



# World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines update - XVI - Nutritional management of cow's milk allergy

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## ABSTRACT

Cow's milk allergy (CMA) is one of the most common presentations of food allergy in early childhood. Management of CMA involves individualized avoidance of cow's milk and other mammalian milk and foods containing these. Optimal elimination of cow's milk avoidance includes: label reading; information about safe and nutritious substitute foods; appropriate choice of infant formula or a plant-based food; establishing tolerance to baked milk and monitoring nutritional intake and growth. Substitute formulas are divided into soy formula (not hydrolyzed), milk-based extensively hydrolyzed formulas, rice based extensive, and partially hydrolyzed formulas and amino acid-based formulas. The use of other mammalian milks is not recommended for the management of cow's milk allergy due to a high level of cross-reactivity and nutritional concerns. For toddlers who are eating well, children, and adults, a suitable plant-based beverage may be a suitable alternative to a specialized formula, following careful nutritional considerations. Families need to be instructed on finding suitable nutritious foods and how to prepare suitable meals at home. Individuals with CMA also need to know how to identify and treat acute severe reactions.

**Keywords:** Cow's milk allergy, Nutrition, Baked milk, Hypoallergenic formulas, Plant based alternatives

## INTRODUCTION

Cow's milk allergy (CMA)<sup>1</sup> is one of the most common presentations of allergy in early childhood.<sup>2</sup> It is estimated that CMA affects 2% of infants and 4.5% of children.<sup>3</sup> Consumption of cow's milk and foods that contain cow's milk have increased rapidly in the developed and developing

world in recent years with the highest level of consumption in Europe, followed by Oceania, the United States, Asia, and Africa.<sup>4</sup> Cow's milk contains a range of proteins of which 80% are casein proteins and 20% whey proteins. Caseins (Bos d8) are the major cows' milk allergens, and include 4 isoforms: a-S1-casein (Bos d9), a-S2-casein (Bos d10), b-casein (Bos d11), and k-casein.

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Whey proteins consist of a-lactalbumin (Bos d4), b-lactoglobulin (Bos d5), immunoglobulins (Bos d7), bovine serum albumin (BSA, Bos d6), and traces of lactoferrin.<sup>5</sup>

CMA can present as IgE and non-IgE mediated forms of food allergy (Table 1). Non-IgE mediated food allergies are further classified into food protein induced enterocolitis syndrome, food protein induced proctocolitis (confirmed through elimination and reintroduction and in some cases endoscopy), food protein induced enteropathy, and other forms of mild to moderate non-IgE mediated food allergies. Symptoms of IgE mediated food allergies typically presents within 2 h of consumption and symptoms may include the skin, gastro-intestinal track, and respiratory tract, or they

can be systemic. Non-IgE mediated food allergies have a longer temporal relationship and then involve mainly the gastro-intestinal track. It is, however, important to avoid overdiagnosis and only make a diagnosis of non-IgE mediated CMA after performing on a thorough clinical evaluation, including dietary history, symptomatology, and in some cases, endoscopic and histological findings.<sup>6-10</sup>

## MANAGEMENT OF COW'S MILK ALLERGY

Management of CMA includes avoidance of cow's milk and foods containing cow's milk proteins by following an individualized avoidance strategy.<sup>11,12</sup> Optimal management of CMA includes education, onlabel reading, information about safe and

Mechanism	IgE-mediated CMA	Non-IgE, cell mediated or mixed pathophysiology CMA
Symptoms	Skin: urticaria, angioedema; GI: throat swelling, crampy abdominal pain, immediate emesis, diarrhea; Respiratory: rhinorrhea, sneezing, laryngospasm, cough, bronchospasm; CV: tachycardia, low blood pressure; Generalized: anaphylaxis	<b>Chronic:</b> Skin: eczematous skin rash; GI: nausea, emesis, reflux, abdominal pain, diarrhea, malabsorption, rectal bleeding Generalized: poor weight gain, failure to thrive, stunting <b>Acute-FPIES:</b> GI: projectile emesis, abdominal pain, diarrhea; CV: tachycardia, hypotension, hypovolemic/distributive shock; Generalized: pallor, lethargy
Onset of symptoms following food ingestion	Within minutes to 2 h	Generally within hours to days; exception acute FPIES-onset of emesis within 2-4 h
Diagnosis	Detection of food-sIgE by skin prick test and serologic tests, oral food challenge	Recognition of symptoms, response to diagnostic elimination diet (2-4 weeks); FPIES-meeting the diagnostic criteria
Management -acute symptoms	Antihistamines, epinephrine, inhaled bronchodilator, oxygen, intravenous fluids	FPIES: rehydration (oral or intravenous), ondansetron (oral or parenteral), single dose of a steroid for severe symptoms
Management-dietary	Dietary food avoidance, majority tolerate cow's milk in the form of baked foods	Dietary food avoidance; a subset of patients might tolerate cow's milk in the form of baked foods
Natural history	Favorable, generally outgrown before school age; children reacting to baked milk or with peak cow's milk-sIgE >50 kUa/L tend to have a more prolonged course	Favorable, usually outgrown by age 1-3 years

**Table 1.** Different presentations of cow's milk allergy

nutritious substitute foods, appropriate choice of infant formula or a plant-based food, establishing tolerance to baked milk, and monitoring nutritional intake and growth. Individuals with CMA also need to know how to identify and treat acute severe reactions.

