

Short Communication

Exploring The Advantages of a Hydrolyzed Rice Formula in the Dietary Management of Infants with Cow's Milk Allergy in Latin America

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Submitted: 01 October 2022

Accepted: 01 November 2022

Published: 04 November 2022

ISSN: 2578-3203

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OPEN ACCESS**Keywords**

- Cow's milk protein allergy
- Hydrolyzed protein
- Infant allergy
- Latin america
- Rice

Abstract

Aim: Allergic diseases such as cow's milk allergy (CMA) are increasing in early childhood. Exclusive breastfeeding is recommended for infants in the first 6 months of life. However, when breast-feeding is insufficient or unavailable, there are differing beliefs about the best formula substitute for infants with CMA, dependent on availability and local healthcare systems. If an infant suffers from CMA, current international food allergy guidelines recommend casein or whey extensively hydrolyzed formulas (eHF) or amino acid-based formulas (AAF) in case of severe symptoms. Hydrolyzed rice formulas (HRF) are considered an alternative to casein or whey eHF where available.

Methods: To understand how HRF are being used, their position in the management of CMA, and generate consensus on indications for use, a HRF-focused workshop of healthcare professionals from Latin America with expertise in pediatric food allergy was convened in October 2021.

Results: Experts provided diverse viewpoints based on their different specialties, locations, and healthcare settings. This short communication briefly summarizes the outputs from this meeting. During the consensus part of the meeting, an approach to the dietary management of CMA was discussed and approved by all participants.

Conclusions: Agreement was reached among experts that where casein or whey eHF is appropriate per international guidelines, extensively HRF could also be considered as a first-line option as part of the dietary management of CMA.

ABBREVIATIONS

AAF: Amino Acid-based Formulas; CMA: Cow's Milk Allergy; DRACMA: World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy; eHF: Extensively Hydrolyzed Formulas; HCP: Healthcare Professionals; HRF: Hydrolyzed Rice Formulas; IU: International Unit; LATAM: Latin America; WHO: World Health Organization

INTRODUCTION

Cow's milk allergy (CMA) is one of the most common food allergies in infants and young children and, if not adequately managed, can adversely impact growth and development

[1,2] and affect a family's quality of life [3]. The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life followed by the introduction of healthy complementary foods. When breastfeeding is not possible, formulas that are hypoallergenic and shown to meet infants' nutritional needs for growth and development are healthy alternatives [4,5].

In European children, CMA prevalence ranges from 1.9% to 4.9% [2]. However, little is known about the frequency of CMA in Latin America (LATAM) [6]. A search of published literature indicates a CMA prevalence of 0.4% to 5.2% [7-12]. Data from Costa Rica and Honduras are not applicable [13,14]. The

prevalence of CMA across LATAM appears to depend on the methodology used to establish a diagnosis of CMA; therefore, predicted estimates may differ from actual rates in real-world settings. As recommended by international food allergy guidelines, challenge tests (open or double placebo) should be used to confirm the diagnosis [15,16].

The diagnosis and management of CMA varies based on clinical setting and location and is a challenge in pediatric practice [17]. Furthermore, as nonallergic food reactions are often confused with CMA symptoms, this leads to overdiagnosis of CMA in LATAM [17]. CMA management is diverse in LATAM and there is poor adherence to the clinical practice guidelines due to these variations in clinical setting and area of specialty [18]. Several regional LATAM cow's milk allergy guidelines and/or publications focus on management of CMA [17-20], with LATAM guidelines recommending using casein or whey extensively hydrolyzed formula (eHF) as a first-line option for infants with CMA [17,20]. HRF is defined as a therapeutic formula according to these guidelines, as it is considered to be one that is tolerated by at least 90% of the patients with CMA (with 95% confidence interval) [17,20]. The Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition recently published a consensus on the diagnostic and therapeutic criteria for CMA. The authors surmised that HRFs, in general, are less costly than eHFs, more palatable, and more trusted by vegan/vegetarian families. Current HRFs have a good safety profile, with reported arsenic levels within permissible exposure limits. If an eHF is not available, unaffordable, or the infant refuses to drink it, HRF can be considered a suitable second-line option [20]. Prominent international food allergy guidelines from leading world allergy organizations endorse casein or whey eHF or amino acid formula (AAF), depending on the diagnosis and severity of symptoms. Hydrolyzed rice formulas are considered an alternative to casein or whey eHF where available [15,16]. Due to these conflicting regional and international CMA guidelines, an Expert LATAM group was convened to provide an up-to-date assessment on the role of HRF in CMA dietary management.

This publication summarizes the discussions and consensus from a 2021 LATAM experts' meeting roundtable discussing the role of HRF in the dietary management of infants with CMA where breastmilk is insufficient or not available.

