



Regional differences in diagnosis and management of cow's milk allergy

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Background: Various guidelines for the diagnosis and management of cow's milk allergy (CMA) have been published.

Purpose: This study aimed to compare voting outcomes of experts from Mexico, the Middle East, and the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) on statements regarding CMA

Methods: The 3 expert groups voted on the same 10 statements. Each participant voted anonymously using a score of 0–9 (≥ 6 meant agreement; < 5 reflected disagreement). If $< 75\%$ of the participants agreed with the statement, it was rejected. None of the groups was aware of the voting outcomes of another group.

Results: There was broad consensus amongst the 3 groups. Agreement was reached that infant colic as a single manifestation is not suggestive of CMA. All groups confirmed that an extensively hydrolysed formula is the preferred elimination diet in mild/moderate CMA cases; however, hydrolysed rice formula is an alternative. Amino acid-based formulas should be reserved for infants with severe symptoms. The discrepancy in voting outcomes regarding soy formulas highlights the differences in opinions. Two of 13 ESPGHAN experts (15%), 1 of 14 Middle East experts (7%), and 6 of 26 Mexican experts (23%) disagreed with the statement that soy formula should not be the first choice for the diagnostic elimination diet but can be considered in some cases for economic, cultural, and palatability reasons. All of the ESPGHAN and Mexican experts agreed that there was no added value of probiotics, prebiotics, or synbiotics to the efficacy of elimination diets on CMA, whereas 3 of 14 Middle East experts (21%) determined that there was sufficient evidence.

Conclusion: Although all statements were accepted by the 3 groups, there were relevant differences illustrating variations according to geography, culture, cost, and formula availability. These findings emphasize the need for region-

specific guidelines.

Key words: Cow's milk allergy, Extensively hydrolysed formula, Amino acid-based formula, Hydrolysed rice formula, Probiotics

Key message

- Although there is broad consensus on many aspects regarding the symptoms, diagnosis, and treatment of cow's milk allergy, the impact of geographical, cultural, and socioeconomic factors remains unestablished.
- Availability and cost of formula for the management of cow's milk allergy have a major impact on the therapeutic choice.
- Region-specific guidelines for the treatment of cow's milk allergy are required.

Introduction

Cow's milk allergy (CMA) is one of the most prevalent food allergies in infants and young children, with a reported prevalence in Europe ranging between 0.36% and 4.9%.¹ Although specific Mexican data are lacking, other Latin American countries report a comparable prevalence of 0.88% to 5.4%.^{2,3}

CMA can be IgE-mediated, non-IgE-mediated, or mixed, and can be of immediate and delayed onset. Symptoms are nonspecific and are characterized by differences in severity. Making an accurate diagnosis followed by appropriate treatment is crucial to prevent over- and underdiagnosis and consequently over- and undertreatment, which both are associated with adverse effects.⁴ Given the variety of symptoms and the absence of an accurate diagnostic test, a detailed clinical history and physical examination is warranted.¹ Early diagnosis is a key factor, as delaying the

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Graphical abstract.

diagnosis of CMA can lead to faltering growth and malnutrition.⁴⁾ Until today, the management of CMA is based on the avoidance of cow's milk protein (CMP). Consensus statements published worldwide consequently mention that management depends upon regional interfering factors, although their impact or importance were not yet evaluated.⁴⁻⁸⁾

Since CMA diagnosis and management is influenced by social contexts, eating habits, and available resources, the purpose of this article is to compare the opinions of a group of Mexican experts with those of European and Middle East experts, and thereby evaluate regional differences.

Methods

An ESPGHAN expert group (n=13) developed recently a Position paper on the prevention, diagnosis and management of CMA, summarizing the most important findings and recommendations from systematic reviews and meta-analyses regarding the prevalence, pathophysiology, symptoms and diagnosis of CMA.⁴⁾

