of Pediatrics (AAP) defined a formula as hypoallergenic if it ensures with 95% confidence that 90% of infants with confirmed CMA will not react with defined symptoms under double-blind, placebo-controlled conditions [58]. In non-breastfed infants with CMA, eHFs are usually the first option. In infants

Table 2

Nutritional compositions of extensively hydrolyzed cow's milk proteins-based formulas adapted for the nutritional management of CMA.

	Energy, for 100 ml		Proteins (g)		Lipids (g)		Carbohydrates (g)	
	kcal	kJ	For 100 kcal	For 100 ml	For 100 kcal	For 100 ml	For 100 kcal	For 100 ml
Allernova (Novalac)	66	278	2.3	1.6	5.3	3.5	10.8	7.2
Allernova AR (Novalac)	67	280	2.4	1.6	5.3	3.5	10.6	7.1
Althéra (Nestlé)	67	280	2.5	1.7	5.1	3.4	11	7.3
APLV 1 (Nutribën)	67	279	2.4	1.6	5.2	3.5	10.7	7.2
APLV 2 (Nutribën)	68	287	2.5	1.7	4.1	2.8	12.9	8.8
Pepticate 1 (Nutricia Nutrition Clinique)	67	280	2.4	1.6	5.2	3.5	10.4	7.0
Pepticate 2 (Nutricia Nutrition Clinique)	68	285	2.4	1.6	4.6	3.1	11.9	8.1
Nutramigen 1 LGG (Mead Johnson Nutrition)	68	280	2.8	1.9	5.0	3.4	11.0	7.5
Nutramigen 2 LGG (Mead Johnson Nutrition)	68	280	2.5	1.7	4.1	2.8	12.9	8.8
Nutramigen 3 LGG (Mead Johnson Nutrition)	68	280	2.28	1.55	5.0	3.4	11.32	7.7
Pepti Junior 1 (Picot)	70	291	2.7	1.9	5.3	3.7	10.3	7.2
Pepti Junior 2 (Picot)	70	291	2.7	1.9	5.3	3.7	10.3	7.2
Pepti Junior 3 (Picot)	69	288	2.8	1.9	5.2	3.6	10.4	7.2
Pregestimil (Mead Johnson Nutrition)	66	280	2.9	1.9	5.8	3.8	10.1	6.9
Pregestimil liquide (Mead Johnson Nutrition)	81	340	2.8	2.3	5.6	4.5	10.2	8.3

Table 3

Nutritional compositions of amino-acids based formulas adapted for the nutritional management of CMA.

	Energy, for 100 ml		Protein equivalent (g)		Lipids (g)		Carbohydrates (g)	
	kcal	kJ	For 100 kcal	For 100 ml	For 100 kcal	For 100 ml	For 100 kcal	For 100 ml
AminA (Novalac)	72	301	2.6	1.9	4.5	3.2	11.8	8.5
Neocate (Nutricia Nutrition Clinique)	67	279	2.7	1.8	5.1	3.4	10.7	7.2
Neocate Advance, neutre et banane vanille (Nutricia Nutrition Clinique)	100	420	2.5	2.5	3.5	3.5	14.6	14.6
Neocate Active (Nutricia Nutrition Clinique)	100	418	2.8	2.8	4.8	4.8	11.0	11.0
Neocate Spoon (Nutricia Nutrition Clinique)								
Puramino (Mead Johnson Nutrition)	68	290	2.8	1.9	5.3	3.6	10.3	7.0

Table 4

Nutritional compositions of hydrolyzed rice proteins-based formulas adapted for the nutritional management of CMA.

