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GUIDELINE

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World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update – XII – Recommendations on milk formula supplements with and without probiotics for infants and toddlers with CMA

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ABSTRACT

Background: Cow's milk allergy (CMA) is the most common food allergy in infants. The replacement with specialized formulas is an established clinical approach to ensure adequate growth and minimize the risk of severe allergic reactions when breastfeeding is not possible. Still, given the availability of multiple options, such as extensively hydrolyzed cow's milk protein formula (eHF-CM), amino acid formula (AAF), hydrolyzed rice formula (HRF) and soy formulas (SF), there is some uncertainty as to the most suitable choice with respect to health outcomes. Furthermore, the addition of probiotics to a formula has been proposed as a potential approach to maximize benefit.

Objective: These evidence-based guidelines from the World Allergy Organization (WAO) intend to support patients, clinicians, and others in decisions about the use of milk specialized formulas, with and without probiotics, for individuals with CMA.

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Methods: WAO formed a multidisciplinary guideline panel balanced to include the views of all stakeholders and to minimize potential biases from competing interests. The McMaster University GRADE Centre supported the guideline-development process, including updating or performing systematic evidence reviews. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used, including GRADE Evidence-to-Decision frameworks, which were subject to review by stakeholders.

Results: After reviewing the summarized evidence and thoroughly discussing the different management options, the WAO guideline panel suggests: a) using an extensively hydrolyzed (cow's milk) formula or a hydrolyzed rice formula as the first option for managing infants with immunoglobulin E (IgE) and non-IgE-mediated CMA who are not being breastfed. An amino-acid formula or a soy formula could be regarded as second and third options respectively; b) using either a formula without a probiotic or a casein-based extensively hydrolyzed formula containing *Lacticaseibacillus rhamnosus* GG (LGG) for infants with either IgE or non-IgE-mediated CMA. The issued recommendations are labeled as "conditional" following the GRADE approach due to the very low certainty about the health effects based on the available evidence.

Conclusions: If breastfeeding is not available, clinicians, patients, and their family members might want to discuss all the potential desirable and undesirable consequences of each formula in infants with CMA, integrating them with the patients' and caregivers' values and preferences, local availability, and cost, before deciding on a treatment option. We also suggest what research is needed to determine with greater certainty which formulas are likely to be the most beneficial, cost-effective, and equitable.

Keywords: Milk allergy, Milk replacement formulas, Probiotics, Clinical practice guidelines, GRADE

SUMMARY OF RECOMMENDATIONS (EXECUTIVE SUMMARY)

The summary of the developed recommendations is provided in Table 1.

Background

The prevalence of cow's milk allergy (CMA) ranges approximately from less than 1%–7.5% in infants. Specialized formulas, either with or without probiotics have been used as a replacement dietary option for infants displaying symptoms of CMA when breastfeeding is not a viable option. Given the wide variety of commercial formulas, it is of great societal importance to balance the potential benefits and harms of choosing one in place of the other option.

Methods

The methods used to develop the Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guideline update by World Allergy Organization (WAO) have been described in a separate accompanying publication (Bognanni et al.[1] submitted). Briefly, we followed the Guidelines International Network (GIN)-McMaster Guideline Development Checklist going over multiple steps which occurred both sequentially and iteratively, including the guideline panel and systematic review team selection, agreeing on confict of interest (COI) management, generating and prioritizing the guidelines' questions, and based on that, the individual PICO questions for the systematic reviews. The reviews were either conducted *de novo* or by updating relevant pre-existing ones. The

evidence synthesis process to inform decision-making has been carried out under the direction of the McMaster University GRADE Centre with international collaborators. The guidelines panel employed best practices for guideline development, as recommended by the National Academy of Medicine and the GIN.[2-4] The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[5,6] was employed to critically appraise the certainty of the evidence (CoE) informing the recommendations on specialized formulas.

Interpretation of strong and conditional recommendations

The strength of a recommendation is defined either as strong ("the guideline panel recommends … "), or conditional ("the guideline panel suggests … "), with the following interpretation:[7]

Strong recommendation.

- For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation.

- For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with their values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy makers: Policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Assumed values and preferences

The guideline panel considered the following outcomes as critical for decision-making across all pairwise comparisons of formulas: acquisition of cow's milk tolerance; failure to thrive; epinephrine use; vomiting; diarrhea and wheezing. The following health outcomes were considered of critical importance for some of the pairwise comparisons: urticaria; change or discontinuation of formula due to lack of tolerance and Food Protein-Induced Enterocolitis Syndrome (FPIES). The development of eczema and its severity, as well as sensitization to administered formulas were regarded as important but not critical to decision-making. The guidelines' panel placed a high value on these outcomes when considering the interventions of interest, still, given the absence of formal research evidence exploring the values and preferences in the field of CMA, these decisions were solely based on the input and opinions by the different representatives of stakeholders in the WAO DRACMA guidelines panel.

Question 1: Which milk replacement formula should be used in infants with IgE-mediated CMA who are not being breastfed, and in what order?
This broader question entailed the comparison of 4 different interventions:
- extensively hydrolyzed formula (eHF-CM)
- amino acid formula (AAF)
- hydrolyzed rice formula (HRF)
- soy formula.

Recommendation 1:
When choosing a formula in infants with **IgE-mediated CMA** who are not being breastfed, we suggest an extensively hydrolyzed (cow's milk) formula or a hydrolyzed rice formula as the first option, an amino-acid formula as the second option, and a soy formula as the third option.
(Conditional recommendation based on very low certainty evidence about health effects)
Remarks
1. Children should not receive the formula to which they previously reacted.
2. A small proportion of children may react to extensively hydrolyzed formula or soy formula when receiving it for the first time (there is no information whether the same applies to hydrolyzed rice formula but there is also no information that it does not)

Question 2: Which milk replacement formula should be used in infants with non-IgE-mediated CMA who are not being breastfed, and in what order?
This broader question entailed the comparison of 4 different interventions:
- extensively hydrolyzed formula (eHF-CM)
- amino acid formula (AAF)
- hydrolyzed rice formula (HRF)
- soy formula.

Recommendation 2:
When choosing a formula in infants with **non-IgE-mediated CMA** who are not being breastfed, we suggest an extensively hydrolyzed (cow's milk) formula or hydrolyzed rice formula as the first option, amino-acid formula as the second option, and soy formula as the third option.
(Conditional recommendation based on very low certainty evidence about health effects)
Remarks
1) In settings where soy formula is a viable option, sensitization to soy should be considered in the decision-making process for managing patients known not to respond to an avoidance diet with eHF-CM (ie, children with FPIES or FPIAP).

Question 3: Should a formula with probiotics vs the same formula without probiotics be used for infants with IgE-mediated CMA?

Recommendation 3:
When choosing a formula with or without a probiotic for infants with **IgE-mediated CMA**, we suggest either a formula without a probiotic or eHF-CM containing *Lacticaseibacillus rhamnosus* (LGG).
(Conditional recommendation based on very low certainty evidence about health effects)
Remarks
1) While DRACMA does not endorse any specific commercial product, current research evidence is only available for extensively hydrolyzed casein formula with *Lacticaseibacillus rhamnosus* (formerly *Lactobacillus rhamnosus*). Other formulas for managing IgE-mediated CMA combined with other probiotics have not been studied.

2) For advice about using formulas without a probiotic see Recommendation 1 3) This recommendation does not apply to children without confirmed CMA.
Question 4: Should a formula with probiotics vs the same formula without probiotics be used for infants with non-IgE-mediated CMA?
Recommendation 4: When choosing a formula with or without a probiotic for infants with **non-IgE-mediated CMA**, we suggest either a formula without a probiotic or eHF-CM containing *Lacticaseibacillus rhamnosus* (LGG). *(Conditional recommendation based on very low certainty evidence about health effects)* **Remarks** 1) While DRACMA does not endorse any specific commercial product, at this moment research evidence is only available for extensively hydrolyzed casein formula supplemented with *Lacticaseibacillus rhamnosus* (LGG) or with L. casei CRL431/B. lactis Bb12 (currently there is no commercially available formula supplemented with L. casei CRL431/B. lactis Bb12). Other formulas used for managing non IgE-mediated CMA combined with other probiotics have not been studied. 2) For advice about using formulas without a probiotic see Recommendation 2. 3) This recommendation does not apply to children without confirmed CMA.