Within the ESPGHAN group, statements circulated 3 times before agreement was reached that they were ready to be voted on. The authors of the ESPGHAN (all pediatric gastroenterologists, except one allergologist) (8 females) voted on 73 statements.⁴⁾ There was only one voting round, which was online and anonymous. A selection of 10 statements was made by the first author of the ESPGHAN paper (YV), and were presented to the Middle East and Mexican expert groups to be voted on. This selection was made based on the relevance of the statements and/or the likelihood for divergence, and selection was needed because of the time restriction related to the face-to-face meetings during which this voting was organized. All participating experts in the 3 groups had more than 15 years experience in the field and are recognised as "key opinion leaders" in their respective countries and regions. The meeting of the Middle East experts was funded by Abbott Nutrition, who invited the

participants, and covered meeting and publication costs.⁹⁾ Fourteen Middle East experts (4 females, all pediatric gastroenterologists, except 1 allergologist) voted on the selected 10 statements. A group of 26 Mexican experts (8 females), in pediatric gastroenterology and nutrition (n= 23), allergy (n=1), neonatology (n=1), dermatology (n=1) representing different regions of the country, was selected based on their interest and experience in the field of CMA. The Mexican participants voted on the same 10 statements as the Middle East group. This meeting was intended to result in a Mexican consensus on the management of CMA, and was supported by Genomma Laboratories.¹⁰⁾

Both the Middle East and Mexican group voted anonymously during a face-to-face meeting, in an identical way to the voting by the ESPGHAN group (which was also anonymous). The voting results of both expert groups were collected, analysed descriptively and the median and mean were calculated. In addition, the range was provided, as well as the number of disagreements (scores <5). Each statement was given a score from 0 to 9. A score of 6 or higher indicated agreement, while a score of 5 and less indicated disagreement. The higher the score, the greater the degree of agreement. The method and interpretation of the voting was the same for the ESPGHAN, Middle East and Mexican group. No participant in any of the groups was aware about the voting outcome in one of the other groups.

Results

The results of the Middle East group are discussed in more detail elsewhere.¹¹⁾ Three statements were selected covering crying, irritability and infantile colic. The 3 groups accepted the statement that a time-limited cow's milk elimination diet should not be considered in infants presenting with crying and irritability as single manifestation. However, more members of the Mexican group, in comparison to both other groups, considered that crying and irritability as isolated symptoms could be considered as suggesting CMA

(Table 1). In the latter group, 5 of 26 experts (19%) expressed disagreement with the statement, in contrast to only 1 of 27 (7%) in the Middle East and none in the ESPGHAN group. The ESPGHAN authors strongly stated that colic by itself is not a symptom of CMA.⁴⁾

All 3 groups agreed that a cow's milk-based extensively hydrolysed formula (eHF) is the preferred option for a diagnostic elimination diet, with the Mexican group being the biggest supporter (Table 2). Furthermore, consensus was reached upon restricting the use of amino acid-based formula (AAF) to the very severe cases, such as faltering growth and anaphylaxis. By consequence, there was broad consensus to not apply a step-down elimination diet starting with AAF for all infants suspected of CMA.

Regarding alternative options to cow's milk-based formula, there are some differences between the groups. Although the statements were accepted by all groups, distinct preferences were apparent. Specifically, the Mexican group pronounced a stronger inclination towards the use of hydrolysed rice formulas (HRF) for both diagnostic and therapeutic elimination diets, alongside endorsing much more explicit soy-based formulas for diagnostic elimination diets. Within the Mexican group, 6 out of 26 experts expressed disagreement with the statement that soy formula should not be used as the first choice for diagnostic elimination diet but can be considered in some cases for economic, cultural and palatability reasons. In contrast to the Middle East and ESPGHAN groups where only 1 and 2 experts, respectively, disagreed.

The statement regarding the absence of an added therapeutic efficacy of probiotic, and synbiotics to eHFs and AAFs was accepted by all European and Mexican experts but was

rejected by 3 out of 14 Middle East experts (Table 3).

Discussion

Overall, all statements were accepted by the 3 groups. However, distinct variations were observed, reinforcing the call of several organizations, such as the British Society for Allergy & Clinical Immunology, The World Allergy Organization and ESPGHAN for region-specific guidelines that meet the needs of children across all socioeconomic strata in the targeted countries.

CMA exhibits a large range of specific symptoms, including cutaneous, gastrointestinal, respiratory tract symptoms, and systemic reactions. IgE-mediated CMA prompts immediate symptoms within minutes to 2 hours, while in non-IgE-mediated allergy the appearance of symptoms is delayed, usually emerging between several hours to 1 week after exposure.⁴⁾ The diagnosis of CMA is based on a thorough history and physical examination, ultimately validated through an oral food challenge (OFC). When CMA is suspected, it is advisable to eliminate CMP for 1 to 4 weeks, followed by an OFC for confirmation.⁴⁾

Most experts agreed that crying, irritability or distress as single manifestations are not suggestive of CMA and should not lead to a cow's milk elimination diet. However, Mexican experts tended to consider CMA more frequently as a possible cause of infant distress and were therefore also more inclined to consider a cow's milk elimination diet, compared to the ESPGHAN group.