MATERIALS AND METHODS

In October 2021, a virtual roundtable was hosted for healthcare professionals (HCPs) in the LATAM region (five pediatric gastroenterologists and two pediatric allergists/immunologists). Representative countries included Ecuador, Panamá, México, Colombia, Chile, and Venezuela. The primary goal of the roundtable was to align on a set of recommendations

HCPs could use to determine when and where to initiate HRF compared with casein or whey eHF (Figure 1).

The workshop was divided into two sections: review of the recent evidence-based research summarizing the clinical evidence of HRF in the dietary management of CMA [2], and a facilitated discussion on consensus statements on the use of HRF for HCPs in the LATAM region. For the development of a regional consensus on the use of HRF for CMA in the LATAM region, a structured quantitative method was used to expedite the discussion and reach a consensus [21]. Statements were developed before the meeting based on the most recent international food allergy guidelines and recommendations [15,16,22]. At the meeting, each statement was discussed comprehensively within the group. All group members (n=7) then voted anonymously on each statement (using an online voting Zoom poll by clicking a box for "agreement" or "disagreement." Poll results were tallied).

RESULTS AND DISCUSSION

All consensus statements were significantly edited/co-created by the HCPs in attendance – stimulus was presented, and the HCPs crafted appropriate statements. Final agreed-upon statements are presented in Table 1.

During the meeting, experts discussed the positive attributes of HRF. Palatability was highlighted as a key differentiating factor compared with other commonly recommended hypoallergenic formulas. There was also consensus on the robustness and quality of the data surrounding hypoallergenicity of HRF, as well as the ability of this formula to effectively alleviate CMA symptoms. These views are based on currently available data from clinical studies, as reviewed by Dupont and colleagues [2]. Other strengths noted during the discussion included HRF's robust protein content and the minimal immunogenicity produced. It was noted that if these advantages are coupled with widespread distribution and a competitive cost, there is great potential for uptake of HRF as a first-line CMA dietary management option.

The experts did note the need for more long-term studies showing that infants who use HRF experience balanced and satisfactory global growth and development, to guarantee a proper evolution and progression of all parameters and biological indicators. During the meeting, it was also noted that more studies on bone mineralization are needed, not only for HRF, but for all formulas indicated for CMA dietary management. It would be interesting to better understand whether HRF are capable of inducing oral tolerance. It is clear more longitudinal long-term studies are needed to clarify these very important issues.

Experts also discussed the key attributes of HRF, such as hypoallergenicity, palatability, competitive cost compared with AAF, free from residual cow's milk protein and lifestyle suitability

1. Review the diagnosis and management of CMA in the LATAM region.
2. Define the evidence-based benefits of HRF specifically in regard to hypoallergenicity, growth and development, efficacy, nutritional validity, and diet suitability.
3. Align on the clinical benefits of HRF in CMA dietary management, compared with other extensively hydrolyzed formulas.
4. Align on a set of recommendations HCPs can use to determine when and where to initiate HRF compared with casein or whey eHF.

Figure 1: Meeting Objectives/Goals

CMA: Cow's Milk Allergy; HCP: Healthcare Professional; HRF: Hydrolyzed Rice Formula; LATAM: Latin America.

Table 1: LATAM Consensus Statements on the Use of HRF.

6 cm	Statement	Agreement
1	Human milk is the gold standard for feeding in healthy infants and for infants with CMA.	100%
2	In infants with suspected CMA, breastfed, strict exclusion of cow's milk-containing foods from the maternal and/or infant diet for 2–4 weeks is recommended in infants <12 months of age, followed by a challenge test to confirm a diagnosis of CMA. It is suggested to supplement the mother with calcium 1000 mg and vitamin D 600 IU/day.	100%
3	In formula-fed infants <12 months of age with suspected CMA, strict exclusion of cow's milk-containing foods and substitution of the formula for 2–4 weeks is recommended. A challenge test to confirm a diagnosis of CMA is recommended.	100%
4	The current strategy for nutritional management of CMA is allergen avoidance. By definition, an extensively HRF does not contain cow's milk protein.	100%
5	In several clinical studies, extensively HRF has shown efficacy in infants and children with CMA.	100%
6	Several studies have shown that children fed the extensively HRF have shown adequate weight and height gain.*	100%
7	Where casein or whey eHF is appropriate per international guidelines, an extensively HRF could also be considered as a first-line option as part of the dietary management of CMA.	100%
8	There are clear and compelling nutritional differences between HRF and plant-based drinks. Plant-based drinks including rice drinks are not an alternative for the nutritional management of CMA in children under 2 years of age.	100%

Abbreviations: CMA: Cow's Milk Allergy; eHF: Extensively Hydrolyzed Formula; HRF: Hydrolyzed Rice Formula; IU: International Unit. *Each specific HRF should be studied. All hypoallergenic formulas should have longer-term studies/measures of other variables (e.g., bone mineralization).