Table 1. Summary of the recommendations

Explanations and other considerations

The development of these recommendations accounted for additional factors such as cost, impact on health equity, acceptability by stakeholders, and feasibility of implementation. The panel observed that different availabilities of formulas across countries, together with different national reimbursement policies based on patient category and acceptability issues will be prime determinants influencing the choice of specialized formula. WAO will develop tools to aid the dissemination and implementation of the recommendations.

INTRODUCTION

Aim of these guidelines and their specific objectives

The aim of this document is to assess the current evidence and provide guidance on the use of specialized formulas with and without probiotics supplementation for individuals with CMA, both immunoglobulin E (IgE) and non-IgE mediated. These guidelines are meant to be from an international perspective, with a primary target audience consisting of allergy doctors, children with CMA, and their caregivers. The guidance hereby presented might also be beneficial for pediatricians, general practitioners, and allied health practitioners. This document could be used in the future as a blueprint for the development and implementation of locally adapted guidance, following the GRADE ADOLOPMENT process,[8] or other equivalent frameworks. Consistently with the GIN-McMaster guidance for guidelines development, our effort was also focused on identifying limitations in current literature, in order to assist future researchers to prioritize topics and study areas in need of further investigation.

This is the second of 3 documents presenting the recommendations of the World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) guidelines updated in 2021/2022/2023. Here we present the recommendations about the use of specialized formulas, with and without probiotics, for the dietary management of CMA, which replace the original WAO DRACMA guidance issued in 2010.[9]

Description of the health problem

Cow's milk allergy (CMA) is amongst the most common causes of food allergies for infants worldwide.[10–15] Generally, CMA affects between less than 1% and 7.5% of infants before 1 year of age,[13,14,16–20] with the disease prevalence being highly variable, depending on factors like age range, geographic location, breastfeeding history, and IgE/non-IgE status.[12–14,21,22] The majority of people with CMA naturally acquire tolerance by the age of 5 with a further increase in the rate of tolerance throughout childhood and adolescence.[15,23–26]

Cow's milk is a ubiquitous food worldwide and it is commonly consumed throughout early childhood irrespectively of the geographical location and local culture. This makes allergen avoidance, which is regarded as the current mainstay of CMA management,[27–29] particularly difficult. As a consequence, accidental exposure to milk is common, resulting in potentially severe health outcomes for sensitized individuals,[30,31] including anaphylaxis[32–34] and death.[35] While avoidance remains of paramount importance, given the highly nutritious properties of milk, especially during the early stages of life,[36] it may result in growth impairment[37] and a reduction in perceived quality of life. It follows that CMA management requires a fine balance between avoiding exposure to the allergen while ensuring an appropriate nutritional support. To this end, specialized milk formula of different types have been widely implemented into clinical practice, even though there is still uncertainty regarding which might be the optimal choice or in which order they should be considered for introduction into patients' diets.

Description of the interventions

Infants with CMA are sensitized to specific components of cow's milk proteins, most commonly whey and caseins. The specialized milk replacement formulas are meant to be hypoallergenic dietary options for these patients, as they are processed in a way to either almost completely lack the allergenic proteins or present them in peptide form, reducing the potential of eliciting an allergic reaction.[38] The hypo-allergenicity of these formulas is then tested through oral food challenges (OFC) in patients with CMA and observing for allergic reactions.[39] Currently, there are 4 major alternative specialized formula types used in CMA management.

Extensively hydrolyzed formula (eHF-CM) is the result of multiple manufacturing processes that thermally and enzymatically break down cow's milk allergenic proteins, followed by an ultrafiltration process to remove remaining proteins or large protein fragments. eHF-CMs are considered hypoallergenic but may still elicit allergic reactions in highly sensitive individuals. They can be based on whey protein, casein, or both.

Amino acid formula (AAF), also known as elemental formula, unlike eHF-CM is not derived from cow's milk and is composed of individual amino acids rather than proteins or peptides. The further reduction in allergenicity of the formula is of particular benefit for patients at high risk of severe allergic reactions, like anaphylaxis.

Soy formula (SF) is based on the proteins found in soybeans, hence containing neither the cow's milk-specific proteins nor lactose, making it a common replacement for patients with CMA. It is fortified with iron compounds to balance the inhibitory effect by soy proteins on iron absorption.[40] However, around 10% of CMA patients also develop an allergy to soy protein, which may lead to SF being an unsuitable replacement.[41]

Hydrolyzed rice formula (HRF) does not contain the relevant allergens found in cow's milk, and its rice proteins are hydrolyzed similarly to other processed cow's milk formulas (ie, eHF-CM or partially hydrolyzed cow's milk formula). Several

clinical trials concluded that HRF was safe in patients with CMA and soy protein allergy,[42,43] and no reactions to HRF have been reported in patients with CMA.

In a systematic review supporting these guidelines (Bognanni et al.[1], submitted) we found that, compared to AAF, eHF-CM could favor tolerance acquisition (risk ratio (RR) 2.32, 95% confidence interval (CI) 1.36 to 3.94; risk difference (RD) 25%, 95%CI 6%–44%), reduce severe vomiting (RR 0.12, 95%CI 0.02 to 0.88; RD -23%, 95%CI -26% to −3%), and decrease the risk of developing FPIES (RR 0.15, 95%CI 0.03 to 0.82; RD -34%, 95%CI -39% to −7%) for IgE CMA patients (very low CoE). On the other hand, eHF-CM might be inferior to AAF as a nutritional supplement, being associated with inferior growth rate both with respect to weight (−5.5% from baseline, 95%CI -9.5% to −1.5%) and length (−0.7 z-score change, 95%CI -1.15 to −0.25) (very low CoE). The review highlighted similar findings also for non-IgE mediated CMA patients. Very low certainty evidence showed that eHF-CM, compared to SF, might favor weight gain for IgE CMA infants (0.23 z-score change, 95%CI 0.01 to 0.45), and tolerance acquisition (RR 1.86, 95%CI 1.03 to 3.37; RD 27%, 95%CI 1%–74%) for non-IgE CMA (both very low CoE). eHF-CM compared to HRF, and HRF compared to SF, showed no significant difference in effect (very low CoE). Finally, the addition of probiotics appeared to potentially favor CMA tolerance (RR 2.47, 95%CI 1.03 to 5.93; RD 27%, 95%CI 1%–91%), and reduce the risk of severe wheezing (RR 0.12, 95%CI 0.02 to 0.95; RD -23%, 95%CI -8% to −0.4%) for IgE CMA patients (low CoE), while showing no effect in non-IgE CMA infants, (low to very low CoE).

We found no research evidence about the estimated direct and indirect costs of formulas either with or without probiotic supplementation. Based on the experience of panel members, the cost of formulas is likely to depend on the specific jurisdictions and local reimbursement policies.

METHODS

We developed these guidelines using GRADE methodology for guideline development, with the original systematic search being conducted on November 2018, and then updated on April 2020, March 2021, and September 2022. The recommendations were drafted, revised, and then finalized in June 2022. The members of the guidelines' panel as well as technical team provided additional input up to March 2023.