In nonexclusively breastfed children suspected of CMA, a formula with reduced allergenicity is recommended.

Table 1. Crying and infant colic as symptoms suggestive of cow's milk allergy

Statements	ESPGHAN (n=13)	Middle East (n=14)	Mexico (n=26)
In infants who present with crying and irritability, there is insufficient data to recommend a time-limited CM elimination diet followed by an oral food challenge			
Mean	8.4	7.6	7.4
Median	9.0	8.0	8.5
Range	6-9	5-9	2-9
Disagreement, n (%)	0 (0)	1 (7)	5 (19)
There is insufficient data to support infant colic occurring as a single manifestation of CMA.			
Mean	8.4	6.7	7.9
Median	9.0	8.0	8.0
Range	6-9	1-9	4-9
Disagreement, n (%)	0 (0)	1 (7)	1 (4)
When treatment for infant colic, fulfilling Rome IV clinical research criteria, is considered, and where CMA is suspected based on additional symptoms, a time-limited elimination diet can be trialled which should be followed by an OFC.			
Mean	7.4	8.4	8.4
Median	9.0	9.0	9.0
Range	4-9	7-9	7-9
Disagreement, n (%)	1 (8)	0 (0)	0 (0)

ESPGHAN, European Society of Pediatric Gastroenterology Hepatology and Nutrition; CM, cow's milk; CMA, cow's milk allergy; OFC, oral food challenge.

Table 2. Diagnostic and therapeutic elimination diet

Statements	ESPGHAN (n=13)	Middle East (n=14)	Mexico (n=26)
In formula fed infants, a CM based eHF is the first choice for a diagnostic elimination diet in mild/moderate cases			
Mean	7.2	8.1	8.7
Median	9.0	8.5	9.0
Range	0–9	4–9	7–9
Disagreement, n (%)	2 (15)	1 (7)	0 (0)
In formula fed infants, AAF for a diagnostic elimination diet should be reserved for severe cases or patients with severe malnutrition.			
Mean	8.5	8.3	8.5
Median	9.0	8.5	9.0
Range	7–9	6–9	7–9
Disagreement, n (%)	0 (0)	0 (0)	0 (0)
Although some consensus papers recommend a step-down approach using AAF as diagnostic elimination diet in every infant suspected of CMA, there is insufficient evidence for this recommendation.			
Mean	8.6	8.0	8.4
Median	9.0	9.0	9.0
Range	6–9	6–9	6–9
Disagreement, n (%)	0 (0)	0 (0)	0 (0)
Although less studied than CM based eHFs, HRFs can be considered as an alternative for a diagnostic elimination diet.			
Mean	7.4	8.1	8.7
Median	8.0	9.0	9.0
Range	1–9	5–9	6–9
Disagreement, n (%)	2 (15)	1 (7)	0 (0)
Soy infant formula should not be used as the first choice for diagnostic elimination diet but can be considered in some cases for economic, cultural and palatability reasons.			
Mean	7.6	8.0	6.7
Median	9.0	9.0	8.0
Range	0–9	5–9	0–9
Disagreement, n (%)	2 (15)	1 (7)	6 (23)
HRF can be considered as an alternative to CM based eHF for a therapeutic elimination diet.			
Mean	7.8	8.2	8.5
Median	8.0	9.0	9.0
Range	5–9	6–9	7–9
Disagreement, n (%)	2 (15%)	0	0

ESPGHAN: European Society of Pediatric Gastroenterology, Hepatology and Nutrition; CM, cow's milk; AAF, amino acid-based formula; eHF, extensively hydrolysed formula; HRF, hydrolysed rice formula

Table 3. Pro-, pre-, and synbiotics

Statements	ESPGHAN (n=13)	Middle East (n=14)	Mexico (n=26)
There is insufficient evidence demonstrating that the addition of probiotics, prebiotics or synbiotics to eHFs and AAFs improves their therapeutic efficacy.			
Mean	8.9	6.6	8.6
Median	9.0	8.0	9.0
Range	8–9	1–9	7–9
Disagreement, n (%)	0 (0)	3 (21)	0 (0)

ESPGHAN, European Society of Pediatric Gastroenterology, Hepatology and Nutrition; AAF, amino acid-based formula; eHF, extensively hydrolysed formula.