### Foods containing cow's milk

Milk is often consumed as a beverage, but it is important to realize that cow's milk proteins can be found throughout the food supply. *Foods Commonly Containing Cow's Milk/Cow's Milk Protein listed in Table 1.*

### Label reading

Food labelling guidance, regulations, and laws differ world-wide and health care professionals should at a minimum give information regarding national labelling laws when educating families. The success of safely avoiding food allergens also depends on the availability and implementation of strict food labelling laws in the country. Milk is considered a major allergen in most countries and is mandated to be fully disclosed on pre-packed food and in the United Kingdom and European Union only, in restaurant foods, foods pre-packed for direct sale, and not pre-packed. Milk should be listed on the ingredient list or in the CONTAINS statement, where CONTAINS statements are allowed (see Table 2). However, the majority of low- and middle-income countries are yet to introduce such regulatory laws despite the rising prevalence of food allergy, especially CMA.<sup>13</sup> See Table 3 for further information on labelling information in Europe/United Kingdom, Australia, United States, and Canada.<sup>13,14</sup>

Allowing or avoiding precautionary advisory labelling (PAL) is a crucial discussion to have during a food allergy consultation and may vary between IgE and non-IgE mediated allergies.<sup>15</sup> It is important that individuals understand that one cannot "risk stratify" based on the term used; for example, foods containing a "may contain" warning are not more likely to be contaminated with milk than foods carrying a warning, "produced in the same facility".<sup>16</sup> Other than in South Africa and Switzerland, PAL is voluntary and not regulated. PAL is however prohibited in Japan and Argentina. One of the most difficult discussions with patients

is to explain that the absence of PAL does not guarantee that a product is not contaminated. Many families get anxious with this knowledge. The likelihood of foods being contaminated with milk also differs between countries and products.<sup>17-19</sup> It is important to inform families that most larger manufacturers have PAL policies and consumers can check the manufacturer website for PAL policy information.

Practical tips on label reading include: 1) read the ingredient list and CONTAINS statement, where used, each and every time an item is purchased as ingredients may change, 2) do not rely on front-of-package information such as "vegan" or "milk free", as this is not covered by allergen regulation laws in most countries, and 3) allergen-free labelling may help guide consumers with food allergy toward safe products; however an allergen-free label does not negate the need for careful label reading as indicated above, as allergen-free labeling is not regulated.

### Level of avoidance required

It is important that each child and adult with food allergy understand to what extent they need to avoid milk. This may include allowing those with food protein-induced enterocolitis (FPIES) to consume products with PAL and making a clinical decision about allowing these products in those diagnosed with eosinophilic esophagitis.<sup>15,20</sup> Other individuals may need to avoid milk and its derivatives more strictly.<sup>21</sup> Some patients with IgE mediated cow's milk allergy may be able to tolerate small amounts of milk and as the clinical practice of oral immunotherapy increases, being able to quantify certain levels of cow's milk intake will become highly important.<sup>22,23</sup> The ability to calculate the milk protein content of food and explain these levels and food portions to patients with IgE mediated cow's milk allergy is a novel and highly interesting aspect of the role of the allergy specialist dietitian.<sup>22,24</sup>

### Baked milk

A high percentage of children with IgE-mediated milk allergy tolerate milk ingredients, when subjected to extensive heating, such as in the form of a baked-goods with a grain matrix.<sup>25</sup> In 2008, Nowak et al<sup>25</sup> reported on 100 children with



cow's milk allergy undergoing baked milk (BM) oral food challenges (OFC), and if negative, unheated liquid milk OFC. Sixty-eight participants were BM tolerant, 9 tolerated both baked and non-baked milk, and 23 reacted to BM. The majority of

children, who were clinically reactive to non-baked milk, tolerated baked forms. If tolerant to baked proteins, patients with CMA display higher reactivity thresholds than the general population of children allergic to milk.<sup>26</sup>

**Milk is a major allergen in most countries and therefore must be labeled using its common name "MILK" and should not be hidden in a vague ingredient term. Look for the word "MILK" in the ingredient list or in the CONTAINS statement, where used. Avoid products that contain MILK.**

- |   |  |
|---|--|
| <ul style="list-style-type: none"> <li>• Butter, butter fat, butter oil, butter acid, butter ester(s)</li> <li>• Buttermilk</li> <li>• Casein</li> <li>• Casein hydrolysate</li> <li>• Caseinates (in all forms)</li> <li>• Cheese</li> <li>• Cottage cheese</li> <li>• Cream</li> <li>• Curds</li> <li>• Custard</li> <li>• Diacetyl</li> <li>• Ghee</li> <li>• Half-and-half</li> <li>• Lactalbumin, lactalbumin phosphate</li> </ul> | <ul style="list-style-type: none"> <li>• Lactoferrin</li> <li>• Lactose</li> <li>• Lactulose</li> <li>• Milk (in all forms including condensed, derivative, dry, evaporated, goat's milk and milk from other animals, low-fat, malted, milkfat, non-fat, powder, protein, skimmed, solids, whole)</li> <li>• Milk protein hydrolysate</li> <li>• Pudding</li> <li>• Recaldent(R)</li> <li>• Rennet casein</li> <li>• Sour cream, sour cream solids</li> <li>• Sour milk solids</li> <li>• Tagatose</li> <li>• Whey (in all forms)</li> <li>• Whey protein hydrolysate</li> <li>• Yogurt</li> </ul> |
|---|--|

**Ingredients that MAY indicate the presence of milk protein (look for the word MILK in the ingredient list or in the CONTAINS statement, where used.)**

- Artificial butter flavor
- Baked goods
- Caramel candies
- Chocolate
- Lactic acid starter culture and other bacterial cultures
- Luncheon meat, hot dogs and sausages, which may use the milk protein casein as a binder. Also, deli meat slicers are often used for both meat and cheese products, leading to cross-contact.
- Margarine
- Non-dairy products, as many contain casein
- Nougat
- Shellfish is sometimes dipped in milk to reduce the fishy odor. Ask questions when buying shellfish.
- Tuna fish, as some brands contain casein
- Some specialty products made with milk substitutes (i.e., soy-, nut- or rice-based dairy products) are manufactured on equipment shared with milk.
- Many restaurants put butter on grilled steaks to add extra flavor. You can't see the butter after it melts.
- Some medications may contain cow's milk

**Table 2.** How to read a food label and foods to avoid

As cow’s milk is a common food allergen in young children,<sup>27</sup> and cow’s milk is a nutritionally important food and ubiquitous in the food supply, the impact of tolerance of BM ingredients is significant. Tolerating BM can result in greater dietary options, improved nutrition, and potentially decrease parental anxiety regarding accidental allergen ingestion.<sup>28</sup> Several small studies reported that regular consumption of BM might accelerate tolerance acquisition of non-baked milk, while others found no difference. A single-center, randomized clinical trial found no difference in tolerance acquisition to non-heated milk with more rapid escalation from lower dose

of more extensively BM to a higher dose, less extensively BM.<sup>29</sup> Further research is needed.

