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Review

Nutritional counseling for cow's milk protein allergy in infants from birth to 2 y of ages: Scoping review

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ABSTRACT

Objectives: Cow's milk protein allergy (CMPA) is a clinical condition that requires appropriate nutritional counseling during breastfeeding and the introduction of complementary feeding. Using evidence-based dietetic advice is critical for correct growth and development during childhood. The aim of this study was to review the most recent literature on nutritional counseling aimed at infants between 0 and 2 y of age diagnosed with CMPA.
Methods: Six databases were searched and updated on August 22, 2020. Retrieved articles were screened in duplicate and independently by all the authors, and these were selected according to the following inclusion criteria: clinical trials, reviews, meta-analyses, and clinical practice guidelines published since 2013 on any dietetic intervention aimed at infant populations between 0 and 2 y of age with CMPA. Critical appraisal through the AGREE instrument and CASP tools enabled the risk of bias assessment.
Results: We obtained 2874 results, of which 40 were included for reviewing. The retrieved information enabled us to answer all the research questions, including aspects of the nutritional counseling aimed at mothers who breastfeed infants with CMPA, as well as infants during breastfeeding and the introduction of complementary feeding. We also reviewed the specific nutritional requirements of infants with CMPA to assess nutritional supplementation and the evidence available on the use of probiotics, prebiotics, and symbiotics.
Conclusions: This scoping review collected, in a structured and comprehensive way, the most recent available information regarding nutritional counseling in CMPA for a successful dietetic intervention of the casuistry that may arise during early infancy.

Introduction

Cow's milk protein allergy (CMPA) is a type of food allergy with high incidence in the infant population (2–5%) [1]. The most common symptoms are cutaneous clinical manifestations, such as dermatitis, urticaria, or oral allergy syndrome, as well as gastrointestinal (GI) disorders, such as changes in stool frequency and consistency, mucous in stools, blood spots in stool, infantile colic, nausea, vomiting, and gastroesophageal reflux. Additionally, clinical manifestations may vary regardless of whether CMPA is or

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is not mediated by immunoglobulin (Ig)E. In the first scenario, the onset of the reaction is typically immediate, with the prevailing symptoms being cutaneous and GI over respiratory. In non−IgE-mediated CMPA, symptoms tend to have a late onset in most cases (from hours to days), preceding GI manifestations such as enterocolitis [2]. However, most severe reactions exhibit an enteropathy similar to that revealed in celiac disease, eosinophilic esophagitis, and enterocolitis syndrome, potentially reaching an anaphylactic reaction typical of severe allergies [3].

CMPA has been associated with nutrient and water loss due to intestinal malabsorption, as well as with reduced milk or food intake in infants if complementary feeding has already been introduced [2]. This situation, which may cause nutritional deficiencies and stunting [4], could be avoided through suitable and evidence-based nutritional counseling for parents whose children are affected by this food allergy [2]. However, the lack of expert knowledge of gastroenterology, nutrition, and dietetics by non-specialized pediatricians may result in a late diagnosis of CMPA and inadequate nutritional counseling. For instance, the National Health System in Spain does not provide dietitians in primary care centers and most care services, such as pediatrics. Additionally, in other surrounding countries, the counseling offered by specialized dietitians in pediatric nutrition is less than one in five patients with CMPA [5].

A recent study on early diagnosis and efficient management of CMPA emphasized the need for simple algorithms and tools to enable the interpretation and implementation of advice gathered in clinical practice guidelines [6]. Therefore, to simplify nutritional counseling aimed at infants affected by CMPA and to serve as a tool for CMPA nutritional management, we propose the following objectives for this scoping review:

- Review and describe the most recent scientific evidence on food practices that should be followed by infants diagnosed with CMPA from birth to 2 y of age;
- Review, given the stage, the guidelines related to type of lactation, the specific recommendations on complementary feeding, the relevant features related to the dairy elimination diet (both for the mother and infant), and the practical aspects regarding the purchase and preparation of foods aimed to this population.

It should be noted before clinical practice in a nutritional consultation that there are some signs to doubt about a proper CMPA diagnosis. For example, if the symptoms are not related to food intake or appear after 2 mo from milk introduction or at advanced ages (3 y of age). Also, when symptoms only involved one organ system [7] or they are more likely related to lactose intolerance and the prick test or the IgE test for CMPA was negative [6].

Methods

Research questions

We decided to work with infants with CMPA from birth to 2 y of age because it is the peak age of onset of the disorder and also considering the high rate of remission before the age of 2 y. Infants born preterm were excluded as they are more sensitive to the development of allergies [3,8]. Moreover, the process of oral immunotherapy was not covered in this scoping review as it goes beyond the nutritional counseling approach. The main outcomes from nutritional counseling were the remission of the symptoms or a reduction in the frequency or intensity of the colic while the correct rate of child growth and development is guaranteed.

Considering these criteria, the main research question was as follows:

- What diet (type of lactation/feeding/vitamin or mineral supplements/milk alternatives/pre- or probiotics) should be recommended in the first 2 y of life for the nutritional management of CMPA, ensuring proper growth and development?

Additionally, the following secondary research questions were formulated to answer the proposed objectives:

- Should mothers of exclusively breasted infants diagnosed with CMPA follow an elimination diet?
- Is it beneficial to switch to adapted artificial feeding in breastfed infants with CMPA after exclusive breastfeeding?
- Should hydrolyzed formula be prescribed to breastfed infants with CMPA after formula feeding?
- What dietetic (elimination diet, milk alternatives) and nutritional (supplementation, fortification) recommendations are encouraged in complementary feeding of infants with CMPA?

Keywords, databases, and searches

The search of articles was mainly performed between January and March 2018 and updated on August 22, 2020, in the following platforms: Practice-based Evidence in Nutrition, National Guidelines Clearinghouse, Epistemonikos, Tripdatabase, National Institute for Health and Care Excellence (NICE) Evidence Search and PubMed. We searched for the following keywords: “milk protein allergy,” “food allergy,” "cow's milk protein allergy", “milk allergy,” “infant allergy,” “breastfeeding,” “infant,” “formula feeding,” “diet,” and “complementary feeding.” Full electronic search strategies used for all databases are presented in Supplementary Table 1. Age ranges (infants, boy and girl, from birth to 2 y of age) and two languages (English and Spanish) were selected. Controlled intervention trials, reviews, guidelines, and meta-analyses on CMPA were considered. Additionally, studies from the reference list of the included articles were retrieved [1], performing a backward citation search [9]. We also included three additional documents [4,8,10] that were indicated by a referee, including the updated NICE guideline on cow's milk allergy in children from birth to 5 y, which was obtained through interlibrary services since its online access is limited to the United Kingdom.