The assessment of the certainty in the body of evidence and the development of recommendations followed the GRADE approach.[5,6,44–47] The overall guideline-development process, including funding, panel selection, conflicIt of interest (COI) management, internal and external review, and organizational approval, was guided by WAO policies based on the GIN-McMaster Guideline Development Checklist (https://macgrade.mcmaster.ca/resources/gin-mcmaster-guideline-development-checklist/) as to uphold the criteria for trustworthy guidance by the National Academy of Medicine and GIN.[2–4]

Organization, panel composition, planning, and coordination

The development of these guidelines was carried out by: (a) a panel of 24 international key stakeholders, including patients with CMA, representatives of patient organizations, dieticians, primary care professionals, and specialists in pediatrics, allergy, and gastroenterology; and (b) a methodology team of 8 researchers with expertise

in conduction of systematic reviews and guideline development.

The synthesis and critical appraisal of the informing evidence, as well as the development of the recommendations, was conducted following the GRADE approach.

The panel co-chairs, AF (pediatrician and content expert) and HJS (internist and expert in guideline-development methodology), supervised the conduction of the project.

WAO vetted and appointed individuals to the guideline panel. The McMaster GRADE Centre vetted and retained researchers for conducting evidence syntheses to inform the recommendations based on the GRADE approach. The membership of the panel and the evidence synthesis team is described in Online Supplement 1.

The evidence synthesis team also supported the guideline-development process, including determining methods, preparing agendas, meeting materials, and facilitating panel discussions. The panel's work was conducted using Web-based tools: SurveyMonkey (www.surveymonkey.com), Google Forms (docs.google.com/forms/), and GRADEpro Guideline Development Tool (www.gradepro.org).[48] The panel discussed in 1 in-person meeting, and throughout subsequent online meetings. WAO staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Guideline funding and the management of competing interests

The conduction of these guidelines was funded by WAO and the McMaster University GRADE Centre. Direct funding by for-profit companies was not accepted. The guideline panel members received travel reimbursement for attendance at in-person meetings but received no other payments. The funding was also used as salary support for the information scientist running the original searches, and for research assistants and students conducting the systematic reviews. Some members of the method team who contributed to the systematic review conduction participated without remuneration to fulfill requirements of an academic degree or program.

COIs of all participants were managed according to WAO policies based on guidance by the National Academy of Medicine[2] and GIN[3]. Before commencing the project, all the participants were asked to disclose any financial and nonfinancial interests relevant to the guidelines by completing the World Health Organization (WHO) declaration of interest forms. An independent and anonymous WAO committee revised the disclosed interests looking for COIs.

The revision committee reviewed the forms and deliberated on including panel members aiming to achieve a diversity of expertise and perspectives, while minimizing the inclusion of panel members with the same or similar conflicts. Specifically, the committee placed a high value on addressing conflicts from direct financial interests from for-profit companies related to the guidelines' field. Throughout the guidelines' development, the members of the panel and method team were asked to update the interest disclosure forms, which were again revised by the WAO committee.

At the time of appointment, most of the guideline panel, including one of the guideline panel co-chair (HJS), had no conflicts of interest. The other co-chair (AF) was aware of economic support by for-profit entities provided to WAO in the form of educational grants; therefore, he abstained from voting on all recommendations in the DRACMA guidelines.

The method team members deemed to have a real, potential, or perceived conflict of interest related to the topic of a systematic review were excluded from partaking in that review. Likewise, guideline panel members with manageable real, potential, or perceived conflict of interest abstained from voting on recommendations related to that interest, while being still able to provide intellectual input and clinical expertise. The Evidence-to-Decision (EtD) tables for each recommendation list individuals who were excused from voting. One proposed panel member was found with disqualifying competing interests and was excluded from the DRACMA project entirely.

Selection of questions and outcomes of interest

Expanding on the previous DRACMA guidelines from 2010,[9] members of the guideline panel and methodology team collaboratively brainstormed potential questions to be addressed in these

guidelines. Using group discussion and online polling software (www.surveymonkey.com), we ranked the questions in terms of priority. The selected interventions and questions represent the top-prioritized issues identified by the group:

1 - Which milk replacement formula should be used in infants with IgE-mediated CMA who are not being breastfed, and in what order?

2 - Which milk replacement formula should be used in infants with non-IgE-mediated CMA who are not being breastfed, and in what order?

These 2 broader questions were assessed with 4 pairwise comparisons among formulas:

A) extensively hydrolyzed formula (eHF-CM) vs amino acid formula (AAF)

B) extensively hydrolyzed formula (eHF-CM) vs hydrolyzed rice formula (HRF)

C) extensively hydrolyzed formula (eHF-CM) vs soy formula (SF)

D) hydrolyzed rice formula (HRF) vs soy formula (SF)

3 - Should a formula with probiotics vs the same formula without probiotics be used for infants with IgE-mediated CMA?

4 - Should a formula with probiotics vs the same formula without probiotics be used for infants with non-IgE-mediated CMA?

The panel selected the outcomes of interest for each question *a priori*, as described in a separate paper. In summary, the panel brainstormed a preliminary list of outcomes based on previously published literature as well as their own expertise, focusing on patient important outcomes, aiming to address relevant domains to issue impactful guidance. The drafted outcomes have then been rated for their relative importance to decision-making following the GRADE approach. Specifically, each panel member was asked to rate the relative importance of the outcomes on a 1–9 scale. Outcomes with a median score between 7 and 9 were considered as critical to decision-making, while those with a median score between 4 and 6 were rated as important.[49]

The following outcomes were deemed critical to decision-making across all questions, irrespectively of the IgE status of CMA: acquisition of tolerance; failure to thrive; epinephrine use; vomiting; and diarrhea. Development of wheezing was considered critical to decision-making for questions on IgE-mediated CMA. Urticaria was listed as a relevant outcome only with respect to IgE-mediated CMA and considered critical when comparing eHF-CM vs AAF, while it was regarded as important across the other pairwise comparisons. Change or discontinuation of formula due to lack of tolerance, and FPIES were considered critical when comparing eHF-CM vs HRF and eHF-CM vs AAF respectively, while being important for

other comparisons independently of IgE mediation. The development of eczema and its severity, as well as sensitization to administered formulas were regarded as important but not critical to decision-making across the compared formulas, both for IgE and non-IgE-mediated CMA.

Evidence review and development of recommendations

For each guideline question, the method team prepared an evidence profile (EP)[50,51] and a GRADE evidence-to-decision (EtD) table[44,45] using the GRADEpro software. For questions 1 and 2, the usual EtD was modified as suggested in the paper from Piggott et al[52] to allow for the comparison of multiple interventions. The EtD tables illustrate the evidence about the effects of interventions on health outcomes, based on the results from a systematic review of the literature, the values and preferences (ie, relative importance of outcomes), resource utilization (cost-effectiveness), health equity issues, acceptability of interventions to stakeholders, and the feasibility of implementation. The EtD for multiple comparisons used for questions 1 and 2 expressed the balance of health effects with a star-based system, ranging from 1 star (lowest score) to 5 stars (highest score). The score of each formula was influenced by the size of the overall balance of health effects across the pairwise comparisons between formulas, as well as the certainty of the evidence informing the effect estimates on health outcomes.

The panel revised the drafted EtD tables before and during the guideline meetings providing feedback for corrections and clarifications. In order to avoid missing recently published evidence we updated the searches in April 2020, March 2021, and September 2022. Furthermore, we asked panel members to review the identified evidence for completeness and, if necessary, suggest any additional studies eligible for inclusion.