- Human milk is the gold standard for feeding in healthy infants and for infants with CMA.
- There is consensus that choosing an appropriate formula is contingent on the patient's diagnosis and age.
- In general, and according to current international food allergy guidelines, Latin-American HCPs prescribe casein or whey eHF as the first-line option for infants with CMA. However, most experts agree that HRF represent an alternative in the management of patients with CMA.
- Positive attributes of HRF cited during the meeting include hypoallergenicity, palatability, cow's milk protein-free, and lifestyle suitability (e.g., vegetarian, Halal, Kosher).*

The 2014 LATAM guidelines note that HRF has been shown to be useful in the treatment of CMA [17]. Therefore, the consensus statements following this roundtable will be a crucial step in promoting a wider and deeper discussion regarding the potential benefits of using HRF as part of the dietary management of infants with CMA.

Consensus statements were developed based on the most recent international food allergy guidelines and recommendations [15, 16, 22]. All statements were significantly edited/co-created by the HCPs in attendance – stimulus was presented, and the HCPs crafted and agreed upon appropriate statements.

This consensus is in alignment with DRACMA guidelines [15], which state HRF can be considered an alternative to eHF where available. DRACMA treatment guidelines are scheduled to be updated in 2022 [23, 24].

There is potential for HRF to be used as a first-line option for dietary management of CMA in the LATAM region. Additional clinical research and experience is necessary to build further confidence in the use of HRF as a first-line treatment for CMA.

Figure 2: *Please check with the infant formula manufacturer to ensure a product is certified vegetarian, Kosher or Halal.

Abbreviations: CMA: Cow's Milk Allergy; DRACMA: World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy; eHF: Extensively Hydrolyzed Formula; HCP: Healthcare Professional; HRF: Hydrolyzed Rice Formula; LATAM: Latin America.

(e.g., vegetarian, Halal, Kosher). [Please check with the infant formula manufacturer to ensure a product is certified vegetarian, Kosher, or Halal].

CONCLUSION

A summary of key findings from this workshop is reported below (Figure 2). This roundtable meeting illustrated that HRF have the potential to be widely used and accepted in the LATAM region and can be used as a first-line option for the dietary management of CMA. The consensus statements developed at

this meeting are based on LATAM expert opinion and consider the use of HRF in the dietary management of CMA.

ACKNOWLEDGEMENTS

FoodMinds and Madano Healthcare compiled the comments of the authors and supported the editorial development of this paper.

CONFLICT OF INTEREST

The consensus statements and supporting evidence

presented in this paper were discussed and formulated at a virtual LATAM workshop. All authors received honoraria from Abbott to attend the LATAM experts' meeting roundtable, held on October 20, 2021. The views expressed in this paper are purely those of the authors without any influence from Abbott. Publication fees were paid by Abbott. Roderick Bejarano has participated as a speaker for Abbott Nutrition, Abbott Pharma, Nutricia, Astra Zeneca, Nestle Nutrition, and Procter & Gamble. Sylvia Cruchet has participated as a speaker for Abbott, Axon Pharma, and BioGaia. Reinaldo Pierre has participated as a speaker for Abbott, BioGaia, Nestlé, and Reckitt Benckiser. Juan Pablo Riveros has participated as a speaker for Abbott Nutrition, Danone-Nutricia, Farma de Colombia, Procter & Gamble, and TQ Pharma. Rodrigo Vázquez-Frias has received support to attend courses and has participated as a speaker for Abbott, BioGaia, Carnot, Ferrer, Kellogg's, Mayoly-Spindler, Medix, Nestlé, Pfizer, Reckitt Benckiser, Sanofi, Schwabe Pharma, and Takeda. Juan Carlos Fernandez de Cordova-Aguirre has participated as a speaker for Sanofi, Bayer, GlaxoSmithKline, Acromax and Bago. Benjamin Zepeda Ortega has participated as speaker for Abbott.