Screening and selection of retrieved articles

The process of selection of studies responding to the research questions and the expected design was performed through a screening process by reading titles and abstracts in duplicate and independently [11]. During the full-text screening of the preselected articles, eligibility criteria previously agreed were applied (Table 1) to identify the studies that would belong to the qualitative synthesis. Such selection followed a strategy in duplicate after the random allocation of the documents within the authors. We included different study designs as eligibility criteria because nutritional counselling in CMPA is not carefully described anywhere, but rather it is spread throughout different documents that address the topic briefly. Also, we wanted to identify nutritional recommendations regarding different questions including both mothers and babies' diets as well as new advances targeting supplementation with micronutrients and pre- or probiotics. These topics are addressed in randomized controlled trials (RCTs).

Data collection

After the full reading of each of the selected articles, we collected the data of the randomly allocated documents and then, the one of us reviewed each of the results requesting further explanations to improve their understanding and to ensure the accurate response to the research questions. Thus, data extraction was performed in duplicate. For each of the selected sources, the retrieved information was displayed in a table (Supplementary Tables 2A−C). Data items collected were author and year, type of CMPA, nutritional counseling for infants with CMPA, target population, and referral to a dietitian. For RCTs, sample population,

Table 1
Eligibility criteria for selection of studies

Inclusion criteria	• Target population: infants from birth to 2 y of age with a diagnosis, or suspected to have, cow's milk protein allergy • Nutritional interventions or treatments including type of lactation, maternal diet, complementary feeding practices, and other nutritional requirements such as supplements or nutraceuticals • Clinical guidelines, expert consensus, position statements, meta-analyses, systematic reviews, narrative reviews, and randomized clinical trials • Published documents from January 1, 2013 • Published documents in English or Spanish
Exclusion criteria	• Patient guides and observational studies • Generic food allergy guidelines

participation of a dietitian, and description of the intervention were also extracted for every study.

Risk of bias assessment and quality appraisal

Risk of bias (RoB) in individual studies was performed at the study and outcome (nutritional advice) levels with the CASP tools for reviews and RCT [12]. We assessed the quality of the guidelines using AGREE II instrument [13]. Two reviewers evaluated every guideline independently. To ensure interrater reliability, we compared the item scores of each appraiser. We considered there to be a low discrepancy if there were <1.5 SD, using the McMaster's AGREE II concordance calculator. Large discrepancies were resolved with the help of a third reviewer. Results are presented in Supplementary Tables 3A–C. RoB across studies and quality of guidelines is discussed in the study limitations section.

Results

Study selection

The performed searches identified 2870 articles, and 4 additional articles were identified through other sources. After removing duplicates (n = 91), most of the retrieved documents (n = 2578) were rejected in the first stage of screening (title and abstract reading) for not being related to the subject allergy or for not dealing with the specific nutritional aspects of interest in the current review. Of the remaining 205 documents, 91 were not retrieved, leaving 114 full-text articles for eligibility assessment. Finally, 74 articles were excluded for not being compliant with the inclusion criteria [14], resulting in 40 selected studies for the qualitative synthesis. Figure 1 summarizes the process of study selection.

Nutritional recommendations in infant population from birth to 2 y of age with CMPA

Nutritional counseling for mothers who breastfeed infants with CMPA

The reviewed literature indicates that the most supported recommendation is to follow a diet eliminating foods and additives that contain or may contain CMPs (Table 2) [2,15–19], since proteins with high allergenic capacity would pass to breast milk, causing an allergic