The method team developed and reported the systematic review in accordance with PRISMA, GRADE, and Cochrane standards.[6,53–55] When existing reviews were used, the original judgments of risk of bias (RoB) were either checked for accuracy or conducted de novo if they were not available or not reproducible. For newly conducted reviews, the RoB was assessed per individual study and outcome using Cochrane RoB 2.0 tool for randomized trials[56] and the Newcastle-Ottawa scale for nonrandomized studies.[57] We appraised the certainty in the body of evidence about the health effects (also known as quality of the evidence or confidence in the estimated effects) for each outcome following GRADE guidance. In brief, we assessed the following domains: risk of bias, imprecision, inconsistency, indirectness, publication bias, presence of large effects, dose-effect relationship, and an assessment of the effect of plausible residual and opposing confounding.[58–63] The judgments for each GRADE domain were accounted together at outcome level, leading to a CoE rating ranging from to very low to high.[64]

Over the course of 3 four-hour online meetings and GRADEpro iterations followed by mail correspondence, the panel developed recommendations based on the evidence summarized and illustrated in the EtD tables. For each recommendation, the panel took a population perspective and iteratively reached an agreement with respect to these domains: the certainty in the evidence, the balance of benefits and harms between the compared interventions, and the assumptions about the values and preferences, resource use associated with the investigated options, potential impact on health equity, acceptability to stakeholders, and interventions' feasibility. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation). All members of the panel reviewed and approved the final guidelines.

Interpretation of strong and conditional recommendations

The issued recommendations are defined either as "strong" or "conditional" following GRADE guidance. The wording "the guideline panel recommends" is employed for strong recommendations, while "the guideline panel suggests" for conditional recommendations. Table 2 illustrates how to interpret GRADE strength of recommendations from the perspective of patients, clinicians, health care policy makers, and researchers.

Implications for:	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	• The majority of individuals in this situation would want the suggested course of action, but many would not. • Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
Clinicians	• Most individuals should follow the recommended course of action. • Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	• Clinicians should acknowledge that different choices will be appropriate for individual patients and must help each patient arrive at a management decision consistent with his or her values and preferences. • Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
Policy makers	• The recommendation can be adopted as policy in most situations. • Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	• Policymaking will require substantial debate and involvement of various stakeholders. • Performance measures should assess whether decision-making is appropriate.
Researchers	• The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation • On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.	• The recommendation is likely to be strengthened (for future updates or adaptation) by additional research. • An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong). The recommendation will help identify possible research gaps

Table 2. Interpretation of strong and conditional recommendations

Document review

The draft recommendations and guideline paper were reviewed by all members of the guideline panel and evidence synthesis team. The document was then submitted to the World Allergy Organization Journal for peer review. All comments by the editor and reviewers were addressed, but no changes were made to the recommendations.

HOW TO USE THESE GUIDELINES

Terminology

In this document we use the term "formula supplements" interchangeably with "milk replacement formulas", "specialized formulas", or "formulas" alone, referring to any of the 4 considered interventions: eHF-CM, AAF, HRF, SF. The term eHF-CM is used to refer to both casein and whey-based formulas unless specifically stated. Furthermore, casein and whey based eHF-CMs have been regarded as a single intervention due unanticipated difference in treatment effects. HRF is sometimes referred to only as rice formula. Unless we specifically mentioned a bacterial/yeast strain (ie, *Lacticaseibacillus rhamnosus*) the term "probiotics" refers to the general addition of live bacteria or yeasts to specialized formulas. Notably, probiotics are different from "prebiotics" as they consist of specialized plant fibers that

work by stimulating the growth of pre-existing microbial populations rather than introducing novel micro-organisms. Lastly, synbiotics refer to a mixture of probiotics and prebiotics and are not subject of these guidelines. We are referring to milk avoidance both as elimination diet and avoidance diet. We use the word "people" or "individuals" whenever we mean both children and adults. Whenever CMA is mentioned without specifying the IgE/non-IgE status, it is referring to both. Finally, unless specified, the term "milk" is used throughout the document to refer to cow's milk only. The different formulas are presented in the recommendations as ranked options (eg, first option, second option etc.). This approach is not meant to resemble a step-wise use of the interventions (first option fails, then the second is administered) rather it suggests in which order specialized formulas should be considered for clinical management.

Intended use

These WAO DRACMA guidelines are primarily intended to help clinicians make decisions about treatment alternatives for elimination diet. They may also be used by patients to facilitate shared decision-making with their treating physicians. Other objectives are to inform health policies, reimbursement strategies, education, and advocacy, as well as to define relevant research needs in the field of allergy.

These guidelines are not meant to serve or to be perceived as a standard of care. Decision-makers should not treat the recommendations in these guidelines as binding mandates. No recommendation can take into account all the variable circumstances that might affect the potential benefits, harms, and burdens of an intervention in individual patients or in a given clinical setting. Clinicians must make decisions based on the clinical presentation of each patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen management option. Clinicians' and patients' decisions may also be constrained by the realities of a specific clinical setting and local resources, including, but not limited to, institutional policies, time limitations, and availability of treatments. Thus, no one charged with overseeing or evaluating the actions of clinicians should apply the recommendations by rote or in a blanket fashion.

These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. WAO does not warrant or guarantee any products described in these guidelines.

Statements regarding the stakeholders' values and preferences, and the qualifying remarks associated with each recommendation, are its integral parts and serve to promote a more accurate interpretation and facilitate an optimal implementation. The users of this document must be aware that the guideline recommendations may change in future updates as new evidence becomes available. WAO plans on periodically reviewing the literature and engaging with clinical experts as well with other relevant stakeholders to determine whether an update will be necessary. The timescale and the development of such updates will be made available to users through online portal notifications as well as in form of publications by the *World Allergy Organization Journal* (*WAO Journal*).

Translation and quoting

When quoting or translating any of the recommendations from these guidelines, any qualifying remarks that accompany each recommendation should not be omitted (including statements regarding special circumstances, relevant subgroups, and assumed values and preferences).

SUMMARY OF FINDINGS AND RECOMMENDATIONS

Question 1

Which milk replacement formula should be used in infants with IgE-mediated CMA who are not being breastfed, and in what order?

Summary of the evidence, benefits, and harms

The evidence profiles and the EtD tables for this question **(**Online Supplements 2-5, 12**)** report detailed information on the estimated health effects in children with IgE mediated CMA by

different formula options, compared amongst each other, on the outcomes of interest, together with the additional considerations relevant for decision making. The evidence informing the benefits, harms and the balance of health effects comes from a systematic review we conducted and published separately.

Our review found very low certainty evidence that eHF-CM could favor achieving CMA tolerance compared to AAF (RR 2.32, 95%CI 1.36 to 3.94; RD 25%, 95%CI 6%–44%), while eHF-CM vs HRF (RR 1.2, 95%CI 0.76 to 1.88; RD 9%, 95%CI -11%–39%), eHF-CM vs SF (RR 0.96, 95%CI 0.63 to 1.46; RD -2%, 95%CI -16%–20%), and HRF vs SF (RR 1.11, 95%CI 0.88 to 1.39; RD 5%, 95%CI -5%–17%) showed no appreciable difference in effect.

We also found that eHF-CM might be inferior to AAF on supporting growth with respect to weight (−5.5% from baseline, 95%CI -9.5% to −1.5%) and length (−0.7 z-score change, 95%CI -1.15 to −0.25), while favoring weight gain (0.23 z-score change, 95%CI 0.01 to 0.45) with no apparent effect on length (0.27 z-score change, 95%CI -0.19 to 0.73) when compared to SF (very low CoE). The review showed no difference on weight or length when comparing eHF-CM vs HRF (weight: 0.04 z-score change, 95%CI -0.53 to 0.45; length: 0.33 z-score change, 95%CI -0.13 to 0.79), and HRF vs SF (weight: 0.25 z-score change, 95%CI -0.11 to 0.60; length: 0.01 z-score change, 95%CI -0.37 to 0.39) (all very low CoE). eHF-CM and AAF appeared to have similar effect with respect to requiring epinephrine because of allergic reactions (RR 0.56, 95%CI 0.24 to 1.29; RD -4%, 95%CI -7%–3%) (very low CoE). Compared to AAF, eHF-CM might reduce the risk of vomiting (RR 0.12, 95%CI 0.02 to 0.88; RD -23%, 95%CI -26% to −3%), while showing no effect on the probability of developing diarrhea (RR 1.41, 95%CI 0.89 to 2.22; RD 19%, 95%CI -5%–57%) (very low CoE).

