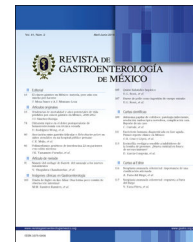




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ORIGINAL ARTICLE

A Latin American 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*[☆]



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KEYWORDS

Cow's milk protein allergy;
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Abstract

Introduction and aim: There are discrepancies in the diagnosis and management of cow's milk protein allergy (CMPA) in Spain and Latin America. The aim of the present study was to find out how Spanish and Latin American pediatric gastroenterologists diagnose and treat CMPA.

Materials and methods: Pediatric gastroenterologists, members of the *Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición*, were invited to fill out a structured survey, the results of which were then compared with the 2012 and 2014 diagnosis and treatment guidelines, respectively.

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Results: The survey results showed that 17% of the participants follow the diagnostic recommendations based on the published consensus and guidelines. To diagnose non-IgE-mediated CMPA, 15% of the participants utilize IgE-specific skin prick tests, 22% use IgE-specific blood tests, and 45% employ oral food challenges. To diagnose IgE-mediated CMPA the percentages for the same diagnostic methods were 57%, 83% and 22%, respectively. Once diagnosis is confirmed, 98% of the participants provide dietary recommendations. In children that are not breastfed, 89% of the participants prescribe an initial extensively hydrolyzed formula, 9% an amino acid formula, 1% a soy formula, and 1% a hydrolyzed rice formula. In patients with IgE-mediated CMPA, 34% of the participants carry out an oral challenge once treatment is completed, 39% according to symptom severity, and 27% in relation to IgE-specific testing.

Conclusion: CMPA management is diverse and there is poor adherence to the clinical practice guidelines.

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PALABRAS CLAVE

Alergia a las proteínas de la leche de vaca;
Alergia alimentaria;
Leche de vaca;
Latinoamérica

Conocimiento sobre el diagnóstico y el tratamiento de la alergia a las proteínas de la leche de vaca por un grupo de gastroenterólogos pediatras en Iberolatinoamérica: resultado de la encuesta del Grupo de Trabajo de Alergia Alimentaria de la Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición Pediátrica

Resumen

Introducción: Existen discrepancias en el diagnóstico y manejo de alergia a las proteínas de la leche de vaca (APLV) en Iberolatinoamérica. El objetivo del estudio fue conocer la forma como el gastroenterólogo pediatra en iberolatinoamérica realiza el diagnóstico y el tratamiento de APLV.

Material y métodos: Se invitó a los gastroenterólogos pediatras miembros de la Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición a contestar una encuesta estructurada y se comparó con las pautas de diagnóstico y tratamiento expresadas en el consenso y la guía publicadas en 2012 y 2014 respectivamente.

Resultados: El 17% sigue las recomendaciones diagnósticas basadas en la evidencia del consenso y guía publicada. Para la APLV no mediada por IgE (APLV-No IgE) el 15% utiliza pruebas cutáneas IgE específicas vs. 57% en las mediadas por IgE (APLV-IgE); el 22% vs. 83% realiza determinación de IgE específica en sangre, respectivamente. La confirmación diagnóstica con prueba de reto oral es realizada por el 45% vs. 22% respectivamente. Una vez confirmado el diagnóstico, el 98% entrega recomendaciones dietarias. En niños no alimentados con leche materna, el 89% inicia con fórmula extensamente hidrolizada, 9% con aminoacídica, 1% fórmula de soja y 1% fórmula de arroz hidrolizada. La prueba de tolerancia en APLV-IgE se realiza en el 34% una vez cumplido el tiempo de tratamiento, en el 39% según la gravedad de los síntomas, y en 27% con la negativización de test IgE específicos.

Conclusión: Existe mucha diversidad en el manejo de la APLV y pobre adherencia a las guías de práctica clínica.

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Introduction and aims

Food allergies encompass a broad spectrum of disorders that are the result of adverse immune responses to dietary antigens. Cow's milk protein allergy (CMPA) is defined as an adverse reaction to one or more cow's milk proteins (CMPs), which are divided into 2 groups: a) caseins and b) serum proteins. In the latter, alpha lactalbumin and beta lactoglobulin stand out, through a specific immune response mediated or not by immunoglobulin E (IgE). CMPs are customarily the first nonhuman dietary proteins ingested by infants, thus CMPA

is the most frequent food allergy within the first months of life.¹⁻³ The prevalence of CMPA in Latin America is unknown, but it appears to be increasing, as is occurring in the rest of the countries of the world.