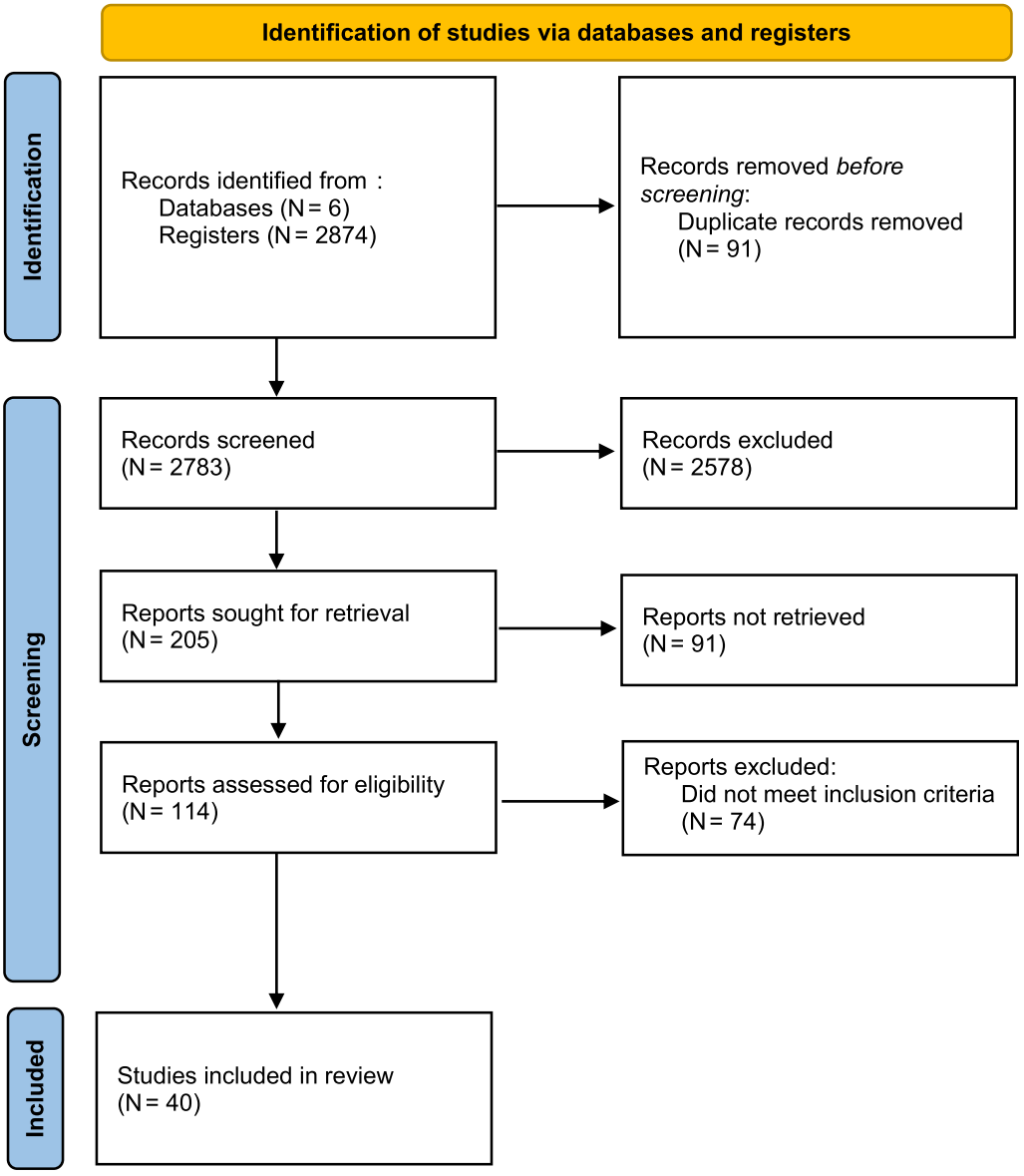

Fig. 1. PRISMA flow diagram. From Page et al [52].

Table 2
Food and additives to avoid in a cow's milk protein elimination diet*

Food	Additives
Cow's milk and other mammal's milks (goat, sheep . . .).	Casein
Yogurt and milk-based desserts: crème caramel, custard, pudding . . .	Lactoferrin
Milk-based ice cream	Whey, whey protein
Butter, mixed margarine, ghee, cream, evaporated milk, powdered milk, white sauce, Alfredo's sauce, milk-based sauces, broth cubes, instant soup, and cocoa butter	Lactose
Cheese, quark, cottage cheese, and curd	Lactulsose
Milkshakes, bakery products, pastries, biscuits, chocolate, pasta, pizza, bread, baby food, and candies	Lactalbumin, lactalbumin phosphate
Processed meat as sausages, cold cuts, burger meat, and minced meat	Calcium caseinate (H-4511)
Frozen food: croquettes, dumplings, fish, nuggets etc.	Sodium caseinate (H-4512)
	Potassium caseinate (H-4513)
	Ferrous lactate (E-585)
	Caramel color (E-150)
	Caustic caramel (E-150 a)
	Caustic sulphite caramel (E-150 b)
	Ammonia caramel (E-150 c)
	Sulphite ammonia caramel (E-150 d)

*These should be identified and highlighted with the term milk.

reaction to the infant [2]. The NICE guideline also advises an elimination diet, but it notes that for managing non−IgE-mediated CMPA, the likelihood of sufficient CMP passing into breast milk and triggering reactions is low, so complete cow's milk exclusion may not be needed [10]. Espín-Jaime et al. and NICE recommend exclusion of soya and egg from the maternal CMP elimination diet when symptoms persist in the infant [10,20]. Some authors recommend that the elimination diet last 3 to 5 d for breastfeeding mothers whose infants had an immediate reaction to cow's milk or for 3 to 5 wk for delayed reactions to assess improvements of symptoms when CMPA is suspected [21]. Other authors propose a period between 2 and 4 wk [10,18,19] and 6 mo when mild to moderate non−IgE-mediated CMPA is confirmed [10].

Along with the elimination of foods that contain or may contain CMPs, some studies contemplate that following this elimination diet, the mother could have an inadequate intake of vitamin D and calcium, thus requiring supplementation for the duration of the elimination diet [4,10,15,22,23]. Others suggest increasing the intake of micronutrient-rich foods rich in vitamin D and calcium during the dairy and milk-containing foods (among their ingredients) elimination diet [16]. Kansu et al. only recommend calcium supplementation for the mother [17]. Prescribed dosages could be of 1000 mg/d [8] of calcium and 400 UI of vitamin D [21].

Infants from birth to 6 mo of age or breastfeeding

Exclusive or mixed breastfeeding

The World Health Organization recommends following exclusive breastfeeding until 6 mo of age, preferably maintaining it along with complementary feeding, until the infant is 2 y of age. The reviewed literature indicates that, in most breastfed infants with CMPA, breastfeeding can be maintained if the mother follows a CMP elimination diet. Diagnosis and Rationale for Action against Cow's Milk Allergy clinical guidelines [24] and those developed by Vandenplas et al. [25] suggest that in infants with an increased risk for allergies such as CMPA, exclusive breastfeeding is the best prevention and treatment method combined with a CMP elimination diet for the mother. If symptoms appear in previously breastfed infants when formula is introduced, the most adequate treatment is to restore exclusive breastfeeding, not further requiring any elimination diet [8,21]. For infants who receive mixed lactation and those without symptom remission even if the mother follows an elimination diet during breastfeeding, a special formula without CMP should be chosen [1,25]. However, breastfeeding should not be discouraged [10,20].

Formula feeding

If formula or mixed feeding is chosen, the use of hypoallergenic formula is encouraged. Those that meet this criterion are extensively hydrolyzed formula (eHF) and elemental amino acid formula (AAF). Hypoallergenic formula is the treatment of choice when the patient cannot consume breast milk or when symptoms are very severe, such as failure to thrive, hypoproteinemia, severe atopic dermatitis, anemia or enterocolitis [2,10,16,21,25,26].

To select an appropriate formula, the age of the patient, the allergy type (IgE or non−IgE-mediated), the severity of the allergy, and its nutritional composition must be considered as milk substitutes not meeting the nutritional requirements may result in nutritional deficiencies and compromise growth and development [2].