Formula choice is a subject of debate, influenced by availability, economics, and scientific evidence.^{12,13} Currently, evidence strongly supports using a cow's milk-based eHF for a diagnostic elimination diet during 1 to 4 weeks. This was recently confirmed in the recommendations published by the World Allergy Organization.¹⁴ This statement was

unanimously accepted by the Mexican experts, in contrast to the European and Middle East experts where 3 of 27 disagreed. Cost considerations favour eHF over AAF in most countries.⁶ However, some recommendations conclude that AAF may exhibit a comparable or even superior cost-effectiveness to eHFs, and advocate a step-down approach.¹⁵

The new recommendation of the World Allergy Organization positions AAF as a second choice option.¹⁴⁾ Therefore, international guidelines should be tailored to align with the specificities of the local healthcare system.⁴⁾ None of the experts in the 3 groups supported such step-down approach.

The statement that AAF should be reserved for severe cases or patients with serious malnutrition was unanimously accepted by all groups. AAF, compared to eHF, does not contain immunogenic peptides that stimulate the immune system. A recent review of Ribes-Koninckx et al.¹⁵⁾ confirms this statement and recommends the utilization of AAF when treatment with eHF is unsuccessful or in severe cases of CMA, particularly with associated nutritional deficiencies. AAF as a diagnostic elimination diet is particularly recommended in CMA causing IgE-mediated anaphylaxis, acute and chronic food protein induced enterocolitis syndrome (FPIES) and eosinophilic esophagitis or in cases of multiple food allergies or faltering height growth.^{4,16)} However, the World Allergy Organization recently published that eHF or HRF is the first option for all infants, independent of the severity of the symptoms.¹⁴⁾ Between 2 and 18% of children with an IgE-mediated CMA are reported to have persistent symptoms while being on eHF diet.¹⁴⁾

Regarding therapeutic elimination diets, an eHF is used when a symptom relapse occurs subsequent to the OFC or the reintroduction of cow's milk into the diet of breastfeeding mothers.⁴⁻⁶⁾

In Europe, formulas containing hydrolysed rice protein have been commercially available since the 2000s and were considered an alternative option for eHF and preferred to soy formulas.^{5,12)} These HRF formulas have demonstrated nutritional adequacy and are well-tolerated plant-based alternatives.¹⁷⁾ However, their utilization is limited by regional availability.⁴⁾

Compared to CM based eHF, HRF has a better palatability and does, similar to AAF, not contain any residues of CMP. Furthermore, in contrast to soy formula, there is no risk for contamination with phytoestrogens. Concerns have been raised regarding the arsenic levels in infant rice products, raising potential long-term health implications, such as an elevated risk of pulmonary disease and cancer in adulthood.¹⁸⁾ Therefore, the European Union (https://european-union.europa.eu/index_en) has enforced a maximum inorganic arsenic concentration of 0.10 mg/kg in rice intended for infants under the age of 3. Meyer et al.¹⁸⁾ concluded that the arsenic content in HRF is very low and falls well within the safety limits set by the European Food Safety Authority, with no significant variance when compared to the arsenic levels found in cow's milk-based formulas. Nevertheless, it is important to note that not all commercially available HRF products provide information about their arsenic content on their labels.⁴⁾ Furthermore, the arsenic concentration

in the water used for formula preparation contributes to the final arsenic content. The statements positioning HRF as an alternative option to eHF diagnostic elimination diet were, in line with the Latin-American Society of Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN)¹⁹⁾ and the World Allergy Organization,¹⁴⁾ accepted by all Mexican experts, whereas 3 experts in the Middle East and ESPGHAN group disagreed.

Soy-based infant formula offers a further alternative providing essential nutrition resulting in a healthy growth of the infants.^{4,20)} While IgE-mediated CMA rarely shows cross-reactivity with soy, there may be some cross-reactivity in non-IgE-mediated CMA.²¹⁾ Data supporting this relationship primarily originate from the United States, where studies indicate that 30% to 50% of children with FPIES react to both cow's milk and soy. Conversely, a majority of studies from outside the US report a substantially lower percentage.^{4,22)} Soy allergy prevalence ranges from 0% to 0.5% in the general population and 0% to 14% in allergic children.²³⁾ The availability of soy infant formula has decreased in several European countries. Soy formula is considered a secondary choice according to ESPGHAN⁴⁾ and even a third choice according to the World Allergy Organization,¹⁴⁾ particularly when other options are constrained because of economic or cultural factors.