The clinical picture of CMPA presentation varies greatly, and its diagnosis is essentially based on the knowledge of its clinical expression. It can manifest in more than one system: gastrointestinal (50 to 60%), dermatologic (30 to 50%), and respiratory (20 to 30%).⁴ Its clinical manifestations can be classified: 1) by the temporality of symptom appearance (immediate or delayed), given that allergic reactions

to foods are characterized by a temporal relation between the exposure to the food and the reaction to it; 2) by the organ or system it affects, which is why the allergy presents as syndromes; and 3) by the immune mechanism involved: IgE-mediated, non-IgE-mediated, or mixed. Knowledge of the clinical presentation of CMPA enables its diagnostic suspicion.⁵

The term non-IgE-mediated CMPA includes all the adverse reactions to CMPs in which the presence of IgE antibodies has not been confirmed against those proteins. Symptoms tend to appear after one hour, or even after several days. Reactions can be generalized or involve only digestive symptoms, digestive and cutaneous symptoms, and much less frequently, respiratory symptoms, often with nutritional compromise. Symptoms are mild or moderate. Diagnosis is based on the oral food challenge (controlled oral food exposure test) and is normally resolved around one year of age.¹⁻³ In the case of IgE-mediated CMPA, symptoms appear within minutes or one hour after CMP exposure and symptomatology can range from mild to severe symptoms of anaphylaxis. Diagnosis is based on the food challenge, but the test is contraindicated in severe cases. Quantification of specific IgE in serum is part of the follow-up in cases of IgE-mediated CMPA and is helpful in deciding when to perform the challenge to measure the tolerance to the protein, which can usually be achieved after one year of age.^{1,2}

The clinical history, with specific questions about the dietary history that includes a detailed description of the different foods related to the appearance of symptoms, enables the potential allergen to be identified and the pathophysiologic mechanism to be detected.⁵ Strict suspension of the CMPs is the first step toward diagnosing allergy.^{2,6} Clinical improvement with symptom resolution, strong suspicion from the clinical history, and disease relapse with the food challenge are the only diagnostic elements for confirming non-IgE-mediated CMPA. The food challenge provides strong evidence in the absence of laboratory tests, both for the diagnosis and the later evaluation of tolerance acquisition in non-IgE-mediated CMPA. In IgE-mediated CMPA, specific IgE quantification or skin prick tests confirm the diagnosis and progressively serve to evaluate the reintroduction of CMPs or the acquisition of tolerance.^{2,7-9}

CMPA treatment consists of CMP restriction. CMPs should also be suspended from breastfeeding mothers' diets, and infants on formula should drink extensively hydrolyzed (EH) protein formulas or those based on amino acids. CMPs should be completely suspended from the diet of infants receiving complementary foods. Infants that present with CMPA with intestinal involvement or CMPA-induced enteropathy often have symptoms of nutrient malabsorption that manifest with chronic diarrhea, abdominal pain, colic, vomiting, steatorrhea and/or failure to thrive. In those cases, the intestinal lesion can also be accompanied by lactase deficiency and consequent lactose intolerance. Such cases could require the restriction of lactose at the beginning of treatment and until the normalization of the intestinal lesion.⁷⁻⁹ Nevertheless, that does not mean that all patients with CMPA require lactose restriction.

In Latin America, experts on CMPA met in 2012 to formulate a consensus¹⁰ and in 2014 to put together guidelines for the diagnosis and treatment of CMPA.¹¹ The aim of

the present study was to determine how Latin American and Spanish pediatric gastroenterologists diagnose and treat CMPA and compare those data with the recommendations for diagnosis and treatment expressed in the consensus and guidelines published in 2012 and 2014, respectively.

Materials and methods

An observational, cross-sectional, exploratory survey-type, multicenter study was conducted on healthcare professionals from countries that belong to the *Sociedad Latinoamericana de Gastroenterología, Hepatología y Nutrición Pediátrica (SLAGHNP)*. The survey was formulated by the researchers of the Food Allergy Working Group of the *SLAGHNP* (MCT, ERR, and RVF) and consisted of 22 questions on diagnostic and therapeutic procedures in CMPA. The survey was applied between June 2016 and June 2017. It was initially sent by email and then placed on the *SLAGHNP* website to be completed online, accessible to all pediatric gastroenterologists and nutritionists that are members of the *SLAGHNP*.