Despite the broad range of formulae and brands, apparently, there are no clear distinctions of specific formulae over others 21. A summary of the groups of formula is presented here:

Hydrolyzed and elemental formulae

Formulae based on hydrolyzed proteins by heat, enzyme action, or both, provide a protein composition in the form of free amino acids and/or peptides [27] that have been tested for their hypoallergenicity as described by the American Academy of Pediatrics [28]. The wide varieties differ on the protein source, the size of the peptides, and palatability. The protein sources may be cow's milk whey protein, casein, or by-products of soya and pork proteins. Regarding the degree of hydrolysis, those containing peptides with a molecular weight <1000 Da are recommended, as they are less allergenic [2]. Partially hydrolyzed formulae (pHF) are used for the prevention of CMPA and other digestive disorders, but because they are not considered as hypoallergenic, they cannot be used for the treatment of CMPA [2,3,26]. However, the Middle East region has recently proposed the use of whey-based pHF in the therapeutic management of CMPA [7]. Nonetheless, eHF should be used as outlined by numerous clinical trials included in position statements of the European Society of Paediatric Allergy and Clinical Immunology, the Spanish Society of Clinical Immunology and Paediatric Allergy [3,27] and the NICE guidelines [10]. Also, the CAMEL group [29] demonstrated through a large randomized, double-blinded, placebo-controlled trial, that eHF are safe, nutritionally adequate, properly tolerated, and associated with a good recovery in terms of growth in patients with CMPA [29]. Canani et al. [30] demonstrated in a nutritional intervention trial lasting 12 months that the use of eHF and AAF had a similar effect both on weight and protein metabolism recovery in patients 6 mo of age with CMPA. Furthermore, Vandenplas et al. [31] observed that these formulae usually diminish regurgitation, both whey and casein-based formulae [32], and this could be improved if certain thickening agents such as pectin are added.

However, eHF from CMP can contain some larger size peptides capable of inducing inflammatory changes in the mucosa and IgE-mediated responses in a minority of patients (<10%) [18], requiring a previous evaluation, a tolerance test under the specialist's supervision and, in the event of a reaction, the use of AAF [2,3,27].

Regarding eHF palatability, their bitter taste may cause rejection, decreasing the level of intake and increasing the risk for nutritional deficiency. Nevertheless, the taste may vary depending on formulation; thus, different options should be tried before

switching to AAF [2,3]. However, if there is a significant decrease in intake, changing to an AAF is encouraged as its taste is more pleasant [26]. The recommended treatment is to try the eHF during a period of 2 to 8 wk to evaluate tolerance and, if symptoms do not diminish, switch to an AAF [1,15–18,21,25,27].

AAF are elemental formulae that consist of synthetic amino acids, a mix of essential and non-essential natural amino acids, glucose polymers, vegetable fats, minerals, and vitamins in a similar proportion to the profile of breast milk [27]. AAF are designated in cases where severe reactions are present, such as anaphylaxis, enteropathy, eosinophilic esophagitis, food protein-induced enterocolitis syndrome (FPIES), multiple food allergies, or intolerance to the eHF [2,3,16,17,25,26,33].

The risk for intolerance or adverse reactions with these formulae is very low as they do not contain proteins or peptides [27]. However, their main disadvantage is their high cost compared with other options [26,27]. Some trials have reported that a worse nitrogen absorption compared with eHF; however, in other cases, a higher promotion and maintenance of growth has been noticed, whereas others do not show significant differences among them [27,30]. In a recent systematic review about the safety and efficacy of hydrolized formula for CMPA management, the evaluated eHF products appear to be well tolerated without growth being compromised [34].

The development of new formulae to avoid or diminish the undesirable effects of elemental formulae is continuing. According to the results of Dupont et al. [33] elemental formulae with added thickening agents, mainly corn-based maltodextrin, could be more effective due to the delay of gastric emptying; whereas Jirapinyo et al. [35] found a higher tolerance with elemental formula whose glucose polymers originated from rice instead of corn. Payot et al. did not find any difference in efficacy, formula consumption, or tolerability between a spoon-fed yogurt-type AAF and a liquid one [36].

Soya formulae

Formulae made with soya protein have appeared as an alternative due to their nutritional profile, low reactivity compared with CMP, lower manufacturing cost, and better palatability [2,8,26,27]. However, several factors must be taken into consideration when choosing soya formulae.

On the one hand, soya has a high antigenicity level, affecting 1 in 10 patients with CMPA, and particularly infants <1 y of age [2,3,21,25,27]. Up to 14% of infants with IgE-mediated CMPA could also react to soya, and this rate increases up to 60% in infants with non-–IgE-mediated CMPA [10,22]. Moreover, soya protein has a lower bioavailability than CMP, as well as a lower content of methionine and cysteine, which need to be enriched [2,27]. Additionally, these formulae must contain a higher amount of isolated protein than CMP formulae, with the aim to fulfill nutritional composition requirements established in Europe (2.25 versus1.8 g/100 kcal) [2].

Furthermore, the presence of phytic acid (about 1.5%) may prevent the absorption of micronutrients such as zinc and iron; as well as the presence of specific glycopeptides, which also act as antinutrients that diminish the thyroid iodine uptake. Therefore, soya formulae are usually fortified with these minerals [27]. The effects of soya's phytoestrogens are unknown in humans [2,25,27].

Lastly, these formulae contain high amounts of aluminium and manganese, which could lead to adverse effects, but none of them have been described after a long-term supply [27].

Despite all the potential adverse effects, recent meta-analyses show that the growth patterns, bone health and metabolic, reproductive, endocrine, immunologic, and neurologic functions in infants fed with soya formulae are similar to those fed a CMP formulae or breast milk [25]. In view of the outlined factors, international and national medical societies such as the European Society for Paediatric Gastroenterology Hepatology and Nutrition and the American Academy of Pediatrics point out that soya formulae are not indicated as the first-line of treatment for CMPA and must not be used in infants <6 mo of age [4,8,10] nor in cases of enteropathy and malabsorption [37,38]. However, Australia and South Africa may consider this option as the first line of treatment in certain CMPA conditions [15].

Therefore, soya formulae could be appropriate in infants >6 mo of age with CMPA if there is a rejection or intolerance toward eHF or other formulae that may compromise their nutritional status, such as cases of galactosemia, or in special situations such as parents who cannot afford the cost of hydrolyzed or elemental formulae or vegan families that cannot offer breastfeeding [2,15,16,25–27,39].

Rice formulae

Rice formulae have shown advantages such as safety, high tolerance, palatability, nutritional adequacy, and lower cost than hydrolyzed formulae [19,21,25,38,40]. Some of their disadvantages are the lack of trials assuring their clinical tolerance, concern about high levels of arsenic, and their scarcity on a global scale [25,26]. Therefore, they are not usually recommended as a first-line treatment and they are only suggested in infants >6 mo of age presenting intolerance or aversion toward other formulae or for vegan families [16,21,25,26].