None of the formulas showed a difference in effect on the risk of experiencing wheezing [eHF-CM vs AAF and eHF-CM vs HRF (RR 1.05, 95%CI 0.61 to 1.80; RD 1%, 95%CI -10%–21%); eHF-CM vs SF (RR 0.95, 95%CI 0.57 to 1.60; RD -1%, 95%CI -12%–17%); HRF vs SF (RR 0.90, 95%CI 0.53 to 1.54; RD -3%, 95%CI -14%–16%)] and urticaria eHF-CM vs AAF (RR 0.76, 95%CI 0.43 to 1.34; RD -7%, 95%CI -16%–10%); eHF-CM vs HRF (RR 0.80, 95% CI 0.45 to 1.42; RD -5%, 95%CI -15%–12%); eHF-CM vs SF (RR 0.89, 95%CI 0.49 to 1.60; RD -3%, 95%CI -13%–15%); HRF vs SF (RR 1.11, 95%CI 0.64 to 1.92; RD 3%, 95%CI -9%–23%)] (all very low CoE). Based on the review, we also noticed no difference on the risk of developing eczema across the investigated formulas: eHF-CM vs AAF (RR 0.70, 95%CI 0.44 to 1.10; RD -12%, 95%CI -23%–4%); eHF-CM vs HRF (RR 0.91, 95%CI 0.56 to 1.50; RD -3%, 95%CI -14%–16%); eHF-CM vs SF (RR 0.83, 95%CI 0.58 to 1.20; RD -7%, 95%CI -17%–8%); HRF vs SF (RR 0.85, 95%CI 0.54 to 1.34; RD -6%, 95%CI -17%–13%) (all very low CoE). The trials[65-67] comparing eHF-CM and AAF measured the change severity using SCORAD, exhibiting no difference in effect (MID 8 points) (MD 1.39 points, 95%CI -1.08 to 3.86 points) (low CoE). eHF-CM might reduce the risk of FPIES, compared with AAF (RR 0.15, 95% CI: 0.03 to 0.82; RD -34%, 95%CI -39% to −7%), while it showed no difference compared to SF (RR 1.57, 95% CI: 0.08 to 30.32; RD 6%, 95%CI -9%–21%) (very low CoE).

The analyses showed that eHF-CM, compared to AAF might increase the risk of sensitization to administered formula (RR 5.44, 95% CI: 0.33 to 89.0; RD 38%, 95%CI -0.1%–75%), while eHF-CM vs SF and HRF vs SF showed no difference (RR 0.15, 95% CI: 0.01 to 2.82; RD -7%, 95%CI -8%–15%; same for both pairwise comparisons) (very low CoE). We found no difference across the formulas with respect to the risk of AEs that would lead either to discontinuation or change of formula: eHF-CM vs AAF (RR 2.47, 95%CI 0.0 to14275.0; RD not estimable); eHF-CM vs HRF (RR 0.69, 95%CI 0.21 to 2.22; RD -5%, 95%CI -13%–20%); eHF-CM vs SF (RR 0.86, 95%CI 0.38 to 1.96; RD -2%, 95%CI -9%–13%); HRF vs SF (RR 1.27, 95%CI 0.43 to 3.78; RD 3%, 95%CI -6%–31%) (very low CoE).

Other decision criteria and considerations

The panel members acknowledged the absence of any formal research investigating values and preferences regarding the identified health outcomes. Despite this, the panelists, based on their expertise, agreed that probably there is no major uncertainty or variability in the relative importance placed by stakeholders on these outcomes. The panel agreed that higher values are placed on the possibility of achieving tolerance to milk and

favoring physiological growth, on one side, while minimizing the risk of severe allergic reactions such as wheezing, urticaria, and gastrointestinal reactions on the other.

The panelists agreed that the major acceptability and equity issues concerning the choice of a formula relate to the local availability of particular formulas, their cost, and the reimbursement policies in different jurisdictions (eg, countries, regions, insurance plans). Specifically, cost was considered to be an important equity and acceptability issue for AAF (usually the most expensive), eHF-CM and HRF (both cheaper than AAF but still expensive in many jurisdictions), while fewer concerns were raised for SF, which usually is the most affordable formula. We list potential implementation issues below (see 4.1.6.). We provide the detailed considerations of values and preferences, acceptability of interventions, feasibility of implementation, and required resources in the Evidence-to-Decision table in the Online Supplement 12.

Conclusions for this recommendation

Based on the best estimates of the health effects observed in the existing studies and in the panel members' clinical practice, the panel members thought that balance of health effects favors eHF-CM, followed by AAF and HRF, compared with SF. However, panel members acknowledged that given the very low certainty in the evidence, and the likely small differences in health effects, the overall balance of desirable and undesirable effects (including but not limited to health effects) will likely depend on individual patient's factors like the severity of disease, tolerance and palatability of the specific formula, caregiver acceptance of potential adverse effects, and the experience of the healthcare provider. The local availability of formulas and their out-of-the-pocket cost to families, accounting for the local reimbursement policies, will also be major determinants of the choice of a formula.

Considering these points, the panel suggested that an individualized decision would be warranted in each case, after appropriately informing the patient's caregiver of every option. The discussion between the patient caregiver and health care provider should cover the relative health benefits of using different formulas, local availability of formulas, and local reimbursement policies based on the severity of the disease that may vary among formulas.

Recommendation 1

When choosing a formula in infants with **IgE-mediated CMA** who are not being breastfed, we suggest an extensively hydrolyzed (cow's milk) formula or hydrolyzed rice formula as the first option, amino-acid formula as the second option, and soy formula as the third option.

(Conditional recommendation based on very low certainty evidence about health effects).

Remarks

1. Children should not receive a formula to which they previously reacted.
2. A small proportion of children may react to extensively hydrolyzed formula or soy formula when receiving it for the first time (there is no information whether the same applies to hydrolyzed rice formula but there is also no information that it does not).

Implementation considerations

When choosing a formula parents and clinicians may find the following acceptability issues worth considering:

- **Extensively hydrolyzed formula:** some parents may find other formulas more acceptable, because they do not contain animal proteins (eg, those who prefer vegan diet)
- **Amino-acid formula:** some parents and/or clinicians may prefer amino-acid formula because it contains no milk or other animal proteins; some parents are concerned about "green stools" or "bad smell" in infants fed with amino-acid formula
- **Hydrolyzed rice formula:** some parents and/or clinicians may prefer rice formula because it contains no milk and no animal proteins.
- **Soy formula:** Some parents may still be concerned about adverse effects of phytoestrogens in soy formula, despite research evidence that it is not a concern; in some countries parents may prefer soy formula, because soy is one of the main foods in their diet.

Implications for further research

When going through the decision-making process and revising the evidence, the panel identified the following priorities for future research endeavors:

A) Qualitative studies specifically investigating the values and preferences by patients, and their families and caregivers, as well as other stakeholders, on the use of specialized milk formulas, focusing on the relative value placed by each category on specific benefits and harms.

B) More and methodologically rigorous large randomized controlled trials (RCTs) should be conducted focusing on: a) including patients with moderate/severe CMA as well as undefined forms of CMA (ie, eosinophilic esophagitis [EoE]); b) identifying and reporting the disease status as IgE or non-IgE mediated with related stratified results; c) standardizing doses and administration modalities of formulas so to minimize inconsistency across studies due to differences in the interventions; d) comparing a wider range of available management options, possibly by having more than 2 parallel arms; e) investigate secondary sensitization to specialized formulas.

C) Measurement and reporting of patient-important outcomes should be improved by prioritizing, if possible, continuous or time-to-event outcomes rather than binary ones (especially for eczema) and providing separate results based on IgE/non-IgE status.

D) Additional, rigorous economic evaluations should investigate the cost-effectiveness/cost-utility as well as general resource requirements for specialized formulas from an international healthcare perspective.