The CMPA questionnaire for pediatric gastroenterologists of the *SLAGHNP* was composed of the following items: for the approach to condition, what reference guidelines or recommendations do you use? Are you familiar with the Ibero Latin American Consensus on the Diagnosis and Treatment of CMPA? Do you employ a scoring system or symptom record for making the diagnosis? Are there blood tests for specific IgE measurement/quantification available in the public healthcare system in your country? Do you perform an endoscopic procedure in the diagnostic approach to CMPA? If non-IgE-mediated CMPA is suspected, do you perform skin prick tests to make the diagnosis? If non-IgE-mediated CMPA is suspected, do you carry out dosing/quantification of specific IgE in serum to make the diagnosis? Do you perform diagnostic food challenges? If so, where are they carried out? Once the diagnosis is confirmed, do you provide recommendations on dietary diversification? In children diagnosed with CMPA that are fed a milk formula, what type of formula do you indicate as initial treatment? Is said treatment subsidized in your country? Is access to special types of formula difficult? How long do you exclude CMPs from the diet? Do you follow a protocol for the controlled oral food challenge to evaluate tolerance acquisition? If tolerance is not achieved and the symptoms reappear, how long do you continue treatment until the next test? Who follows the IgE-mediated CMPA? If IgE-mediated CMPA is suspected, do you perform skin prick tests for making the diagnosis? If IgE-mediated CMPA is suspected, do you carry out dosing/challenge/quantification of specific IgE in serum to make the diagnosis? Do you perform diagnostic food challenges? If so, where are they carried out? What are the criteria you employ for carrying out the controlled oral food challenge?

Statistical analysis

Descriptive statistics were carried out, utilizing frequencies and proportions for the qualitative variables.

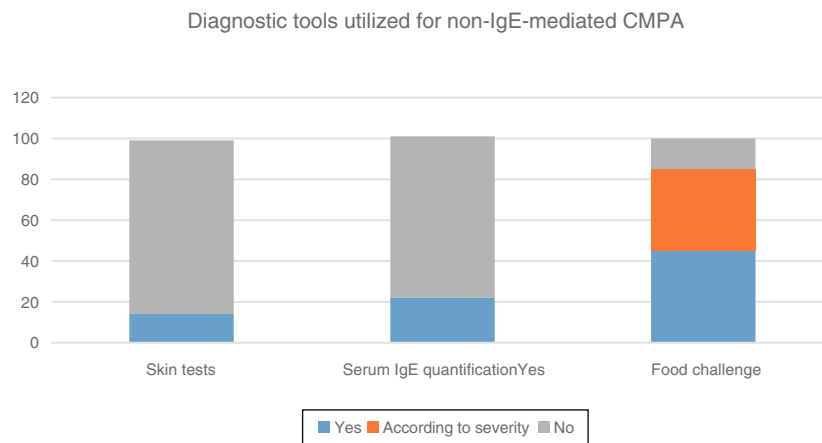


Fig. 1 Diagnostic tools utilized for non-IgE-mediated cow's milk protein allergy (CMPA) by the Latin American and Spanish pediatric gastroenterologists surveyed.

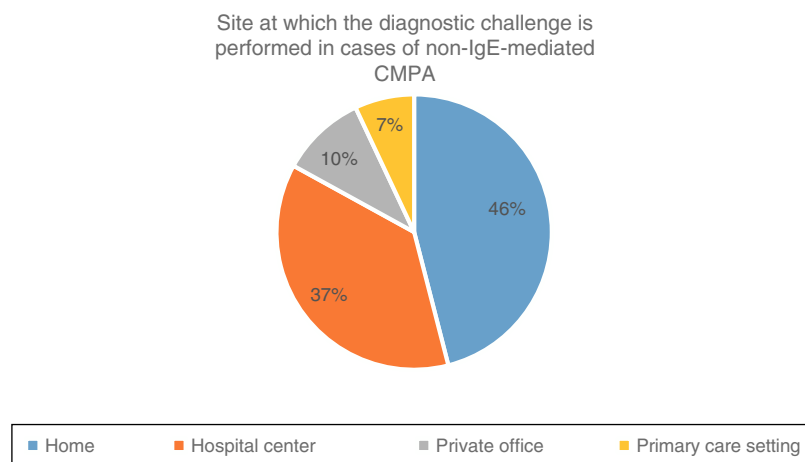


Fig. 2 Site at which the diagnostic challenge is performed in cases of non-IgE-mediated cow's milk protein allergy (CMPA) utilized by the Latin American and Spanish pediatric gastroenterologists surveyed.