Other beverages

Regarding the use of other substitutes for cow's milk, formula, or breastfeeding, there is agreement to avoid milk from other mammals such as goat or sheep due to the high risk for cross-reactivity of their proteins [4,10]. Despite being less similar to CMP, milk proteins from other mammals, such as camels, female donkeys, mares or sows, are not encouraged due to the lack of evidence in terms of nutritional adequacy, food safety, and scarcity [2,3,8,17,21,26,27]. Nevertheless, these milks may be a safe alternative for those patients with an improvement in costs and palatability, so the publication of new clinical trials is essential to make solid evidence-based recommendations on their use [41].

Plant-based milks, such as almond, hazelnut, coconut, oat, rice, potato, quinoa, or soya milks, are not recommended as the main beverage for infants up to 1 or 2 y of age as they are nutritionally inadequate and particularly low in calories and proteins, compared with breast or cow's milk, and they present a great variability in their macro- and micronutrient content [2,16,25,26,37]. Rice milk, specifically, is not recommended in children <4 to 5 y of age due to its high content of inorganic arsenic [10,25].

After 6 mo of age or overlapping the introduction of complementary feeding

What should be done with breastfeeding?

There is scarce information in the literature reviewed. The first option must always be breastfeeding [21] and, therefore, mothers should be encouraged to continue breastfeeding despite CMPA, following, if necessary, nutritional advice for themselves and their children, which, ideally, should be provided by health professionals in the pediatric area. Otherwise, the infant should be fed with adapted formula milk for infants of ≤2 y of age as the main source of dairy [2,37], and, simultaneously, the infant should be introduced to complementary feeding, excluding dairy products as well

as foods and beverages containing milk or milk proteins within their ingredients.

What foodstuffs should not be introduced as part of complementary feeding?

Based on the reviewed literature, the only possible treatment is to avoid CMP of any kind, as well as milk from other mammals [2,3,16,17,21,25–27,35,37], presumably until 9 to 12 mo of age [4]. To prevent incidents, special care should be taken when informing all family members and people in charge of the infant's care, as milk, its by-products, and components can be found in a wide range of foodstuffs [2,27]. It is not necessary to exclude beef unless sensitization along with clinical manifestations are demonstrated [21,27,37].

The cross-sectional study performed by Kavammen et al. on micronutrient status and nutritional intake in infants from birth to 2 y of age following a CMP elimination diet highlighted that the introduction of complementary feeding at 4 to 6 mo of age is advisable for improving the nutritional status of micronutrients such as vitamin D, B_{12}, iron, and zinc [42].

Former recommendations suggesting the delay of the introduction of potentially allergenic foods have been replaced to encourage just the opposite. Currently, there is no convincing evidence indicating that the delayed introduction of highly allergenic foods after 4 to 6 mo of age may reduce allergies in breastfed infants who were at higher risk for developing allergic conditions [37].

Considering the available evidence, CMPA usually has a good prognosis in most children, being faster in non–IgE-mediated allergy than IgE-mediated allergy [2]. Tolerance should be evaluated $\geq$6 mo after the beginning of the elimination diet and from 12 mo of age [2,4].

CMP's reintroduction should be made individually and gradually, as indicated in the "milk ladder," starting with less allergenic forms (e.g., baked products containing milk) and then adding sequentially more allergenic forms to finally try fresh cow's milk [2,10,22,33,43]. Lambert et al. evaluated the inclusion of foods containing CMP that have undergone heat treatment, such as baking, and it was confirmed that, because heating induces protein denaturation, it could enable oral tolerance of these foods [44]. Nicolaou et al. also pointed out that there is some evidence supporting that the introduction of baked milk in the diet of patients with CMPA may promote tolerance acquisition [43]. The British Society for Allergy and Clinical Immunology guideline suggests beginning the reintroduction of CMP in children who have experienced a mild reaction to this protein through cooked dairy products [2]. However, the Committee on Nutrition of the French Society of Pediatrics recommends testing the tolerance to baked milk through an oral challenge under medical supervision before its introduction in children with long-lasting CMPA from 1 y of age onward [4]. Despite being a developing theory, and with all the available information, it cannot be concluded that these foods may avoid symptomatology or improve the tolerance over other strategies.

Cow's milk reintroduction is a process that could last from weeks to months, using both clinical and laboratory indices to guide reintroduction. Tolerance is established when no symptoms occur after regular ingestion of age-appropriate quantities of cow's milk at home [2]. If symptoms recur, it is suggested that the challenge be repeated at 4- to 6-mo intervals. If there is milk tolerance to a certain threshold, the level at which it is tolerated should be continued and a challenge with larger amounts or less heated/cooked milk should be made again in 4 to 6 mo [22].

Cow's milk reintroduction can be performed at home, but only in those children who had mild symptoms after a relevant exposure, no reaction to milk in the past 6 mo, or a significant reduction in laboratory parameters. In the remaining cases, reintroduction needs to be supervised in the hospital [2]. For those children with CMPA persistence, oral tolerance induction may be a treatment option [2,10,16,33].

Specific nutritional requirements of infants with CMPA

Infants with CMPA must exclude these proteins, removing all dairy products, as well as beverages and foodstuffs containing milk or milk proteins within their ingredients. The problem that arises for health professionals is to ensure the supply of calcium and vitamin D [4].

The common recommendation is daily consumption of 500 mL of cow's milk or formula. Special formulae, either hydrolyzed, elemental, soya, or rice-based are fortified with calcium and vitamin D (Spanish Royal Decree 867/2008). Breastfed infants must take a vitamin D supplement beginning in their first month of age if the mother does not take one or they must do so starting when they are 6 mo of age if the mother does take it [2,37]. The review by Lifschitz et al. pointed out that infants consuming less than the adequate quantity must be supplemented with calcium, phosphorous, and vitamin D [26]. According to the clinical guideline by Vandenplas et al., if an elimination diet is followed, a calcium supplement must always be administered [19]. In another study, emphasis was placed on vitamin D, aiming for the supplementation of 10 μg/d in infants from birth to 2 y of age [3]. The type of the infant feeding may be a confounding factor, thus, in the review by Luyt et al., it is shown that calcium-rich foods must be prioritized and professionals should inform families about these foods and beverages, reaching for calcium and vitamin D supplementation only in situations where it is necessary [2]. Other studies show the need to educate caregivers in the prioritization of calcium and vitamin D-rich foods [4,6,10].