However, following a BM diet approach may result in more proactive management of cow’s milk allergy and leads to earlier introduction of non-baked milk compared to strict avoidance diet.<sup>30</sup>

For performing OFCs, many food allergy centers use a published baked muffin recipe containing 1.33 g milk protein in a wheat matrix that is baked in a 350 °F (±180 °C) oven for 30-35 min (Table 4). In addition to the application of extensive heat, the wheat/grain matrix may play a role in tolerance by

		US	EU	Canada	Aust/NZ
	Milk covered by mandated labelling laws	✓	✓	✓	✓
Labelling statements allowed	"Contains"	✓		✓	✓
	Allergen emphasized in ingredient list	✓	✓	✓	✓
Precautionary allergen labelling	Voluntary	✓	✓	✓	✓
	Regulated				
Type of food labeled	Prepacked	✓	✓	✓	✓
	Prepacked for direct sale		✓		
	Non-prepacked		✓ <sup>a</sup>		
Foods covered under allergen labelling laws	Over the counter or prescription drugs				
	Cosmetics and beauty products		✓		
	Restaurant foods		✓		
Exemptions	Milk (casein) products used as fining agents in cider and wines		✓		
	Whey used in distillates for spirits		✓		
	Lactitol		✓		

**Table 3.** Cow’s milk allergen labelling laws in the US, EU, Canada and Australia/New Zealand (Adapted from Durban et al.)<sup>b</sup> <sup>a</sup>Allergen information must be supplied to the consumer, but labelling is not required. <sup>b</sup>Durban R, Groetch M, Meyer R et al. Dietary Management of Food Allergy. *Immunol Allergy Clin North Am* 2021; 41(2):233-270. (In eng). <https://doi.org/10.1016/j.jiac.2021.01.009>.

## Baked Milk Recipe

Yield: 6 muffins

### Ingredients:

#### Dry Ingredients

1 1/4 cup (155g) of all-purpose flour (wheat)

1/2 cup (100g) sugar

1/4 tsp. (1.5g) salt

2 tsp. (10g) baking powder

#### Wet Ingredients

1 cup (240 mL) of Milk

2 Tbsp. (30 mL) vegetable oil (corn, soy, canola or other tolerated vegetable oil)

1 tsp. (5 mL) vanilla extract

1 Egg<sup>a</sup> (50g) **or** 1 1/2 tsp. (4g) powdered egg replacer if child is allergic to egg

<sup>a</sup>DO NOT use egg if allergic to egg

1. Preheat oven to 350° F (±180 °C). This step may take 30–45 min. Bake muffins only in an oven that is **completely preheated** to 350° F (±180 °C).
2. Line a muffin pan with 6 muffin liners.
3. Stir together the liquid ingredients until well combined: milk, canola oil, vanilla extract, egg or egg replacer (although the egg replacer is a dry ingredient, please add at this step). Set aside.
4. In a separate mixing bowl, mix together the dry ingredients (flour, sugar, salt, baking powder).
5. Add liquids ingredients to dry ingredients all at once and gently stir with a wooden spoon (about 15–20 light strokes) until wet and dry ingredients are just combined. Do not over-stir. Some small lumps may remain.
6. Divide the batter into the six prepared muffin liners.
7. Bake 30–35 min or until golden brown and firm to the touch. Cool completely before serving.

**Table 4.** Baked milk recipe<sup>a</sup>. <sup>a</sup>Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Wegrzyn A. Baked milk- and egg-containing diet in the management of milk and egg allergy. *J Allergy Clin Immunol Pract* 2015; 3:13–23; quiz 4.

reducing exposure of the proteins to the immune system in the gut although these interactions are poorly understood.<sup>31</sup> Miceli Sopo et al evaluated the impact of the wheat matrix and found that it may not be relevant for all BM tolerant patients.<sup>32</sup> The temperature and baking time is also not standardized in BM recipes; however, most clinical trials used temperatures ranging from 350 to 400 °F (±180–200 °C) and baking times between 20 and 35 min. This is an important point as leaving the middle/inside of baked food too moist will greatly increase its allergenicity.<sup>33</sup> Numerous recipes with slight variations in protein content, matrix volume, and baking times and temperatures

have been published.<sup>34</sup> The use of a standardized recipe provides the health care practitioner with information regarding how much BM ingredient is tolerated. If the patient reports they eat store purchased baked goods that contain milk, it is not easy to determine the threshold level or know if they will tolerate other products, potentially with more BM ingredient. Therefore, a BM OFC using a standardized recipe is helpful.

Although the majority of children will tolerate BM, there remains a smaller percentage who will not tolerate these ingredients and several studies report anaphylaxis upon oral food challenge.<sup>34</sup> These

Factor	Milk ladder not recommended	Milk ladder might be considered for gradual home introduction
Age	5 years and older	Younger than 5 years
IgE-CMA	Prior anaphylaxis	No prior anaphylaxis
Non-IgE CMA	Severe FPIES with documented low blood pressure, fluid resuscitation, hospitalization	Food protein-induced allergic proctocolitis, food protein-induced enteropathy
Eliciting dose	Low previous reaction threshold to baked or no-baked CM, reactions to trace amounts or cross-contamination	High previous reaction threshold to baked or non-baked CM
Reactivity to baked milk	Reactions to baked milk	Ingestion of small amount of baked milk without symptoms
Asthma	Poor control	Optimal control
Laboratory tests	High and or increasing SPT wheal or serum CM-specific IgE levels	Small and or decreasing SPT wheal or serum CM-specific IgE levels
Adherence to chronic therapies, e.g., for asthma, eczema	Poor/sub-optimal	Adequate
Shared decisions	Caregivers apprehensive about the ladder approach, language or comprehension barrier	Caregivers seeking/accepting ladder approach, no language or comprehension barriers

**Table 5.** Factors in favor and against home introduction of milk

children are more likely to have higher casein specific IgE antibodies;<sup>33</sup> however there are no consistent predictive values for skin prick tests or food specific IgE levels to determine which patient will react to BM.<sup>35</sup> As a result, and because severe allergic reactions including anaphylaxis are possible, physician-supervised oral food challenge to BM is usually recommended.<sup>36</sup> Table 5 summarizes factors against and in favor of home introduction using so called “milk ladder”.