	Energy, for 100 ml		Proteins (g)		Lipids (g)		Carbohydrates (g)	
	kcal	kJ	For 100 kcal	For 100 ml	For 100 kcal	For 100 ml	For 100 kcal	For 100 ml
Modilac Riz 1 (Sodilac)	68	284	2.4	1.6	5.0	3.4	11.2	7.6
Modilac Riz 2 (Sodilac)	68	286	2.9	2.0	4.6	3.1	11.9	8.1
Modilac Riz AR 1 (Sodilac)	68	285	2.4	1.6	5.0	3.4	11.2	7.6
Modilac Riz AR 2 (Sodilac)	67	280	2.9	1.9	4.5	3.0	11.8	7.9
Modilac Riz Croissance (Sodilac)	68	285	2.5	1.7	4.6	3.1	12.4	8.4
Novalac Riz (Novalac)	69	290	2.6	1.8	5.0	3.4	11.0	7.6

reacting to eHFs, other options are available, among which the use of AAFs [4]. Over the past 15 years, the eHCF Nutramigen® (Mead Johnson Nutrition) has been tested in 92 children with CMA in three studies: its tolerance ranged from 64.6% (31/48) [59] to 93.8% (15/16) [60] and 96.4% (27/28) [61]. More recently, the same eHCF supplemented with *Lactobacillus rhamnosus* GG (Nutramigen LGG®) was tolerated by 31 children with confirmed CMA [62]. The eHWF Nutrilon-Pepti® (Nutricia) was tolerated by 30 out of 31 children with CMA [63]. Another eHCF (Allernova®, Novalac) was tolerated by the 30 children tested with IgE-mediated CMA [61]. Recently, the same eHCF, thickened or not, proved to conform to the criteria of the AAP in three clinical trials totaling 186 infants with challenge-proven CMA [14,16,64]. Only two rice hydrolysate-based formulas have recently been tested in infants with CMA (Blemil Arroz®, Ordesa Group and NovaRice®, Novalac), with evidence of their hypoallergenicity [65,66]. Recent trials conducted on AAFs are more numerous. The AAF Sineall® (Humana) was tolerated by all 29 and 31 subjects with IgE- and

non-IgE-mediated CMA, respectively [67]. Another AAF, Alfamino® (Nestlé Health Science), met the AAP criteria in 33 subjects with CMA [68], as well as the AAF Neocate® (Nutricia) enriched with a symbiotic (oligofructose, long-chain inulin, acidic oligosaccharides, *Bifidobacterium breve* M-16 V) [69]. The new AAF Aminova® (Novalac), containing a pectin-based complex, was compared to Neocate® (Nutricia) as a control AAF in 75 subjects for whom AAFs were recommended, i.e., infants with CMA and allergy to eHFs [70,71]. Its tolerance reached 100% of subjects. Compared to Neocate®, Aminova® significantly improved stool consistency and decreased the SCORing Atopic Dermatitis index after 3 months, suggesting a role for the thickening agent.

3.3. Nutritional adequacy of cow's milk-based eHFs

In case of CMA, CMP-based eHFs constitute 100% of the nutrient source in the first 4–6 months of life and half of the daily nutrient intake up to 12 months [72], so that their nutritional adequacy

should also be tested in the appropriate population, where the disease may largely impact growth [4,72]. However, most published growth data in children fed these formulas were obtained in term infants who were either healthy [73–75] or only at risk of atopy [76]. Comparison of the eHWF Althera® (Nestlé) to the eHCF Nutramigen® (Mead Johnson Nutrition) in children with CMA did not detect any differences in weight, length, head circumference, and BMI z-scores during the 1st month [77]. A post-hoc analysis was made on a trial whose primary aim was the evaluation of probiotics supplementation to the eHCF Allernova® (Novalac) on cow's milk tolerance acquisition [14,78]. The population of 119 infants, the largest number of children with CMA included in a trial to date, after 6 months showed a significant improvement in WFA, LFA, and WFL z-scores, a BMI restored to normal and decreased percentages of children with WFA and LFA z-scores ≤ 2 . The same eHCF (Allernova®) was tested as a pre-thickened version in 37 infants with CMA: the WFA z-score improved from the 1st month of feeding and increased from $-0.7 (\pm 1.4)$ at baseline to $0.6 (\pm 0.8)$ after 6 months ($P < 0.001$) [64]. Anthropometric indices were similar between the thickened and non-thickened versions of the formula. In 30 patients with CMA aged 4.8 ± 3.0 months at inclusion, 4-month feeding with the same pre-thickened eHCF induced a significant increase of all anthropometric indices [16].