The study by Kyammen et al. suggests that infants with CMPA, following exclusive breastfeeding and whose mothers are on a CMP elimination diet, have a higher prevalence of insufficient blood levels of vitamin B_{12} [42].

Use of probiotics, prebiotics, and symbiotics

Currently, the use of probiotics, prebioticsm and symbiotics is being broadly studied in various diseases, including CMPA.

The evidence on the use of these supplements is very limited; so much that in the review by Lifschitz et al., their use is not recommended [26]. Some studies indicate that the tolerance toward artificial formulae may improve with the use of *Lactobacillus rhanomsus* [33,37,45]. The systematic review by Tan-Lim et al. also observed beneficial effects from the supplementation with this probiotic, but in children suspected of having CMPA [46]. A clinical trial by Ahanchian et al. showed that the administration of a symbiotic containing 1 colony-forming unit of a mix of strains of *Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis,* and *Lactobacillus bulgaricus*, together with a fructo-oligosaccharide may improve growth parameters, but not symptomatology [47]. Nowak-Wegrzyn et al. evaluated the hypoallergenicity of a whey-based eHF supplemented with two human milk oligosaccharides with positive results [48].

Currently, even though formula supplemented with probiotics could improve tolerance and allergic manifestations [8], it is stated that RCTs are short-term, have small samples, and the methodology among them is quite diverse. Thus, a recommendation on the use of probiotics cannot be made [34,46,49].

Discussion

Summary of evidence

This study reviewed the most recent scientific literature on the nutritional counseling that must be offered to families, guardians, and caregivers of infants of ≤2 y of age with CMPA. There is a sizeable bibliography on this condition; however, there is less information about the nutritional strategies to implement in these situations and it is often dispersed in different sections of the articles, which mainly deal with the diagnosis of the disease. According to our knowledge, this is the first scope review consisting almost exclusively of the available information on the nutritional counseling that must be considered when there is a new diagnosis of CMPA. The nutritional recommendations reviewed are summarized in Table 3.

Table 3
Summary of the nutritional management of CMPA in infants

- For the diagnosis of CMPA in infants, the first line of action would be an ED from foods and additives containing CMP. The diet should last a minimum of 3 d and up to 4 wk to assess symptom remission or control. Simultaneously, it is suggested that breastfeeding mothers be supplemented with calcium and vitamin D.
- If maternal ED does not mitigate symptoms, breastfeeding should be stopped while, in mixed breastfeeding, breastfeeding along with the maternal ED and artificial breastfeeding with adapted formula could be maintained concurrently if successful. If onset of CMPA occurs after introduction of formula, after a previous phase of breastfeeding, it is encouraged to restart exclusive breastfeeding, as far as possible or, otherwise, recur to adapted formulae.
- It is recommended to use a hypoallergenic formula, being eHF the first choice due to its high tolerance and affordability. It is advisable to start for 2–8 wk to assess its tolerance and move to an AAF if symptoms do not diminish. Although there is not enough evidence on the superiority of eHF over AAF, the main disadvantage of the latter is its high cost.
- AAFs are specifically indicated as first treatment for those patients with a higher reactivity to CMP and other food proteins, particularly cases with more severe symptomatology (anaphylaxis, enteropathy, eosinophilic esophagitis, food protein-induced enterocolitis syndrome, or multiple food allergies).
- Soya-based formulae are not recommended as first-line treatment in infants <6 mo of age, but they can be valuable options in children without soya allergy when all the previous interventions have failed or when families follow a plant-based diet.
- Rice-based formula are starting to be recommended when other formulae are not tolerated or for families that follow a plant-based diet when child is >6 mo of age [23].
- When complementary feeding is initiated from 4 to 6 mo of age onward, infants should follow a CMP ED. There is no need to avoid beef if clinical manifestations do not appear after its consumption. The remaining foods will be introduced similarly as in infants without CMPA. Currently, there is no convincing evidence that the late introduction of highly allergenic foods will reduce food allergies in breastfed infants [26].
- Milk from other mammals and plant-based milks are not appropriate as milk substitutes.
- Pay special attention to meet nutritional requirements for calcium, vitamin D, vitamin B_{12}, iron, zinc, and phosphorus.
- Breastfed infants should be supplemented with vitamin D as described in the NICE maternal and child nutrition guidelines [50].
- There is no current recommendation on the consumption consumption of prebiotics, probiotics, and symbiotics.
- Cow's milk reintroduction should be evaluated after at least 6 mo following an ED in children from 12 mo of age. Reintroduction should be made individually and gradually according to the milk ladder, offering milk from less to more allergenic forms and increasing the amounts to age appropriated portions. Reintroduction can be performed at home or in hospital depending on the severity of the allergy.

AAF, amino acid formula; CMP, cow's milk protein; CMPA, cow's milk protein allergy; ED, elimination diet; eHF, extensively hydrolyzed formula; NICE, National Institute for Health and Care Excellence.

It is essential that health professionals train and inform families or caregivers of the infant with CMPA on the nutritional management of the condition. The given information must provide tools to identify the wide variety of foods and products containing CMP, but also regarding the most potentially deficient micronutrient richer foods to support and guarantee a good nutritional status of the infant.

Limitations

The studies included in this scoping review have some bias, which limit the accuracy and truthfulness of the present study. More than 50% of the guidelines did not describe specifically the target population nor the systematic methods to search for evidence, the selecting criteria, the strengths and limitations of the evidence, and the facilitating factors and barriers for its application. The NICE guideline is expected to be well designed based on the manual for developing them [51], but we could not retrieve the full guideline explaining its development from the evidence, so its quality appraisal is based on the NICE guideline where any methodological details are described. Almost all reviews did not include confidence intervals for the results and about 60% presented moderate to high RoB for the inclusion of relevant studies, efforts made to assess the quality of the studies included, the adequacy of mixing studies to obtain combined results, the results considered to make the decisions and evaluation of benefits over costs. Across RCTs, we found a low RoB for most items assessed except for follow-up of the recruited patients until the end of the study (50% with high risk), blinding (43% with moderate-high risk), consideration of important outcomes (43% with high risk), and worthing over risks and costs (50% with moderate risk).