Recent reports highlighted an alternative approach of a careful home introduction of BM products in younger children (less than 3 years old) with milder phenotype defined as no history of anaphylaxis or any wheezing (unrelated to food ingestion) and skin prick test (with commercial extract) wheal less than 8 mm for milk.<sup>37</sup> The authors reported a positive experience with low rate of mild allergic reactions during home introduction. These protocols might be considered in select cases, especially in the settings with limited access to

allergy specialists’ services, for example, due to geographic location or restrictions due to pandemic.<sup>38</sup>

After a successful BM challenge, detailed instructions on how to safely incorporate BM ingredients is required. Table 6 lists detailed instructions that were used successfully during clinical research trials.<sup>25</sup>

#### Identify and treat acute severe reactions (anaphylaxis)

There is no reliable in-vitro test able to predict severe reactions in individuals with CMA. STAT6 (signal transducer and activation of transcription 6) gene variants have been associated with more severe allergic reactions during both peanut and cow’s milk OFC.<sup>39</sup> Significant association has been found between anaphylaxis during the OFC with cow’s milk and the sIgE levels for caseins, as well as with higher basophil reactivity.<sup>40</sup> There is however, no

	Include	Avoid	Unknown
Volume of milk protein	The amount of baked milk allowed is dependent on the amount tolerated in the oral food challenge. The recipe provided in Table 4 provides 1.33g baked milk protein per serving.	More baked milk than tolerated in the oral food challenge.	The amount of baked milk protein tolerated may also depend on other factors such as the degree of baking (time/temperature), the size of the finished product, and the volume of wheat matrix.
Grain matrix	Based on the recipe provided, the ratio should be no more than 1 cup of milk per 1 1/4 cups flour with a yield of 6 servings unless the patient has tolerated less matrix on a prior oral food challenge.	Please continue to use milk-free chocolate chips as chocolate chips will melt during baking but not mix into a grain matrix. Items such as baked macaroni and cheese, and custards, will not have a grain matrix.	It is unknown how a different grain matrix (such as gluten-free flour) or less grain matrix will affect the immune response. The cooking time, temperature, and size of finished product may also affect the immune response to the food product in addition to the grain matrix.
Time/Temperature	All items must be baked in the oven to a dry crumb texture, must be cooked throughout and not be wet, gummy or soggy in the middle. The recipe provided requires a full size muffin to be baked at 350° for 30 min. Other recipes have been published with varying times/temperatures	Continue to avoid any unbaked milk item that is cooked but not baked like pudding, stovetop macaroni and cheese, or heated milk.	Smaller baked items such as mini muffins/crackers/cookies will bake for a shorter time. Ensure they are baked thoroughly to a dry crumb texture. It is unknown if less baking time will be change allergenicity.
Store-bought baked goods	Commercial baked products with milk ingredient listed as the third ingredient or further down the list of ingredients. This approach has been used successfully in multiple clinical trials.	Any baked item that also has an unbaked milk ingredient such as a <i>frosted</i> cupcake or an <i>iced</i> cookie or a <i>filled</i> pastry or a cracker with a <i>topically applied flavoring</i> after the item has been baked. Any item that has a milk ingredient as the first or second ingredient.	It is unlikely to find a commercial baked good, such as bread, cookies, crackers, muffins that have more milk protein than the recipe provided, when that ingredient is listed as the third ingredient or further down the list of ingredients.

**Table 6.** Instructions after a baked milk challenge<sup>a</sup>. <sup>a</sup>Leonard SA, Caubet JC, Kim JS, Groetch M, Nowak-Wegrzyn A. Baked milk- and egg-containing diet in the management of milk and egg allergy. *J Allergy Clin Immunol Pract* 2015; 3:13-23; quiz 4.





reliable in-vitro test able to predict the occurrence and the severity of in-vivo reactions.

Not only should families be advised on food avoidance, but they also need advice on the steps to take on inadvertent exposure. Severe reactions should be identified and managed according to the consensus on DEfinition of Food Allergy SEverity (DEFASE).<sup>41</sup>

### Human milk

The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life. B-lactoglobulin has been detected in human milk of up to 95% of mothers consuming cow's milk.<sup>42</sup> Yet, the amounts secreted in human milk are very small in the region of nanogram per milliliter. The amounts present in human milk vary widely, irrespective of the amounts consumed by the mother and the timing of consumption.<sup>43</sup> Timing of detecting of milk proteins is around 1–2 h from consumption for milk.<sup>44</sup> For most infants with cow's milk allergy, there will be no need to restrict the maternal diet. Maternal avoidance of cow's milk during breastfeeding may be required in some infants with non-IgE mediated cow's milk allergy; in around 5% of infants of FPIES);<sup>45</sup> between 18 and 50% of infants with proctocolitis<sup>46,47</sup> and the number of children with eosinophilic esophagitis

(EoE) who react to milk via human milk is not clear.<sup>45</sup> The need for maternal avoidance of cow's milk in children with IgE mediated cow's milk allergy, needs to be assessed on a basis.<sup>45,47–49</sup> If a maternal dietary restriction is required, a dietetic assessment is required to ensure the maternal diet is nutritionally sound and the necessary supplementation provided when required.<sup>47</sup>

When infants are not breastfed or human milk is not sufficient, cow's milk infant formulas provide the mainstay of nutrition.<sup>50</sup> For infants, children and adults with CMA, a milk alternative should be provided.

### Specialized formulas

For infants fed with formula, a substitute formula is recommended. Substitute formulas are divided into soy infant formula (not hydrolyzed), milk-based extensively hydrolyzed formulas, rice-based extensive and partially hydrolyzed infant formulas and amino acid-based formulas. Extensively hydrolyzed cow's milk formulas<sup>51</sup> are the result of enzymatic hydrolysis and ultrafiltration of cow's milk. Amino acid based formulas are based on pure amino acids and therefore peptide free.<sup>52</sup> Special hypoallergenic formulas with an adjusted nutrient profile are available for children

over 12 months and in some cases, may even be used in teenagers and adults.