Question 2

Which milk replacement formula should be used in infants with non-IgE-mediated CMA who are not being breastfed, and in what order?

Summary of the evidence, benefits, and harms

The EPs and the EtD tables for this question **(Online Supplements 6–9, 13)** illustrate the fully synthesized information on the effect estimates by different formulas in children with non-IgE mediated CMA.

We found very low certainty evidence that eHF-CM, compared to SF, might increase the probability of acquiring tolerance (RR 1.86, 95%CI 1.03 to 3.37; RD 27%, 95%CI 1%–74%), while having no effect compared to AAF (RR 1.84, 95%CI 0.89 to 3.80; RD 27%, 95%CI -3%–88%), or HRF (RR 1.03, 95%CI 0.64 to 1.64; RD 2%, 95%CI -20%–36%). Also HRF and SF appear to have similar effects (RR 1.81, 95%CI 0.97 to 3.38; RD 25%, 95%CI -1%–74%).

If compared to AAF, eHF-CM appeared to possibly induce a reduction in weight (−5.5% from baseline, 95%CI -9.5% to −1.5%) and length (−0.7 z-score change, 95%CI -1.15 to −0.25), while showing no effect on weight gain compared to SF (0.19 z-score change, 95%CI -0.07 to 0.45) (very low CoE). Then HRF vs SF showed no relative effect on weight or length (weight: 0.07 z-score change, 95%CI -0.47 to 0.61; length: 0.25 z-score change, 95%CI -0.57 to 1.07) (very low CoE). Also in children with non-IgE mediated CMA, eHF-CM appeared equal to AAF at avoiding reactions requiring epinephrine use (RR 0.56, 95%CI 0.24 to 1.29; RD -4%, 95%CI -7%–3%) (very low CoE) and preventing diarrhea (RR 1.41, 95%CI 0.89 to 2.22; RD 19%, 95%CI -5%–57%), while reducing the risk

of vomiting (RR 0.12, 95%CI 0.02 to 0.88; RD -23%, 95%CI -26% to −3%) (all very low CoE).

The analyses showed no difference when comparing eHF-CM with AAF measuring eczema severity with SCORAD scale (MD 1.39 points, 95% CI -1.08 to 3.86 points) (low CoE), and with SF (RR 0.93, 95% CI: 0.52 to 1.68; RD -4%, 95%CI -29%–41%) (very low CoE).

Very low certainty evidence suggested that eHF-CM might reduce the risk of developing FPIES when compared with AAF (RR 0.15, 95% CI: 0.03 to 0.82; RD -34%, 95%CI -39% to −7%), while it showed no difference compared to SF (RR 1.57, 95% CI: 0.08 to 30.32; RD 6%, 95%CI -9%–21%). We found that eHF-CM, compared to AAF, might increase the risk of sensitization (RR 5.44, 95% CI: 0.33 to 89.0; RD 38%, 95%CI -0.1%–75%) (very low CoE), while very low certainty evidence suggested that none of the investigated formulas had a relative effect with respect to the risk of reactions leading to discontinuation or change of supplement: eHF-CM vs AAF (RR 2.47, 95%CI 0.0 to 14275.0; RD not estimable); eHF-CM vs SF (RR 0.61, 95%CI 0.09 to 4.17; RD -5%, 95%CI -1%–40%) (very low CoE).

Other decision criteria and considerations

Panel members thought that the additional considerations (ie, other that direct health effects) for the choice of a formula in infants with non-IgE-mediated CMA would be similar or the same as for children with IgE-mediated CMA (see 4.1.2.-4.1.3., 4.1.6.).

We provide detailed considerations of values and preferences, acceptability of interventions, feasibility of implementation, and required resources in the EtD table in the Online Supplement 13.

Conclusions for this recommendation

The panel members thought that the overall balance of effects favors eHF-CM, first, and then equally AAF and HRF, compared to SF. However, given the very low certainty in the evidence, and the small difference in effects, they acknowledged that the balance will likely be dependent on individual patient factors like the severity of disease, tolerance and palatability of the formula, caregiver acceptance of potential adverse effects, and the experience of the healthcare provider.

Therefore, like for patients with IgE-mediated CMA, an individualized approach is suggested based on a thoughtful shared decision between the healthcare provider and patient.

Recommendation 2

When choosing a formula in infants with **non-IgE-mediated CMA** who are not being breastfed, we suggest an extensively hydrolyzed (cow's milk) formula or hydrolyzed rice formula as the first option, amino-acid formula as the second option, and soy formula as the third option.

(Conditional recommendation based on very low certainty evidence about health effects).

Remarks

In countries where SF is a viable option, sensitization to soy should be considered in the decision-making process for managing patients known not to respond to an avoidance diet with eHF-CM (ie, children with FPIES or FPIAP).

Subgroup considerations

- In infants with **eosinophilic esophagitis** (EoE) evidence is only available for amino-acid formula. Panel members agreed that in infants with EoE it might be beneficial to avoid using other formulas (ie, extensively hydrolyzed formula, hydrolyzed rice formula, and soy formula) until more evidence about their effects is available. They also agreed that if amino-acid formula is not available then hydrolyzed rice formula could be the second option.
- In infants with milk or rice-related **food protein-induced enterocolitis syndrome** (FPIES) or in whom tolerance of rice is unknown, panel members agreed that it is more beneficial not to use hydrolyzed rice formula until more evidence is available.

Implementation considerations

When choosing a formula for children with non-IgE CMA parents and clinicians may consider the same implementation issues related to the use for children with IgE-mediated CMA (see 4.1.6).

Implications for further research

The panel agreed that the implications for future research in the setting of IgE-mediated CMA apply also to the setting of non-IgE-mediated CMA (see 4.1.7).

In addition, the panelists argued that future research should prioritize the conduction of well-designed and executed trials with a focus on: a) investigating eHF-CM vs AAF for EoE and other well-defined forms of the non-IgE-mediated CMA, including FPIES; b) head-to-head comparison of HRF with other formulas, given the little evidence found on this intervention.

Question 3

Should a formula with probiotics vs the same formula without probiotics be used for infants with IgE-mediated CMA?

Summary of evidence, benefits, and harms

The EP and the EtD table for this question **(Online Supplements 10, 14)** illustrate the evidence on the effect by adding probiotics to formulas in children with IgE-mediated CMA.

Based on our review, the addition of probiotics to extensively hydrolyzed casein formula, compared to eHF-CM alone, might favor tolerance acquisition (RR 2.47, 95%CI 1.03 to 5.93; RD 27%, 95%CI 1%–91%) (low CoE), and reduce the risk of developing wheezing (RR 0.12, 95%CI 0.02 to 0.95; RD -7%, 95%CI -8% to −0.4%) (very low CoE). On the other hand, adding probiotics showed no effect on the probability of requiring epinephrine because of allergic reactions (RR 0.33, 95%CI 0.04 to 2.62; RD -3%, 95%CI -5%–8%) (very low CoE), experiencing severe urticaria (RR 0.97, 95%CI 0.14 to 6.74; RD -0.1%, 95%CI -2%–12%) (very low CoE), changing formula due to adverse reactions (RR 0.77, 95%CI 0.26 to 2.28; RD 2%, 95%CI -7%–11%) (very low CoE) or developing eczema (RR 0.16, 95% CI: 0.02 to 1.32; RD -5%, 95%CI -6%–2%) (low CoE). Additional evidence on the effect of probiotics addition on the risk and severity of eczema could not be quantitatively synthesized and is available in the Online Supplement 11.