3.4. Nutritional adequacy of hydrolyzed rice protein-based formulas

Healthy infants exclusively fed a hydrolyzed rice protein-based formula (HRF) over the first few months of life had growth comparable to the WHO standards [79]. WFA, LFA and WFL z-scores were similar in infants with CMA aged 4.3 months on average at baseline and fed either a CMP-based eHF or an HRF (Bleimil Arroz®, Ordesa Group, S.L.) [65]. From the 1st month of feeding, 36 infants with CMA fed an HRF (NovaRice®, Novalac) for at least 6 months showed increased WFA, WFL, and BMI z-scores, with complete catch-up growth based on the WHO standards by the end of the study period [66].

3.5. Nutritional adequacy of AAFs

Among other indications, AAFs are the first-line dietary treatment in children with FA and severe growth faltering [2,48,80–82]. The nutritional adequacy of some AAFs has recently been tested in nonallergic children [69,83]. In children with CMA, 4-month feeding with an AAF with symbiotic (Neocate® Syneo™) or not (Neocate®, Nutricia) induced adequate catch-up growth [84]. The new thickened AAF Aminova® (Novalac) was tested as previously explained in children with CMA and failing to respond to eHFs [70,71]. The WFA z-score increased from the 1st month of feeding, and catch-up growth was confirmed after 6 months of feeding. Similar catch-up growth was observed after a 12-week feeding period with the AAF Nutramigen AA® (Mead Johnson Nutrition) in 30 infants with CMA suspected prior to study inclusion because of weight loss and unsuccessful feeding with an eHF [85] but not proven by milk challenge (23.3% had IgE-positive testing). A nutritional intervention with the AAF Neocate® (Nutricia) or the eHWF Hypolac® (DMF srl) was equally effective in normalizing WFA z-scores after 12 months of feeding in 21 and 19 infants, respectively, with isolated CMA proven by a DBPCFC [15].

4. Dietary counseling during CMA

4.1. The use of formulas according to clinical patterns

In 2010, the World Allergy Organization's Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA)

published recommendations on formulae to use depending on the CMA disorder [2]. These recommendations are not all evidence-based [86]. A French series of milk-related FPIES suggested the need for an AAF in half of the cases [87]. Dietary treatment of EoE is based on either AAF feeding for complete removal of food allergens, on the so-called six-food elimination diet, on a diet oriented by allergy testing or a combination of the last two [38]. CMPs are the main food antigens in EoE, and a retrospective study showed that eliminating only CMP from the diet in 17 children with EoE induced remission in 11, with histological remission complete in seven and partial in four [88]. More recently, nine out of 14 children treated with a single elimination of cow's milk had a decrease of the peak esophageal eosinophil counts below 15 eosinophils/high power field, an observation made in a similar proportion of children treated with swallowed fluticasone [89].

4.2. The use of baked milk

As generally accepted, infants with proven CMA should remain on a cow's milk-free diet until 9–12 months of age and for at least 6 months before attempting to reintroduce it [80]. High temperature largely destroys conformational epitopes to which IgE are primarily directed, the majority (68/91) of children with CMA tolerating products containing extensively heated (baked $> 170^\circ\text{C}$) milk [90]. Casein- and milk sIgE levels, milk-specific basophil reactivity, and milk skin prick tests' (SPT) wheal diameter were all significantly greater among patients with CMA who reacted to baked milk than those who tolerated it [91]. In milk proteins transformed by baking, gel electrophoresis strongly stained casein bands that persisted for up to 60 min of heating [92]. In contrast, β -lactoglobulin and α -lactalbumin bands became progressively weaker with increasing heating times, with no detectable β -lactoglobulin after 15–20 min of heating. All heated milk-reactive children possessed IgE binding to the casein fraction regardless of heating time. Presence of wheat during heating decreased IgE binding to milk proteins, suggesting a role for the matrix in the tolerance of baked milk. Practical issues have been reviewed, such as the duration and temperature of baking, the setting of baked milk introduction, whether at home or medically supervised [93]. Anaphylaxis and epinephrine use during baked milk challenges have been reported. Potential biomarkers are not available in routine use. Thus, when parents cannot reliably report that their child is already consuming foods with baked milk, the most prudent approach is to perform a supervised oral food challenge to determine its tolerability [93]. Also, heating goat's and ewe's milk might not decrease their immunogenicity [94].