The claim of “hypoallergenicity” is regulated in most countries. Hypoallergenic formulas sold in the European Union must comply to European Food Safety Authority (EFSA) regulations<sup>53</sup> and in the United States to Food and Drug Administration (FDA) regulations.<sup>54</sup> The definition of hypoallergenic formulas are based on 2 historical definitions. Host et al stated that the regulations of the European Union for labelling infant formulas as having reduced allergenicity (or antigenicity), are based arbitrarily on a content of immunoreactive protein of <1% of total nitrogen containing substances, but there is no evidence that such a threshold of immunogenic protein would ensure a reduced clinical allergenicity.<sup>55</sup> The American Academy of Pediatrics (AAP) defines a hypoallergenic formula as a formula that is tolerated by 90% of individuals with cow’s milk allergy with a 95% confidence when given in prospective randomized, double-blind, placebo-controlled trials.<sup>56</sup>

The macro and micronutrient content of substitute formulas for CMA must comply with both EFSA and FDA regulations, which implies limited differences between formulas based on these ingredients. Infants therefore consuming sufficient volume of any of these specialist CMA formulas will achieve their requirements. There are differences with the addition of cow’s milk protein free lactose, prebiotics, human milk oligosaccharides, probiotics and synbiotics in formulas, aimed at supporting the microbiome to more closely align with an infant who has been breastfed and to induce tolerance.<sup>57-61</sup> A recent systematic review concluded that there is currently insufficient evidence to choose one

cow’s milk based extensively hydrolyzed formula over another.<sup>62</sup> Healthcare professionals may consider the lactose content, the osmolality and the presence of thickening agents (pre-thickened hypoallergenic formulas exist in some countries) in these formulas, in particular in children with gastrointestinal symptoms including diarrhea and vomiting.<sup>63-65</sup> For amino acid based formulas, which are advised for severe CMA, no specific recommendation can also be made to choose one formula above another based on novel ingredients with the current available evidence.<sup>65,66</sup>

Hydrolyzed infant formula can be either partially or extensively hydrolyzed. Although rice is rich in essential amino acids, it lacks some amino acids that are present in human milk. For this reason and to ensure nutritional safety and growth in infants allergic to cow’s milk, hydrolyzed rice protein infant formulas are supplemented with lysine, threonine, tryptophan and, similar to other hypoallergenic formulas, they also meet the micronutrient requirements for infant formulas.<sup>67</sup> There are currently no studies assessing the bone mineral density of long-term use of hydrolyzed rice infant formula; however, these are data that are also not available for many other formulas used in CMA. Future research in this area is welcome, in particular as reduced bone mineral density has been reported in CMA.<sup>68,69</sup>

In terms of concerns about the inorganic arsenic content of these formulas, a recent study reassures the arsenic content is within safe limits.<sup>70</sup> However, it is advised that arsenic content should be declared on these formulas. The main characteristics of formulas suitable for the treatment of cow’s milk allergy are reported in Table 7.

Milk alternative	Characteristics
Soy infant formula	Soy proteins not similar to cow’s milk proteins
Extensively hydrolyzed cow’s milk based formulas	Based on milk proteins which are hydrolyzed
Amino acid/Elemental formulas (AAF)	Amino acids are derived from non-milk sources
Rice hydrolysates (partially or extensively hydrolyzed options)	Rice based hydrolysates

**Table 7.** Suitable infant formula substitutes for the management of cow’s milk allergy. *Partially hydrolyzed formulas based on cow’s milk are not recommended for the management of cow’s milk allergy.*

### Soy infant formula

A further option for the management of cow's milk allergy, is the use of soy infant formula. And infant formula milk contains completely different proteins than those derived from cow's milk. Soy-based infant formulas are well tolerated in the majority of infants with IgE mediated CMA, but data from some countries points towards more children with non-IgE mediated CMA also reacting to soy.<sup>65,71,72</sup> Current soy infant formulas are enriched with amino acids (methionine, taurine and carnitine), iron, zinc, calcium, phosphorus.<sup>52</sup> There are however concerns regarding the use of soy infant formulas and the potential hormonal effects on the reproductive system, due to the isoflavones present in soy proteins.<sup>73</sup> The negative influence of isoflavones, demonstrated in some animals models, has not been evidenced with the same relevance in humans. Only children with congenital hypothyroidism can have problems and require remodulation of thyroid hormone replacement doses. However, this does not mean that the potential harmful effects of isoflavones can be fully excluded.<sup>74</sup> On the other hand, it is acknowledged that soy has a significantly better taste, which may affect acceptance of formula and carries less of a financial burden for families in particular in resource poor countries.<sup>75,76</sup> This is reflected in the newly published guidelines of the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) that suggest that soy infant formulas can be considered for certain economical, cultural and palatability reasons.

The 2023 DRACMA guidelines make the following conditional recommendations.

- 1) Extensively hydrolyzed (milk) formula or a hydrolyzed infant formula can be used as the first option for managing infants with IgE and non-IgE-mediated CMA if breastfeeding is not possible or available
- 2) An amino-acid formula can be a second option
- 3) A soy infant formula would be regarded as the last option
- 4) Formulas without a probiotic or an extensively hydrolyzed (milk) formula containing *Lactobacillus rhamnosus* (formerly *Lactobacillus rhamnosus*) GG can be used for infants with either IgE or non-IgE-mediated CMA

The issued recommendations are labeled as "conditional" following GRADE approach due to the very low certainty about the health effects based on the available evidence.

### Other mammalian milks

The use of other mammalian milks is not recommended for the management of cow's milk allergy due to a high level of cross-reactivity and nutritional concerns.