There is no thorough and precise definition of a CMP elimination diet that avoids the allergic reaction in the infant. This complicates the clinical approach of the cases for the professionals who must treat the patient and give advice to their caregivers. This becomes a challenge even for dietitians as the amount and diversity of foods and beverages that may contain CMPs is extremely broad within the market.

In future research studies, it will be recommended to go in depth in more specific aspects of nutritional counseling, such as the awareness of a CMP elimination diet, the suitability of formula to ensure the proper growth and development of infants with CMPA or the most adequate guidelines to facilitate the introduction of the complementary feeding in these patients. Additionally, more studies would be required to establish the suitability of the use of plant-based formulae, as well as the details of a proper supplementation for the mother and the infant, either with minerals, vitamins, or prebiotics and/or probiotics.

Conclusions

In this scoping review study, the lines of action for an appropriate nutritional approach in infants with CMPA, from birth and ≤2 y of age, are presented in a structured manner. Having the specific information about nutritional counseling will contribute to gaining more specialized knowledge as to the nutrition of the infant with CMPA for specialized professionals who work with these patients. Additionally, pediatric dietitians who advise families affected by this early allergy will have improved guidance to facilitate their professional decision making.

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Supplementary materials

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References

[1] Vandenplas Y, De Greef E, Devreker T. Treatment of cow's milk protein allergy. Pediatr Gastroenterol Hepatol Nutr 2014;17:1–5.
[2] Luyt D, Ball H, Makwana N, Green MR, Bravin K, Nasser SM, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. Clin Exp Allergy 2014;44:642–72.
[3] Host A, Halken S. Cow's milk allergy: where have we come from and where are we going? Endocr Metab Immune Disord Drug Targets 2014;14:2–8.
[4] Dupont C, Chouraqui JP, Linglart A, Bocquet A, Darmaun D, Feillet F, et al. Nutritional management of cow's milk allergy in children: an update. Arch Pediatr 2018;25:236–43.
[5] Sladkevicius E, Nagy E, Lack G, Guest JF. Resource implications and budget impact of managing cow milk allergy in the UK. J Med Econ 2010;1:119–28.
[6] Lozinsky AC, Meyer R, Anagnostou K, Dziubak R, Reeve K, Godwin H, et al. Cow's milk protein allergy from diagnosis to management: a very different journey for general practitioners and parents. Children 2014;2:317–29.
[7] Vandenplas Y, Al-Hussaini B, Al-Mannaei K, Al-Sunail A, Ayesh WH, El-Degeir A, et al. Prevention of allergic sensitization and treatment of cow's milk protein allergy in early life: the Middle-East step-down consensus. Nutrients 2019;11:1444.
[8] Martorell-Aragonés A, Echeverría-Zudaire L, Alonso-Lebrero E, Bone-Calvo J, Maartin Munoz MF, Nevot-Falco S, et al. Position document: IgE-mediated cow's milk allergy. Allergol Immunopathol 2015;43:507–26.
[9] Cecile A, Janssens JW, Gwinn M. Novel citation-based search method for scientific literature: application to meta-analyses 2015;84.
[10] National Institute for Health and Care Excellence. Cow's milk allergy in children. Contin Med Educ 2019;29:30–4.
[11] Higgins J, Deeks J. Selecting studies and collecting data. In: Higgins J, Green S, editors. Cochrane Handbook for systematic reviews of interventions Version 5.1.0, The Cochrane Collaboration; 2011 www.handbook.cochrane.org.
[12] Cabello JB. Instrumentos para la lectura crítica | CASPe. Avaulable at: http://www.redcaspe.org/herramientas/instrumentos. Accessed July 17, 2018.
[13] Consorcio AGREE. INSTRUMENTO AGREE II.; 2009. Available at: http://www.guiasalud.es.
[14] Piekkala A, Kaila M, Virtanen S, Luukkainen P. The effect of elimination diet on the growth of a child with milk allergy - a systematic review. Duodecim 2016;132:2335–41.
[15] Venter C, Brown T, Meyer R, Walsh J, Shah N, Nowak-Wegrzyn A, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP—an international interpretation of the MAP guideline. Clin Transl Allergy 2017;7:26.
[16] DynaMed Plus. Milk protein allergy. Ipswich: EBSCO Information Services; 1995.
[17] Kansu A, Yüce A, Dalgıç B, Şekerel BE, Çullu-Çokuğraş F, Çokuğraş H. Consensus statement on diagnosis, treatment and follow-up of cow's milk protein allergy among infants and children in Turkey. Turk J Pediatr 2016;58:1–11.
[18] Vanderhoof JA, Kleinman RE. Iron requirements for infants with cow milk protein allergy. J Pediatr 2015;167:S36–9.
[19] Vandenplas Y, Alarcon P, Alliet P, De Greef E, De Ronne N, Hoffman I, et al. Algorithms for managing infant constipation, colic, regurgitation and cow's milk allergy in formula-fed infants. Acta Paediatr Int J Paediatr 2015;104:449–57.
[20] Espín Jaime B, Díaz Martín JJ, Blesa Baviera LC, Monzon AC, Hernandez AH, Burriel JIG, et al. Non-IgE-mediated cow's milk allergy: consensus document of the Spanish Society of Paediatric Gastroenterology, Hepatology, and Nutrition , the Spanish Association of Paediatric Primary Care , the Spanish Society of Extrahospital Paediatric. An Pediatr 2019;90:193. e1–11.
[21] Mousan G, Kamat D. Cow's milk protein allergy. Clin Pediatr 2016;55:1054–63.
[22] Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-ige-mediated cow's milk allergy in infancy - a UK Primary Care Practical Guide. Clin Transl Allergy 2013;3:23.
[23] Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Wegrzyn A, et al. An update to the Milk Allergy in Primary Care guideline. Clin Transl Allergy 2019;9:40.