REFERENCES

- Bocquet A, Dupont C, Chouraqui JP, Darmaun D, Feillet F, Frelut ML, et al. Efficacy and safety of hydrolyzed rice-protein formulas for the treatment of cow's milk protein allergy. *Arch Pediatr*. 2019; 26: 238-46.
- Dupont C, Bocquet A, Tome D, Bernard M, Campeotto F, Dumond P, et al. Hydrolyzed rice protein-based formulas, a vegetal alternative in cow's milk allergy. *Nutrients*. 2020; 12: 2654.
- Lozinsky AC, Meyer R, Anagnostou K, Dziubak R, Reeve K, Godwin H, et al. Cow's Milk Protein Allergy from Diagnosis to Management: A Very Different Journey for General Practitioners and Parents. *Children (Basel)*. 2015; 2: 317-29.
- Verduci E, D'Elisio S, Cerrato L, Comberiat P, Calvani M, Palazzo S, et al. Cow's Milk Substitutes for Children: Nutritional Aspects of Milk from Different Mammalian Species, Special Formula and Plant-Based Beverages. *Nutrients*. 2019; 11: 1739.
- Breastfeeding - World Health Organization (WHO). 2022.
- Sanchez J, Sanchez A. Epidemiology of food allergy in Latin America. *Allergol Immunopathol (Madr)*. 2015; 43: 185-95.
- Acevedo N, Sánchez J, Zakzuk J, Bornacelly A, Quiróz C, Alvarez Á, et al. Particular characteristics of allergic symptoms in tropical environments: follow up to 24 months in the FRAAT birth cohort study. *BMC Pulm Med*. 2012; 12: 13.
- Arancibia ME, Areneda C, Decerra C, Borzutzky A, Cornejo VC, S Guzman, MA Guía Clínica Alergia a Proteína de Leche de Vaca. Santiago: Minsal, 2012.
- Arancibia ME, Lucero Y, Miquel I, Marchant P, Rodriguez L, Alliende F, et al. Association of Cow's Milk Protein Allergy Prevalence With Socioeconomic Status in a Cohort of Chilean Infants. *J Pediatr Gastroenterol Nutr*. 2020; 71: 80-e3.
- Marrugo J, Hernandez L, Villalba V. Prevalence of self-reported food allergy in Cartagena (Colombia) population. *Allergol Immunopathol (Madr)*. 2008; 36: 320-4.
- Mehaudy R, Parisi C, Petriz N, Eymann A, Jauregui MB, Orsi M. Prevalence of cow's milk protein allergy among children in a university community hospital. *Arch Argent Pediatr*. 2018; 116: 219-23.
- Vieira MC, Morais MB, Spolidoro JV, Toporovski MS, Cardoso AL, Araujo GT, et al. A survey on clinical presentation and nutritional status of infants with suspected cow' milk allergy. *BMC Pediatr*. 2010; 10: 25.
- Gonzales-Gonzalez VA, Diaz AM, Fernandez K, Rivera MF. Prevalence of food allergens sensitization and food allergies in a group of allergic Honduran children. *Allergy Asthma Clin Immunol*. 2018; 14: 23.
- Soto-Quiros M, Gutierrez I, Calvo N, Araya C, Karlberg J, Hanson LA, et al. Allergen sensitization of asthmatic and nonasthmatic schoolchildren in Costa Rica. *Allergy*. 1998; 53: 1141-7.
- Fiocchi A, Brozek J, Schunemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. *World Allergy Organ J*. 2010; 3: 57-161.
- Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012; 55: 221-9.
- Montijo-Barríos E, Lopez-Ugalde MV, Ramirez-Mayans J, Anaya-Florez MS, Arredondo-García JL, Azevedo-Tenorio I, et al. [Guía latinoamericana para el diagnóstico y tratamiento de alergia a las proteínas de la leche de vaca (GL-APLV)]. *Rev Invest Clin*. 2014; 66: S9-S72.
- Toca MC, Roman-Riechmann E, Vazquez-Frias R, Batista de Morais M, Sosa P, Boggio-Marzet C, et al. A Latin American and Spanish pediatric gastroenterology group's understanding of cow's milk protein allergy diagnosis and treatment: Results of a survey by the Food Allergy Working Group of the Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición Pediátrica. *Rev Gastroenterol Mex (Engl Ed)*. 2020; 85: 382-9.
- Larrosa-Haro A. Cow's milk protein allergy in pediatric patients: The vision of the Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Rev Gastroenterol Mex (Engl Ed)*. 2020; 85: 379-81.
- Toca MC, Morais MB, Vazquez-Frias R, Becker-Cuevas DJ, Boggio-Marzet CG, Delgado-Carbajal L, et al. Consensus on the diagnosis and treatment of cow's milk protein allergy of the Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition. *Rev Gastroenterol Mex (Engl Ed)*. 2022; 87: 235-50.
- Centers for Disease Control and Prevention Evaluation Research Team. Gaining consensus among stakeholders through the nominal group technique. 2022.
- D'Auria E, Salvatore S, Acunzo M, Peroni D, Pendezza E, Di Profio E, et al. Hydrolysed Formulas in the Management of Cow's Milk Allergy: New Insights, Pitfalls and Tips. *Nutrients*. 2021; 13: 2762.
- Fiocchi A, Bognanni A, Brozek J, Ebisawa M, Schunemann H, WAO DRACMA guideline group. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - I - Plan and definitions. *World Allergy Organ J*. 2022; 15: 100609.
- Strozyk A, Ruszcynski M, Horvath A, Dahda L, Fiocchi A, Nowak-Wegrzyn A, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines update - IV - A quality appraisal with the AGREE II instrument. *World Allergy Organ J*. 2022; 15: 100613.