### Alternative plant-based beverages

Allergists, pediatricians and pediatric gastroenterologists are increasingly seeing caregivers who choose to feed their infants and young children plant-based beverages over cow's milk for reasons such as, medical conditions (allergies), cultural dietary preferences, or health related perceptions such as a possible beneficial effect on the gut microbiome.<sup>77</sup> However, plant-based beverages are nutritionally inadequate to support normal growth and development compared to infant formulas or human milk, particularly in children <1 year of age. Adverse effects from inappropriate use of plant-based beverages can lead to poor growth, malnutrition, electrolyte disorders, kidney stones, and severe nutrient deficiencies including iron deficiency anemia, rickets, and scurvy. It is however difficult to tell if this is a direct association or indirectly associated with milk avoidance.<sup>78-81</sup>

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) Nutrition Committee, recently published a document<sup>77</sup> stating that "In young children beyond the first year of life requiring a dairy-free diet, commercial formula may be a preferable alternative to cow's milk, when such formula constitutes a substantial source of otherwise absent or reduced nutrients (e.g., protein, calcium, vitamin D) in the child's restricted diet."

Milk Type	Calories (per 100 mls)	Fat (g)	Protein (g)	Carbohydrates (g)	Dietary Fiber (g)	Added sugar (g)	Calcium (mg)	Vitamin D (mcg)	Potassium (mg)	Vitamin B12 (mcg)
Oat milk	34-68	0.6-4	0.8-3.4	4.6-10.5	0-0.8	0-7.2	51.1-194.1	0.8-1.9	56.1-173	0-1
Soy milk	30-55	1.5-2.5	3-5.1	1.3-7.6	0-1.3	0-2.1	16.9-189.9	0-2.1	0-181.4	0-1.3
Almond milk	15-55	1-4.6	0.4-2.1	0.4-3.4	0-0.4	0-3	3-189.9	0-2.1	0-71.7	0
Hazelnut milk	13-69	1.3-3.8	0-0.8	0.4-13.9	0-0.4	0-5.5	0-51.9	0-0.8	0-44.3	0
Cashew milk	11-55	0.8-4.2	0-1.7	0.4-3.4	0	0-2.1	6.3-189.9	0-1.1	0-63.3	0-1.3
Walnut milk	17-51	1.5-4.6	0.4-1.3	0.4-2.1	0-0.4	0-1.7	10.1-189.9	0-2.1	32.5-54.9	0
Pea milk	30-59	1.9	3.4	0-7.2	0-0.4	0	194.5-198.3	2.5	189.5-189.9	1.1
Coconut milk	19-46	1.9-4.6	0-0.4	0.4-3.8	0-0.4	0-3	0-194.1	2.5	0-71.7	0-1.3
Sesame milk	38-68	2.1-3.8	1.7-3.4	0.8-8.4	0-1.3	0	32.9-164.6	2.5	0-80.2	0
Hemp milk	21-59	2.1-3.4	0.8-1.7	0.4-8	0-0.4	0-5.1	111-164.6	2.5	0-61.2	0-0.4
Rice milk	30-51	1.1	0-0.4	4.6-9.7	0	0	12.7-164.6	2.5	0-16.9	0-0.3
Tigernut (Chufa) milk	56-84	2.1-2.5	0.4	9.7-13.5	0	0-13.1	0	2.5	0	0
Quinoa milk	29	1.3	0.4	3.4	0	0	0	2.5	0	0

**Table 8.** Plant based beverages and food alternatives available in the US and online per 100 ml of plant based beverage. *The quality of the protein and absorption is different from infant formulas or cow's milk.*

They further emphasized that inadequate nutritional intake can adversely affect a child’s nutritional status, growth, and development and that milk intake plays a particular important role in a child’s overall diet. The working group letter concluded that alternative plant-based beverages should provide a comparable nutritional content to conventional cow’s milk to prevent adverse nutritional effects, with a particular focus on protein content. They recommended that growth studies and bone mineralization studies of young children fed plant-based beverages are needed, similar to those performed to assess the nutritional effect of infant formulas.

Plant-based beverages include those made from soy, coconut, almond, rice, oat, hazelnut, cashew, walnut, pea, sesame, hemp, tigernut, and quinoa (Table 8). These beverages differ in terms of nutrition composition and characteristics. Availability of these beverages also differ internationally but the majority can be ordered on-line. A simple guide to buying these plant-based beverages is listed in Table 7. It is important to be aware of the cost of alternative beverages and compare their nutrient composition against that of cow milk, particularly in terms of protein, energy, calcium, vitamin B12, Vitamin D, and iodine. Fat content is also important in children under the age of 2 years. In addition, protein quality of these plant based beverages needs to be considered, as the amino acid profile may not be similar to cow’s milk. Bioavailability of nutrients added to plant based

beverages may also be less than nutrients naturally occurring in cow’s milk.<sup>77</sup>