Other decision criteria and considerations

Panel members thought that, in most children with IgE CMA, the additional considerations (ie, other that direct health effects) for the choice of a formula with added probiotic would be similar as for the formula without a probiotic (see 4.1.2.-4.1.3., 4.1.6.). However, the panelists observed that caregivers of children with severe comorbidities (see 4.3.6. Subgroup considerations) may place a higher value on avoiding possible adverse effects related to the addition of probiotics to standard formulas, making the combination less acceptable. The panelists agreed that, as long as the out-of-the-pocket cost of a formula with or without an added probiotic would be similar, the addition of probiotics to a formula would not further influence the acceptability or equity related to these interventions.

We provide the detailed considerations of values and preferences, acceptability of interventions, feasibility of implementation, and required resources in the Evidence-to-Decision table in the Online Supplement 14.

Conclusions for this recommendation

Panel members thought that the balance of health effects favored neither the addition of probiotics or formulas alone. Given that the evidence was of very low certainty, they acknowledged the difficulty in choosing one intervention over the other and making a definite recommendation. Future evidence, if available, will likely influence the direction and/or strength of this recommendation. The panel argued that immunodeficient patients might be at higher risk of adverse effects related to the addition of probiotics, yet no studies investigated this population in detail.

Recommendation 3

When choosing a formula with or without a probiotic for infants with IgE-mediated CMA, we suggest either a formula without a probiotic or casein-based eHF-CM containing *Lacticaseibacillus rhamnosus* (LGG).

(Conditional recommendation based on very low certainty evidence about health effects).

Remarks

1) While DRACMA does not endorse any specific commercial product, current evidence is only available for extensively hydrolyzed casein formula with *Lacticaseibacillus rhamnosus* (LGG) (formerly *Lactobacillus rhamnosus*), while other

formulas used for the treatment of IgE-mediated CMA combined with other probiotics have not been studied.

2) For advice about using formulas without a probiotic see **Recommendation 1**

3) This recommendation applies only to the choice of a formula in children with confirmed CMA. It does not apply to children in whom the formula is considered for other reasons than confirmed CMA.

Subgroup considerations

Children affected by primary or acquired immunodeficiencies might be at higher risk of bacterial overgrowth following probiotic administration, yet there is no published evidence about this population. The studies used for evidence synthesis excluded children with a history of anaphylaxis due to CM and children with chronic conditions (food protein-induced enterocolitis syndrome, other food allergies and allergic diseases, eosinophilic disorders of the gastrointestinal tract, chronic systemic diseases, active tuberculosis, autoimmune diseases, immunodeficiency, chronic inflammatory bowel diseases, metabolic diseases, malignancy, chronic pulmonary diseases, malformations of the gastrointestinal and/or respiratory tract). Considering this, it is unclear how these populations would react to the addition of a probiotic.

Implementation considerations

When evaluating the addition of probiotics to specialized formulas for children with IgE-mediated CMA, clinicians and patients' families should consider all implementation issues associated with formulas alone for IgE CMA (see 4.1.6.)

Implications for further research

The general implications described for the use of formulas in children with IgE CMA apply also here. In addition, the panel members stressed the importance of conducting more high-quality large RCTs using a wider combination of formulas and probiotics so that future guidance will cover a more comprehensive array of management options.

Question 4

Should a formula with probiotics vs the same formula without probiotics be used for infants with non-IgE-mediated CMA?

Summary of evidence, benefits, and harms

The evidence on the effect of formulas with probiotics vs formulas alone in non-IgE-CMA, together with additional considerations relevant to decision-making, are summarized in a dedicated EP and EtD table (Online Supplements 11, 15).

The addition of probiotics appeared to have no effect, compared to formulas alone, in inducing tolerance to milk (RR 1.32, 95%CI 0.70 to 2.52; RD 24%, 95%CI -22%–100%), improving growth rate (weight: 0.1 kg, 95%CI -0.34 to 0.54; length: 0.2 cm, 95%CI -1.07 to 1.47), reducing the need for epinephrine injections (RR 0.33, 95%CI 0.04 to 2.62; RD -3%, 95%CI -5%–8%), or changing formulas due to AE RR 0.77, 95%CI 0.26 to 2.28; RD 2%, 95%CI -7%–11%) (all very low CoE).

Furthermore, we found that adding probiotics showed no effect on reducing the risk of developing eczema (RR 0.68, 95% CI: 0.20 to 2.28), or its severity (MD -0.71 points, 95% CI: 4.07 to 2.66 points; measured as change from baseline), (MD -1.48, 95% CI: 4.59 to 1.64; measured as end-of-study value) (low CoE).

Other decision criteria and considerations

Panel members thought that, in most children with non-IgE CMA, the additional considerations (ie, other that direct health effects) for the choice of a formula with added probiotic would be similar as for the formula without a probiotic (see 4.2.2.-4.2.3., 4.2.6.). Furthermore, the same additional considerations on cost, acceptability, and equity related to the addition of probiotics in managing IgE-mediated CMA apply here (see 4.3.2.). However, the panelists observed that caregivers of children with severe comorbidities (see 4.4.6. Subgroup considerations) may place a higher value on avoiding possible adverse effects related to the addition of probiotics to standard formulas, making the combination less acceptable. The panelists agreed that, as long as the out-of-the-

pocket cost of a formula with or without an added probiotic would be similar, the addition of probiotics to a formula would not further influence the acceptability or equity related to these interventions.

We provide the detailed considerations of values and preferences, acceptability of interventions, feasibility of implementation, and required resources in the Evidence-to-Decision table in the Online Supplement 15.

Conclusions for this recommendation

Panel members observed that the very low certainty evidence on the balance of health effects, together with other EtD criteria did not allow to clearly favor one intervention over the other, therefore, future evidence, if available, will likely influence the direction and/or strength of this recommendation. Also in this case, the panel argued that patients with immunodeficiencies might be at greater risk of adverse effects due to the addition of probiotics, still, no current scientific evidence investigates this subpopulation.

Recommendation 4

When choosing a formula with or without a probiotic for infants with non-IgE-mediated CMA, we suggest either a formula without a probiotic or casein-based eHF-CM containing *Lacticaseibacillus rhamnosus* (LGG).

(Conditional recommendation based on very low certainty evidence about health effects).

Remarks

1) While WAO DRACMA does not endorse any specific commercial product, at this moment research evidence is only available for extensively hydrolyzed casein formula with *Lacticaseibacillus rhamnosus* (LGG; formerly *Lactobacillus rhamnosus*) or with L. casei CRL431/B. lactis Bb12. However, currently, there is no commercially available formula supplemented with L. casei CRL431/B. lactis Bb12.
2) For advice about using formulas without a probiotic see Recommendation 2.
3) This recommendation applies only to the choice of a formula in children with confirmed CMA. It does not apply to children in whom the formula is considered for other reasons than confirmed CMA.

Subgroup considerations

The studies included for evidence synthesis excluded children with a history of anaphylaxis due to CM and children with chronic conditions (food protein-induced enterocolitis syndrome, other food allergies and allergic diseases, eosinophilic disorders of the gastrointestinal tract, chronic systemic diseases, active tuberculosis, autoimmune diseases, immunodeficiency, chronic inflammatory bowel diseases, metabolic diseases, malignancy, chronic pulmonary diseases, malformations of the gastrointestinal and/or respiratory tract). Considering this, it is unclear how these populations would react to the addition of a probiotic.

Implications for further research

The same implications for future research illustrated for the addition of probiotics in IgE-mediated CMA (see 4.3.8) apply here.

STRENGTHS AND LIMITATIONS OF THESE GUIDELINES

The recommendations in these guidelines may help support informed decision-making by clinicians, as well as individuals with CMA and their caregivers. The strength of these guidelines lies in the diverse, international guideline panel including clinicians treating CMA, researchers, and patients with CMA themselves, who provided nuanced and insightful perspectives on the topic, as well as employment of rigorous methods in performing the systematic reviews of available evidence and followed the systematic GRADE approach to develop recommendations.