Ethical considerations

Given the characteristics of the present study, it was exempt from review by an ethics committee and was carried out in accordance with the principles of the Declaration of Helsinki.

Results

A total of 121 pediatric gastroenterologists from 15 countries that belong to the *SLAGHNP* participated in the survey: 51 from Argentina, 6 from Bolivia, 9 from Chile, 2 from Colombia, one from Cuba, one from the Dominican Republic, one from Ecuador, 4 from Brazil, 2 from Spain, 26 from Mexico, one from Nicaragua, 3 from Paraguay, 2 from Peru, one from Uruguay, and 11 from Venezuela. Of all the participants that answered the questionnaire, 79% ($n = 86$) were familiar with the recommendations in the abovementioned consensus and/or guidelines for the diagnosis and treatment of CMPA, but only 17% followed them. Forty-two percent of the participants utilized the guidelines of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition

(ESPGHAN) or of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), and 30% utilized the national guidelines from their respective countries.

Sixty-nine percent of the participants stated that the diagnosis was usually made by the pediatrician or family physician, before consulting with the gastroenterologist. Fifteen percent of the participants utilized some type of scoring system or symptom record to make the diagnosis. As to the availability of tests for measuring/quantifying specific IgE in the public healthcare sector, the response was affirmative in 20% for blood tests, 5% for blood tests and skin tests, and 19% for skin tests. Regarding the diagnostic approach, 25% carried out some type of endoscopic study: 12% upper endoscopy, 5% rectosigmoidoscopy, 1% colonoscopy, and 7% upper and lower endoscopy.

When non-IgE-mediated CMPA was suspected, 15% utilized skin tests and 22% carried out a blood test to determine specific IgE. Eighty-five percent of the participants utilized food challenges, but 47% did so according to symptom severity (Fig. 1). Forty-six percent indicated carrying out said test at the patient's home, 37% in a controlled manner at a hos-

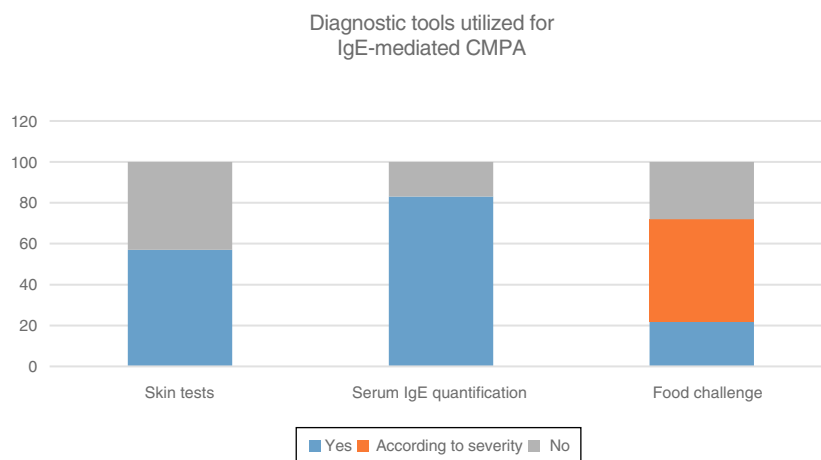


Fig. 3 Diagnostic tools utilized for IgE-mediated cow's milk protein allergy (CMPA) by the Latin American and Spanish pediatric gastroenterologists surveyed.

pital center, and 17% in a controlled manner at a private consultation office or primary healthcare setting (Fig. 2).

When IgE-mediated CMPA was suspected, 66% carried out follow-up together with an allergist, 22% carried out the follow-up alone, and 22% referred the patient to an allergist. Likewise, 57% carried out skin tests, and 83% dosing/quantification of specific IgE in serum to make the diagnosis. Twenty-two percent of the participants utilized food challenges, 28% never used a food challenge in IgE-mediated CMPA, and 50% used it depending on symptom severity (Fig. 3). A total of 72% of the participants indicated conducting the test in a controlled setting at a hospital center, 10% at the patient's home, and 18% in a controlled setting at a private consultation office or a primary care center (Fig. 4).

When the diagnosis of CMPA was confirmed, 98% of the participants surveyed provided dietary diversification recommendations to the patient's parents or guardians. After confirming the diagnosis in infants fed with milk formula, 89% prescribed EH CMP formula, 9% amino acid formula,

1% soy protein formula, and 1% hydrolyzed rice protein formula, as initial treatment (Fig. 5). Treatments were government-subsidized in the countries of 32% of the participants, partially subsidized in the countries of 33%, and not subsidized in the countries of 35% of the participants. Forty-nine percent of the participants stated that access to EH formulas was difficult for the patients with CMPA.