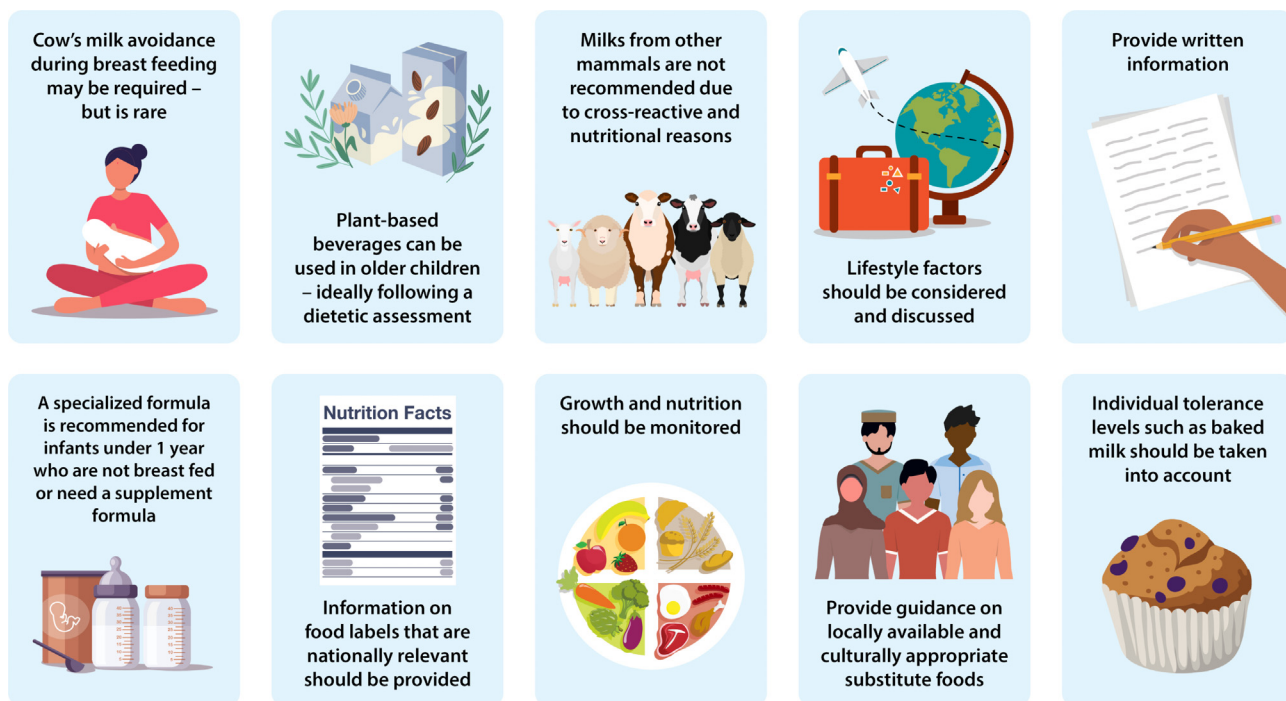
For toddlers who are eating well, children and adults, a suitable plant based beverage may be considered.<sup>82</sup> These beverages should ideally only be used in children under 2 years of age following a dietary assessment, however when access to alternative formulas are limited, the health care provider can provide counseling to improve the diet using the following recommendations.

Factors to consider that *may* indicate a toddler is ready to transition to a plant-based beverage are the child:<sup>83</sup>

- Is at least one year of age
- Eats a varied solid food diet with a variety of foods from each food group;
- Gets at least 2/3 of their energy from the varied solid food diet;
- Consumes no more than 2 servings/day (1 serving = 8 ounces/240 mls of milk substitute day or yogurt substitute):
- Eats age-appropriate textures
- Gets enough protein and fat and micronutrients in the diet from the solid foods and the available milk substitute
- Has no feeding difficulties that may reduce food variety
- Has no known micronutrient deficiencies; AND

Calcium	calcium-fortified plant based beverages including soy and products made there-of, calcium-set tofu, canned sardine or salmon with bones, fortified breakfast cereals, mineral water rich in calcium
Vitamin D	Vitamin D fortified foods (in particular, milk and plant-based beverages but also breakfast cereals), Fatty fish, cod liver oil, UV light exposed mushrooms, egg yolk
Iodine	Seaweed, fish, egg, enriched grains, iodized salt
Protein	Meat, fish, poultry, eggs, nuts, seeds, legumes
Fat	Vegetable oils, fatty fish, meats, nuts, seeds
Vitamin B12	Animal products and fortified foods (breakfast cereals, fortified beverages, fortified nutritional yeast)

**Table 9.** Food sources of important nutrients excluded during cow’s milk avoidance



**Fig. 1 CMA and dietary management tips.** Dietary management of cow's milk allergy involves food elimination, choosing appropriate alternatives, monitoring nutritional intake and status, and taking lifestyle factors into account. (Images were legally obtained through Adobe Stock and should not be extracted for reuse.)

- Has no religious/cultural dietary requirements that reduces the variety of foods consumed

This guide also highlights when a toddler should *not* be transitioned to a plant based beverage when a substitute formula is available. Plant based beverages should also not be used as a main drink in children under 1 year of age. It is important to consider that some of the plant-based beverages are based on high allergenic ingredients and should not be recommended to those with food allergies to any of the ingredients.

### Alternative foods

Families need to be instructed on finding suitable nutritious foods and how to prepare suitable meals at home.<sup>11</sup> Alternative sources of foods rich in important nutrients and free from cow's milk can be found in [Table 9](#).

### Lifestyle factors

When eating outside of the home whether it be at a friend/family's home, restaurant, on vacation or at school, it is important that families contact the

food provider before-hand to establish ingredients of foods and discuss risk of cross contact. In restaurants, it may be helpful to speak to the chef, but some chefs may also be insufficiently informed too.<sup>84</sup> There is always the option to bring along allergen-free foods. Chef cards are helpful, particularly when there is a language barrier. Understanding local labeling laws is important as some cover freshly prepared foods such as in the European Union/United Kingdom. Lastly, provide tips with suitable foods and recipes ([Fig. 1](#)).

## NUTRITIONAL ASPECTS OF MANAGEMENT OF CMA

### Growth

Growth faltering (GF) is included as part of the clinical presenting features of cow's milk allergy in current guidelines.<sup>8,67,85,86</sup> Although, it is assumed that GF presents together with other IgE or non-IgE mediated symptoms, a recent study has highlighted the importance of considering CMA in children who present with GF as primary symptom, where other diagnoses have been ruled out.<sup>87</sup> Whilst, there is no debate on the inclusion of