4.3. The nutritional adequacy of the diet

Among measures to be taken in children with CMA, dietary counseling therefore becomes, as for other FAs, one of the most prominent recommendations. Nutrition counseling proved to significantly improve nutrient intakes. Among children with FAs, the number of children meeting 67% of the Dietary Reference Intake for calcium and vitamin D was higher in families with nutrition counseling [22]. In Italy, the latter restored the total energy intake of 85 children with FA to values of control children and improved anthropometric and laboratory biomarkers of nutritional status [12]. The extent of the food elimination diet had no impact on growth or nutritional status of children with FA, when the diet was adequately supplemented [9]. Infants and young children benefit from the suitable replacement formulas described above, whereas alternative nutrient sources may not always be available in older children. In 131 children aged 23.3 (9.4–69.2) months, with 94.8% of them following a cow's milk

elimination diet and counseled by dieticians for 4 weeks to diagnose non-IgE-mediated gastrointestinal FAs, WFA and WFL z-scores improved, and a hypoallergenic formula positively impacted WFA z-scores [95]. In the largest American retrospective study, cow's milk avoidance was deleterious on weight and height only in children aged 2–5 years, suggesting that parents may not substitute cow's milk as well as between 0 and 2 years [11]. Since solids become a larger portion of the diet in older children, parents/caregivers may not feel milk substitution is important. Also, the elimination of typical snack foods, frequently consumed by preschoolers and mostly containing cow's milk, leads to lower energy, as well as lower protein and other nutrient intakes [96]. The changes in the impact of CMA over time were monitored by using the Food hypersensitivity famILy ImPact (FLIP) questionnaire [97]: even after tolerance to cow's milk occurred, families revealed continuing nutritional concerns. Adhering to a CMP-elimination diet during infancy has persistent and long-term effects on eating habits (such as a higher avoidance behavior) and food preferences (lower liking for dairy foods) [98]. The vitamin D status was significantly lower in Finnish schoolchildren with a history of CMA, indicating that restricting the diet may have long-term consequences on dietary habits and subsequently on later vitamin D status [99]. Follow-ups should be offered even after the child has outgrown CMA to encourage progression to unrestricted diet and to prevent eating disorders.

4.4. The prevention of bone metabolism disorders

A subset of children with CMA, with a BMD approximately 0.7 SD lower than that of healthy peers, should undergo an assessment of bone quality. Based on available evidence, risk factors for decreased BMD include multiple FAs, the patient's age, the lack of compliance to the diet, comorbidities (severe asthma), therapies affecting bone health (steroids), signs of rickets, and/or evidence of severe vitamin D deficiency [100]. Monitoring should be based on basal, then annual, assessment of calcium, protein, and energy intakes; the evaluation of growth and dental health; and levels of weight-bearing physical activity and sun exposure. In high-risk CMA children, monitoring should be extended to the assessment of the bone profile and BMD and assessment levels of calcium, phosphate, alkaline phosphatase, 25(OH)D, and parathyroid hormone in serum, and calcium and creatinine in urine [100]. According to international guidelines, BMD is measured by dual x-ray-absorptiometry at the lumbar spine and total body except the head [101]. Reference values exist only for children older than 5 years. The work-up aims at adjusting nutritional and environmental factors to optimize bone growth and peak bone mass acquisition, ensuring adequate vitamin D status until adolescence, appropriate calcium intake for age, and sufficient physical activity [47]. Mean vitamin D intake was estimated in prepubertal allergic children in Quebec, with and without CMA, to 300 and 345 IU/day. Both groups had similar vitamin D supplementation and 25(OH)D serum levels (70.1 nmol/L vs 75.1 nmol/L) but vitamin D deficiency (defined as a level < 30 nmol/L) occurred in three out of 43 children (7%) with CMA vs none in children without CMA [40]. In the NHANE Survey, children with CMA aged 2–17 years showed a trend toward lower mean vitamin D daily intake, 212.2 IU compared with 308.4 IU in children without CMA, [10]. In some countries, e.g., the United States, dairy products are fortified with vitamin D, so they highly contribute to daily vitamin D intake. Conversely, in France, dietary vitamin D in children is mainly provided by fish, eggs, as well as poultry, meats, followed by dairy products [44]. Therefore, in most children with CMA, vitamin D supplementation should be implemented following the recommendations [102]. In those at higher risk of low BMD and fractures, as defined above, vitamin D