To evaluate tolerance acquisition once the food exclusion period was over, 54% of the participants followed a protocol for the controlled oral food challenge.

Regarding the criteria for carrying out the oral food challenge in patients diagnosed with IgE-mediated CMPA, 34% of the participants carried it out according to treatment period, 39% according to symptom severity, and 27% according to specific IgE testing (8% utilized skin prick tests and 19% measured specific IgE in serum). If the test showed that tolerance had not been achieved, 68% continued treatment for 6 more months until the next test, 24% continued treatment for 12 more months, and 8% for more than 12 months.

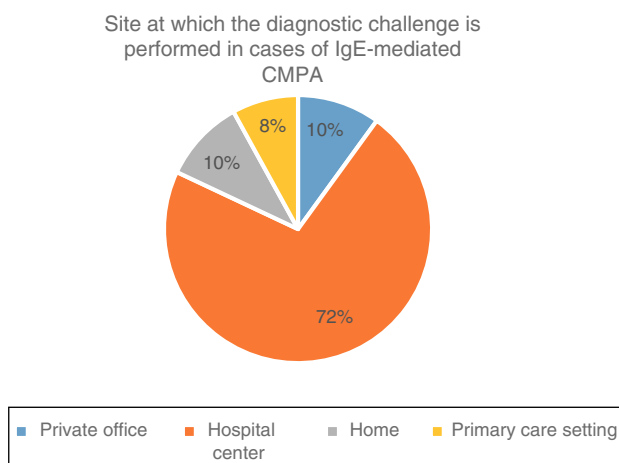


Fig. 4 Site at which the diagnostic challenge is performed in cases of IgE-mediated cow's milk protein allergy (CMPA) utilized by the Latin American and Spanish pediatric gastroenterologists surveyed.

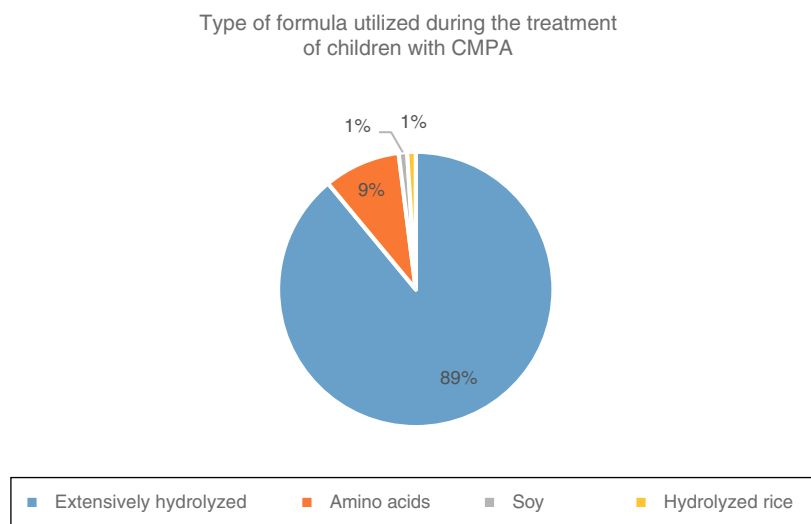


Fig. 5 Type of formula utilized during the treatment of children diagnosed with IgE-mediated cow's milk protein allergy (CMPA) by the Latin American and Spanish pediatric gastroenterologists surveyed.

Discussion

The results of the present survey indicate that the diagnostic focus among the participants varies widely. A small minority (17%) follows the diagnostic recommendations based on consensus and guideline evidence, even though 79% are familiar with them. Regarding treatment, the responses were more uniform and in agreement with the recommendations. The variability in the number of responses per country must be kept in mind, as it largely reflects the varying number of specialists in pediatric gastroenterology in each country.

In relation to diagnosis, knowledge of the clinical presentation of CMPA increases the possibility of diagnostic suspicion.¹²⁻¹⁵ Even though 15% of those surveyed utilize a symptom scoring system that can apparently facilitate the diagnostic process, there are no validated or recommended scoring systems in the current guidelines. The Latin American guidelines recommend carrying out a clinical history, specifically asking about the patient's dietary history, taking special care to include the different foods associated with the appearance of symptoms, and detecting the pathophysiologic mechanism involved.¹¹

Regarding diagnostic methods, specific IgE testing is available to one-third of the participants surveyed. The correct use of food challenges is essential for confirming any CMPA diagnoses.