CMA is associated with intestinal dysbiosis, characterized by a decreased gut microbiota diversity with reduced levels of *Bifidobacteria*, *Lactobacilli*, and *Bacteroides*.²⁴⁾ Several eHFs contain also pre-, pro-, syn- or postbiotics. However, their influence on the gut microbiota and additional efficacy in progression and management of CMA is an ongoing matter of debate and requires further research.^{4,25)} All ESPGHAN and Mexican experts agreed there was no added value of prebiotics, probiotics and synbiotics in the efficacy of elimination diets, whereas 3 of 14 authors of the Middle East group considered there is evidence.

The 2021 Middle East Consensus Statement described that adding prebiotics and synbiotics to a therapeutic formula may improve the tolerance to CMP by the end of the first year of life.²⁶⁾ Synbiotics have been shown to improve gut microbiota in non-IgE-mediated CMA, aligning it with the profile of healthy infants.²⁷⁾ Combining synbiotics with AAF yields comparable reduction of allergic symptoms and normal growth as AAF alone, although improvements in dysbiosis and a potential decrease in infection rates, hospital admissions, and antibiotic use have been noted.^{25,27)} Several studies have demonstrated that antibiotic use in children aged 0 to 3 years results in a less diverse microbiome, with reduced abundance of *Bifidobacteria*, *Lactobacilli*, and *Bacteroides* ultimately increasing the risk of developing hay fever, eczema, and food allergy, including CMA.^{24,28)} The strongest associations with food allergies were observed

at lower ages and varied by antibiotic class, especially with penicillin and cephalosporins in infants under the age of 2 years.²⁹⁾ Administration of probiotics during and after antibiotic courses may mitigate these harmful effects and potentially yield economic benefits.²⁸⁾ This could ultimately result in an economic advantage with lower costs.²⁵⁾

Multiple studies showed that the addition of *Lactocasei-bacillus rhamnosus* GG (LGG) is a cost-effective in the management of CMA. Based upon data from an Italian observational study in 260 infants by Berni Canani et al.,³⁰⁾ Guest et al.³¹⁾ developed a country specific cost-effectiveness decision model that showed that eHF + LGG formulas were a more cost-effective strategy than eHF alone or AAF, as it improved outcomes. This was also shown in the United States, Italy, the United Kingdom, Poland, and Spain. Other studies revealed similar results. Martins et al.³²⁾ showed a casein eHF + LGG formula to be the most cost-effective strategy for treating CMA in the United Kingdom. According to a French study conducted by Paquete et al.,³³⁾ the combination of casein eHF and LGG was associated with longer symptom-free periods, greater immune tolerance, and reduced costs.

An important limitation of this report is its exclusive reliance on the opinions of a select group of experts. A more comprehensive understanding of the clinical management of CMA could be achieved by incorporating insights from a wider array of professionals such as general pediatricians, family doctors, allergologists, dietitians, and parents. Moreover, extending this analysis to a larger and more diverse population would unveil more discernible variations influenced by cultural and regional factors.

In conclusion, CMA presents with a diverse range of non-specific symptoms. A timely and accurate diagnosis is of paramount importance to prevent complications such as faltering growth and delayed development. While broad consensus was reached among experts from Europe, the Middle East and Mexico, discrepancies in opinion of experts were as well highlighted.

The consensus leans towards using cow's milk-based eHF or HRF for elimination diets as preferred options. Soy formula is considered a valid second choice option. Severe cases may require an AAF. There is no convincing evidence that prebiotics, probiotics or synbiotics increase the efficacy of eHFs.

There is a need to develop region-specific guidelines, accounting for available resources and the social context.

Footnotes

Conflicts of interest: YV has participated as a clinical investigator, and/or advisory board member, and/or con-

sultant, and/or speaker for Abbott Nutrition, Alba Health, Arla, Ausnutria, Biogaia, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Pileje, Sanulac, United Pharmaceuticals (Novalac), Yakult, Wyeth. All other authors reported no conflict of interest.

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