[24] Fiocchi A, Dahda L, Dupont C, Campoy C, Fierro V, Nieto A. Cow's milk allergy: towards an update of DRACMA guidelines. World Allergy Organ J 2016;9:1–11.
[25] Vandenplas Y, Abuabat A, Al-Hammadi S, Aly GS, Miqdady MS, Shaaban SY, et al. Middle East consensus statement on the prevention, diagnosis, and management of cow's milk protein allergy. Pediatr Gastroenterol Hepatol Nutr 2014;17:61–73.
[26] Lifschitz C, Szajewska H. Cow's milk allergy: evidence-based diagnosis and management for the practitioner. Eur J Pediatr 2015;174:141–50.
[27] Plaza Martín A. Alergia a proteínas de leche de vaca. Protoc diagn ter pediatr 2013;1:51–61.
[28] Baker SS, Cochran WJ, Greer FR, et al. Hypoallergenic infant formulas. Pediatrics 2000;106:346–9.
[29] Dupont C, Hol J, Nieuwenhuis EES. Cow's Millk Allergy Modified by Elimination and Lactobacilli study group. An extensively hydrolysed casein-based formula for infants with cows' milk protein allergy: tolerance/hypo-allergenicity and growth catch-up. Br J Nutr 2015;113:1102–12.
[30] Canani RB, Nocerino R, Frediani T, Lucarelli S, Di Scala C, Varin E, et al. Amino acid-based formula in cow's milk allergy: long-term effects on body growth and protein metabolism. J Pediatr Gastroenterol Nutr 2017;64:632–8.
[31] Vandenplas Y, De Greef E. Extensive protein hydrolysate formula effectively reduces regurgitation in infants with positive and negative challenge tests for cow's milk allergy. Acta Paediatr Int J Paediatr 2014;103:243–50.
[32] Vandenplas Y, Steenhout P, Planoudis Y, Grathwohl D. Treating cow's milk protein allergy: a double-blind randomized trial comparing two extensively hydrolysed formulas with probiotics. Acta Paediatr Int J Paediatr 2013;102:990–8.
[33] Dupont C, Kalach N, Soulaines P, Bradatan E, Lachaux A, Payot F, et al. A thickened amino-acid formula in infants with cow's milk allergy failing to respond to protein hydrolysate formulas: a randomized double-blind trial. Pediatr Drugs 2014;16:513–22.
[34] Stróżyk A, Horvath A, Meyer R, Szajewska H. Efficacy and safety of hydrolyzed formulas for cow's milk allergy management: a systematic review of randomized controlled trials. Clin Exp Allergy 2020;50:766–79.
[35] Jirapinyo P, Densupsoontorn N, Kangwanpornsiri C, Wongarn R, Tirapongporn H, Chotipanang K, et al. Reconfirmation of improved tolerance to a new amino acid-based formula by infants with cow's milk protein allergy. Asia Pac J Clin Nutr 2017;26:1088–91.
[36] Payot F, Lachaux A, Lalanne F, Kalach N. Randomized trial of a yogurt-type amino acid-based formula in infants and children with severe cow's milk allergy. J Pediatr Gastroenterol Nutr 2018;66:135–40.
[37] Montijo-Barrios E, López-Ugalde MV, Ramírez-Mayans J, Anaya-Florez MS, Arredono-Garcia JL, Azevedo-tenorio I, et al. Latin American guide for the diagnosis of allergy to cow's milk proteins. Rev Invest Clin 2014;66:S9–72.
[38] Vandenplas Y, De Greef E, Hauser B. Safety and tolerance of a new extensively hydrolyzed rice protein-based formula in the management of infants with cow's milk protein allergy. Eur J Pediatr 2014;173:1209–16.
[39] De Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. Acute and long-term management of food allergy: systematic review. Allergy Eur J Allergy Clin Immunol 2014;69:159–67.
[40] Vandenplas Y, De Greef E, Hauser B, Srudy Group Paradice. An extensively hydrolysed rice protein-based formula in the management of infants with cow's milk protein allergy: Preliminary results after 1 month. Arch Dis Child Educ Pract Ed 2014;99:933–6.
[41] Navarrete-Rodríguez EM, Ríos-Villalobos LA, Alcocer-Arreguín CR, BE Del-Rio-Navarro, Del Rio-Chivardi JM, Saucedo-Ramirez OJ, et al. Cross-over clinical trial for evaluating the safety of camel's milk intake in patients who are allergic to cow's milk protein. Allergol Immunopathol 2018;46:149–54.
[42] Kvammen JA, Thomassen RA, Eskerud MB, Rugtveit J, Henriksen C. Micronutrient status and nutritional intake in 0- to 2-year-old children consuming a cows' milk exclusion diet. J Pediatr Gastroenterol Nutr 2018;66:831–7.
[43] Nicolaou N, Tsabouri S, Priftis KN. Reintroduction of cow's milk in milk-allergic children. Endocr Metab Immune Disord Drug Targets 2014;14:54–62.
[44] Lambert R, Grimshaw KEC, Ellis B, Jaitly J, Roberts G. Evidence that eating baked egg or milk influences egg or milk allergy resolution: a systematic review. Clin Exp Allergy 2017;47:829–37.
[45] Basturk A, Isik İ, Atalay A, Yılmaz A. Investigation of the efficacy of Lactobacillus rhamnosus GG in infants with cow's milk protein allergy: a randomised double-blind placebo-controlled trial. Probiotics Antimicrob Proteins 2020;12:138–43.
[46] Tan-Lim CSC, Esteban-Ipac NAR. Probiotics as treatment for food allergies among pediatric patients: a meta-analysis. World Allergy Organ J 2018:11.
[47] Ahanchian H, Nouri Z, Jafari S-A, Moghiman T, Amirian MH, Ezzati A, et al. Synbiotics in children with cow's milk allergy: a randomized controlled trial. Iran J Pediatr Iran J Pediatr 2014;24:29–34.

[48] Nowak-Wegrzyn A, Czerkies L, Reyes K, Collins B, Heine RG. Confirmed hypoallergenicity of a novel whey-based extensively hydrolyzed infant formula containing two human milk oligosaccharides. Nutrients 2019;11:1447.
[49] Qamer S, Deshmukh M, Patole S. Probiotics for cow's milk protein allergy: a systematic review of randomized controlled trials. Eur J Pediatr 2019;178:1139–49.
[50] National Institute for Health and Clinical Excellence. Maternal and child nutrition. NICE Public Heal Guid 2008:107.
[51] NICE. Developing NICE guidelines: The manual process and methods; 2014. Available at: www.nice.org.uk/process/pmg20. Accessed July 27, 2021.
[52] Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.