intake should be adjusted based on yearly measurement of 25(OH)D serum. Most of the calcium intake originates from dairy products, which also provide other key nutrients crucial for bone health such as proteins and phosphate [40]. No interventional studies measured the effect of calcium supplementation on bone mineralization in children with CMA, but restoring the RDA in calcium, at best with dietary sources, can be safely recommended. In adolescents, dietary calcium is more beneficial than calcium supplements on BMD [103,104]. Many patients may not reach their RDA in calcium despite supplements of this nutrient or nutritional counseling [105].

5. CNSFP recommendations

Guidelines are lacking for bone health management in children with CMA. The following recommendations of the Comité de nutrition de la Société Française de Pédiatrie (CNSFP) arise from the analysis of the literature and the authors' clinical expertise:

- food allergy, and more specifically CMA, can manifest with several types of digestive, cutaneous, and respiratory symptoms, some appearing in the form of syndromes, since risks and handling differ greatly depending on the syndromes. Early diagnosis and, in case of proven CMA, a timely elimination diet are needed to avoid growth retardation;
- even though the adapted formulas available in most industrialized countries are generally tolerated by a majority of infants with CMA, their efficacy has not always been proven by a clinical trial. In our last commentary in 2012, we regretted the absence of safety and nutritional efficacy information for most of the products available. Although this situation has improved slightly, with more studies focusing on allergic populations, proper growth has still not been shown for many formulas. A formula with proven safety and suitability in children with CMA should therefore be favored;
- once solid foods are introduced, parents should be carefully and regularly advised on how to adequately replace dairy products and be aware that diversification should not be restricted except in cases of other proven food allergies. Likewise, parents still need dietary advice when CMA is outgrown;
- baked milk largely helps feeding children with long-lasting CMA, but the appropriateness and timing of its introduction should be individually and carefully assessed by physicians. An appropriate challenge under medical supervision is needed to test the tolerance of baked milk in children from 1 year of age;
- all children with CMA should have an assessment of their calcium and vitamin D intakes and receive counseling to reach RDA for these nutrients;
- counseling to caregivers and families should include the importance of calcium intake, sources of dietary calcium, and the expected objectives and timeline;
- the assessment of bone metabolism (BMD and metabolic bone profile) is advised only in a small subset of CMA patients with suspected bone fragility. This includes fracture(s); rickets; CMA associated with another chronic disease or multiple FAs; the association of low calcium intake, low vitamin D intake, low energy intake, period of rapid growth, and persisting CMA such as during EoE.

Disclosure of interest

Dupont C: Scientific Advisory Board, Nestlé, Nutricia; Clinical Trials, Novalac.
Chouraqui JP: Lectures, Mead-Johnson, Nestlé.

Bocquet A: Clinical Trials, Nestlé, Novalac; Lectures Blédina, Nestlé, Novalac, Sodilac.

Darmaun D: Lectures, Danone, Nestlé.

Feillet F: Scientific Advisory Board, Nutricia, Vitaflo; Lectures, Nutricia, Vitaflo.

Simeoni U: Scientific Advisory Board, Sodilac; Lectures, Danone, Nestlé.

Linglart A, Frelut ML, Girardet JP, Hankard R, Rozé JC and Briend A declare that they have no competing interest.

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