However, we would like to stress that the evidence informing these guidelines itself has important limitations and allows only very low certainty about the relative health effects of different formulas. Despite those limitations, in order to help clinicians and families of children with CMA the panel provided specific recommendations based on the available research evidence and the observations in the guideline panel members' practice. All recommendations are labeled as conditional which implies that there is considerable uncertainty about the choice of the best formula and that it may depend on various additional considerations such as the severity of CMA, possible coexisting clinical conditions, local availability of specific formulas, and their cost.

An important limitation of the available evidence is that most studies focused on a single outcome of the time to outgrowing the CMA. No study investigated the overall quality of life of either the patients or their caregivers that might provide information about the effects of the choice of a formula not captured by measuring only the symptoms of CMA and selected adverse effects. Several of the outcomes selected by the guideline panel as critical to the decision about the choice of a formula were either not measured or not reported in the published studies, or lacked direct evidence for some of the pairwise comparisons of formulas. These outcomes included: failure to thrive, severe vomiting, severe diarrhea, abdominal pain or cramping, discontinuation or change of formula due to lack of tolerance, admission to hospital, intensive care unit or an emergency department visit, anaphylactic shock, epinephrine (adrenaline) administration, laryngeal edema, severe asthma or shortness of breath, severe tongue edema, IgE-mediated reaction to protein in the formula, severe dehydration with hypotension or shock, lethargy, moderate to severe irritability (colic), development of eosinophilic esophagitis, resolution of symptoms of eosinophilic esophagitis, and the development of FPIES, enteropathy, enterocolitis, or proctocolitis.

Therefore, the guideline panel provided specific suggestions for further research needs for each recommendation. We are confident that the findings of future well designed and executed studies measuring and transparently reporting important outcomes will change the confidence in the effects of various formulas in CMA and may change the recommendations in these guidelines and make them more specific.

WHAT OTHERS ARE SAYING AND WHAT IS NEW IN THESE WAO GUIDELINES

The latest Australian Society of Clinical Immunology and Allergy (ASCIA) guidelines were updated in 2023.[68] They provided up to 3 choices of formulas based on the severity of the cow's milk allergy, with the second and third options being suggested in case the previous was not tolerated. Specifically, for IgE CMA with no history of anaphylaxis, they recommended eHF-CM or rice formula (RF) as first option and AAF as the second choice for infants younger than 6 months. For older children SF or RF were recommended as first option, eHF-CM as second and AAF as third. For infants with a history of anaphylaxis, they recommended every formula except for eHF-CM. For infants with non-IgE CMA they also recommended HRF or eHF-CM/SF based on patients' age as first options and AAF as second line except for infants with EoE.

The GA^{2}LEN Task Force recently suggested using eHF-CM or AAF for CMA infants up to 1 year of age needing a breastmilk alternative (moderate CoE). They issued a conditional recommendation against the use of partially hydrolyzed cow's milk formula and mammalian milks in general, and against SF for infants under 6 months. The Task Force deemed the evidence on the use of HRF and probiotic supplementation as insufficient to issue proper recommendations.[69]

The ESPGHAN GI Committee Practical, and the BSACI Guidelines, published respectively in 2012 and 2014, recommended the use of hypoallergenic infant formulas in case breastfeeding was not possible, with eHF-CM being the first-line and AAF as the second option for more severe cases and non-responders to eHF-CM.[70–72] This is further confirmed in a more recent ESPGHAN position paper from 2022, in which SF and HRF

are also considered as alternative management options.

Furthermore, ESPGHAN and EAACI recommend against the use of soy protein-based formulas in infants below the age of 6 months.[70,73-75]

Compared to the 2010 DRACMA guidance[36] on the use of replacement formulas, the current update presents several novelties. First, the panel actively sought to also issue guidance also for infants affected by non-IgE cow's milk allergy, producing dedicated guideline questions and recommendations. Second, the questions and the recommendations were not limited to the pairwise comparison of 2 formulas, with one being recommended over the other, rather they aimed to resemble clinical practice more closely, suggesting an order in which the options should be considered for patient management. Lastly, the current guidance expanded the spectrum of different management options, addressing the supplementation of probiotics to formula, as compared to formulas alone.

REVISION OR ADAPTATION OF THESE GUIDELINES

After the publication of these guidelines, WAO will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Adaptation of these guidelines may be necessary in many circumstances. We encourage all stakeholders who would like to adapt the recommendations to their local circumstances to use the attached evidence-to-decision tables and to follow the systematic and transparent GRADE-ADOLOPMENT process.[8]

Abbreviations

AAF, aminoacid formula; CI, confidence interval; CMA, cow's milk allergy; CoE, Certainty of the evidence; DRACMA, Diagnosis and Rationale for Action against Cow's Milk Allergy; EoE, eosinophilic esophagitis; EtD, Evidence-to-Decision; eHF-CM, extensively hydrolyzed cow's milk formulas; HRF, hydrolyzed rice formula; SF, soy formula; LGG, *Lacticaseibacillus rhamnosus* (formerly *Lactobacillus rhamnosus*) GG; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; IgE-CMA, IgE-mediated cow's milk allergy; non-IgE-CMA, non-IgE-mediated cow's milk allergy; FPIES, Food Protein-Induced Enterocolitis Syndrome; FPIAP, Food protein-induced allergic proctocolitis; RD, risk difference; RF, rice formula; RoB, Risk of Bias; RR, relative risk; sIgE, specific immunoglobulin E; SPT, skin prick test; WAO, World Allergy Organization.

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Availability of data and materials

Upon request.

Author contributions

JLB, AF, HJS originally conceived this work. AB, DKC, RTF, SA, JLB, wrote its first draft. SW, AB, YR, and JLB did the literature search. AB, RTF and JLB screened records, evaluated full texts, and extracted data. AB and RTF evaluated risk of bias. JLB and AB did the statistical analyses. HJS, DKC, SA, and SW provided critical methodological input. All authors reviewed the manuscript and provided critical intellectual contributions to the analysis and interpretation of the data, and the revision of the manuscript.

Ethics approval

Ethics approval was not required.

Consent for publication

All authors approved the final version and its submission.

Declaration of competing interest

S Arasi, S Bahna, A Bognanni, J Brozek, D Chu, L Dahdah, P Dziechciarz, E Galli, R Kamenwa, H Li, A Martelli, R Pawankar, H Schunemann, R Targino, L Terracciano, and A Warner have no conflicts to disclose. Relationships reported related to the submitted work: IJ Anstotegui – Abbott, Amgen, Astra Zeneca, Bayer, Bial, Faes Farma, Hikma, Menarini, Merck, Mundipharma, Roxall, Sanofi, Stallergenes, UCB. A Assa'ad – Aimmune Therapeutics, DBV Technologies, Astella, ABBVIE, Novartis, Sanofi, FARE, NIH and an intellectual property patent licensed to Hoth. R Berni Canani – Ch.Hansen, Danone, DVB, Humana, iHealth, Kraft Heinz, Mead Johnson, Nestlè, Novalac, Nutricia, Sanofi. M Bozzola – Danone. C Dupont – Nestle Health Science, Nestle France, Nutricia, Novalac, Sodilac, Abbott, Danone, and stock ownership at DBV Technologies. M Ebisawa – DBV Technologies, Mylan, ARS Pharmaceuticals, Novartis. A Fiocchi – Abbott, Danone. G Lack – FARE, National Peanut Board (NPB), The Davis Foundation, Action Medical Research, UK Food Standards Agency, Medical Research Council, DBV Technologies, Mission Mighty Me, Novartis, Sanofi-Genyzme, Regeneron, ALK-Abello, Lurie Children's Hospital. A Nowak-Wegrzyn – Nestle, Nutricia, Novartis, Gerber, Aimmune. N Papadopoulos – Novartis, Nutricia, HAL Allergy, Menarini/Faes Farma, Sanofi, Mylan/Meda, Biomay, AstraZeneca, GSK, MSD, ASIT Biotech,

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100888.

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