growth assessment as part of the allergy focused history,<sup>88</sup> it is clear from published studies, that growth continues to be a concern in children with CMA also after the diagnosis. Isolauri et al highlighted ongoing poor height growth in a study of 100 children with CMA, who were managed with a cow's milk elimination diet and appropriate milk replacements. The study from 1998 has been followed by several other studies, indicating in particular short stature as a problem in CMA,<sup>90,91</sup> which continues in those with persistent CMA into young adulthood.<sup>92,93</sup> Cow's milk contributes important nutrients for growth and bone mineralization and the milk proteins have been shown to have a positive correlation with serum IGF-1.<sup>94</sup> Although most research has focused on nutrient deficiencies, including energy, protein, calcium and vitamin D, as the most plausible explanation for poor growth in CMA,<sup>92,93</sup> other hypotheses exist. Already in 1998, Isolauri et al<sup>89</sup> theorized low-grade ongoing gastrointestinal inflammation (due to inadvertent exposure to cow's milk or ongoing reactions to an extensively hydrolyzed formula or other allergens) as a possible factor and since then Beck et al<sup>95</sup> has also highlighted atopic co-morbidities, in particular atopic eczema, as being associated with poor growth. The most recent DRACMA guidelines<sup>3</sup> supported by other publications<sup>66,96,97</sup> have found limited evidence of low certainty, that children with IgE mediated CMA who were fed amino acid-based formula may have an improved growth pattern when compared to extensively hydrolyzed (milk) formula. It should however be noted that the included studies are old, and the formulations of formulas have changed and these studies did not aim to assess failure to thrive and therefore catch-up growth. Further research is therefore needed, to answer the question about whether certain formulas better support catch-up growth. Compared to soy infant formula extensively hydrolyzed (milk) formula may favor weight gain but there is no difference on length growth. There was no difference when comparing extensively hydrolyzed (milk) formula to hydrolyzed rice infant formula or hydrolyzed rice infant formula to soy infant formula. In terms of non-IgE mediated CMA, the DRACMA guidelines suggest that compared to amino acid-based formulas, there may be reduced length growth seen with extensively hydrolyzed (milk) formula based, however this study included only patients with IgE mediated CMA, so

the certainty of evidence is very low and further research is required. No difference was found when comparing extensively hydrolyzed (milk) formula to hydrolyzed infant formula or hydrolyzed rice infant formula to soy infant formula.

Most publications have focused on growth faltering; however, obesity should also be considered in CMA. Data from Meyer et al<sup>90</sup> found that 8% of the surveyed children with food allergy were obese. In this context, food quality is also an important consideration in CMA. A recent study has highlighted that the pressure-to-eat behaviour towards food allergic children, drives unhealthy food choices and the need to make children eat more of their free-from foods.<sup>98</sup>

### Micronutrient deficiencies

Calcium and vitamin D deficiency are most commonly described in cow's milk allergy, but studies have also highlighted concerns about iodine, iron and zinc and in theory children on any elimination diets are at a higher risk of nutritional deficiencies.<sup>99-104</sup> Many of these micronutrients are co-factors in growth (eg, zinc), bone mineralization (eg, calcium and vitamin D) and cognitive development (eg, iodine and iron). Whilst many countries have guidelines in place for vitamin D supplementation and there is great awareness of calcium deficiencies in CMA, other micronutrients are often forgotten and difficult to predict with a diet history alone and targeted nutritional bloods may be required.<sup>105,106</sup> Concerns have also been raised in those with persistent CMA on sufficient calcium supplementation that still have sub-optimal bone mineralization,<sup>69,81</sup> and have highlighted other nutrients in cow's milk, including phosphate and magnesium that may aid bioavailability of the calcium and also the role of medication (i.e. proton pump inhibitors and inhaled steroids). These factors also need to be considered when advising carers of and patients with CMA.

### Feeding difficulties

Feeding difficulties are commonly reported in food allergic patients, in particular those with non-IgE mediated allergies, where cow's milk is a common allergen.<sup>107-109</sup> Although vomiting, pain and discomfort may lead to alteration in sensory perception, impacting on food intake,<sup>110</sup> studies in

IgE mediated egg allergy mice-models have also observed increased food aversion and anxiety related to food consumption.<sup>111,112</sup> Parental modelling is also critical in the positive relationship with food from early on.<sup>113</sup> However, in CMA, this can be disrupted because of dietary elimination and increased child and parental anxiety. Food allergy associated feeding difficulties can limit the variety of accepted foods, including important nutritional meal replacements, which in turn can impact on growth and vitamin and mineral deficiencies.<sup>114</sup> Management of feeding difficulties includes encouraging caregivers to provide age-appropriate textures and serving sizes, relaxed mealtimes without distraction and neutral caregiver responses, self-feeding and food exploration, and frequent presentation of a variety of foods.<sup>108</sup> Early recognition and referral to feeding specialists, which may include multiple disciplines, may help prevent or limit the nutritional risks associated with feeding difficulties.

It is clear that multiple factors are involved in the development of nutritional disorders, including growth faltering, vitamin/mineral deficiencies and feeding difficulties in children with CMA.<sup>99</sup>

Whilst, they may present as individual nutritional disorders, growth is closely linked to micronutrient adequacy and both are linked to optimal dietary intake that can be affected by feeding difficulties and also parental food choices. It is therefore important in children with CMA, to not only assess growth and dietary intake, but perform targeted bloods where required, and ask about mealtimes and eating patterns.

## CONCLUSION

Educating families regarding cow's milk avoidance goes to the core of personalized nutrition. Cow's milk allergy management advice depends on complex aspects such as the range of allergens involved and the effect of baking on the different allergens, which impact the level of avoidance required, and is unique to milk and egg allergy. Cow's milk formula forms a staple for infants not breast fed or sufficiently breast fed. Cow's milk and products made of cow's milk form a staple for young children. Exclusion can have far reaching nutritional and growth complications. The management of cow's milk allergy is further

complicated by having to choose a suitable hypoallergenic supplement or plant-based beverage. The future of cow's milk allergy is however exciting with progress being made on understanding gut microbial difference in infants with and without cow's milk allergy, epigenetic modifications, and factors associated with prevention and tolerance induction. Management of cow's milk allergy is therefore an evolving field and requires all health care professionals to be aware of and informed about the latest guidance such as the WAO DRACMA guidelines. Health care professionals world-wide should be encouraged to stay updated on the latest research and guidelines.

## Abbreviations

AAP, American Academy of Pediatrics; BM, Baked milk; CMA, Cow's milk allergy; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy; EFSA, European Food Safety Authority; ESPGHAN, European Society for Pediatric Gastroenterology Hepatology and Nutrition; FDA, Food and Drug Administration; GF, Growth faltering; NASPGHAN, North American Society for Pediatric Gastroenterology; Hepatology; and Nutrition; EoE, Eosinophilic esophagitis; FPIES: food protein induced enterocolitis; OFC: oral food challenges; PAL: precautionary advisory labelling.

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