It is striking that up to one-fourth of the gastroenterologists surveyed employ endoscopic examinations to confirm the diagnosis of CMPA. Said situation is not supported in the guidelines and endoscopy is not recommended as a diagnostic method in CMPA because it is invasive, costly, and can be substituted by other methods that are simpler and have higher sensitivity and specificity.

To diagnose non-IgE-mediated CMPA, a considerable number of the participants utilize skin tests or specific IgE determination in serum, which are not indicated in the Ibero Latin American consensus or Latin American guidelines due to their low diagnostic yield and high prob-

ability of false-positive and false-negative results. The Latin American guidelines do not recommend the use of those tests (level of evidence 2b; recommendation grade B).

Both the consensus and the guidelines recommend the food challenge with CMPs as a definitive test and gold standard. However, the Latin American guidelines recognize that there is an ongoing debate as to which children should undergo the test and how it should be performed (level of evidence 2b, recommendation grade B). Fifteen percent of the participants still do not utilize a diagnostic food challenge, whereas 46% indicate its performance at the patient's home, following the consensus recommendation for patients that are not at risk for severe reactions. Seventeen percent indicate its performance in the consultation office for patients that are not at risk, following the recommendation of the Latin American guidelines (level of evidence 4, recommendation grade C).

Eighty-eight percent of the gastroenterologists surveyed utilize skin tests and specific IgE measuring for diagnosing IgE-mediated CMPA. According to the consensus, they can be useful for patient follow-up, marking the time a food challenge test can be performed to evaluate tolerance recovery (level of evidence 3a, recommendation grade B). The challenge test is not frequently used by the gastroenterologists in that group of patients, even though the consensus and Latin American guidelines recommend it when there is no risk for severe reactions, and always under medical supervision at a hospital center (level of evidence 4, recommendation grade C).

Eighty-nine percent of the study participants prescribe treatment using formulas with EH CMP formulas, in accordance with the consensus and Latin American guidelines (level of evidence 4, recommendation grade C), as well as formulas with amino acids in severe cases or in patients that do not respond to the EH formulas (level of evidence 4, recommendation grade C). According to the Latin American guidelines, hydrolyzed rice formulas have been shown to be useful in CMPA. Nevertheless, there are few studies on the

subject at present, and so a recommendation with a high level of evidence cannot be made.

The guidelines do not recommend soy-based formulas for the treatment of CMPA. A soy-based formula could be used in children with CMPA that are above 6 months of age, present with IgE-mediated forms, do not accept or tolerate an EH formula, whose family is not able to afford a hypoallergenic formula, or whose parents have strong preferences, such as a vegetarian diet (level of evidence 4, recommendation grade C).

Treatment response depends on the compliance with the CMP-free diet, making recommendations on how to follow a strict CMP-free diet necessary. Ninety-eight percent of the gastroenterologists inform the parents as to which foods must be suspended and the inadvisability of unnecessarily avoiding other nutrients. The cost of formulas is another basic factor, with a low percentage of subsidized treatments in half of the countries included in the survey. Thus, the benefits of breast milk are reinforced by the abovementioned reasons, as well as numerous others, highlighting immunologic, emotional, and nutritional factors.

The responses to the questions on treatment duration were diverse, which most certainly is associated with the different recommendations published, with low levels of evidence. The Latin American guidelines recommend maintaining the elimination diet for 12 months for non-IgE-mediated CMPA and up to 18 months for IgE-mediated CMPA. However, duration is guided by patient symptomatology. The consensus recommends up to 12 months of age and having completed at least 6 months of treatment. Importantly, due to the lack of evidence, both the consensus and the Latin American guidelines make that recommendation based on expert consensus.

Conclusions

The present study is the first to analyze the knowledge about and application of the guidelines for the diagnosis and treatment of CMPA in Latin American countries. The results show much diversity in the management of CMPA and poor adherence to the guidelines. From the platform of the *SLAGHNP*, we must make the commitment to update the guidelines, unify criteria, and publicize the recommendations to improve healthcare resource use, prevent overdiagnosis, and make sure that all children with CMPA receive adequate treatment.

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Conflict of interest

MCTE has received funds to attend congresses and has been on the advisory committees of Nutricia Bagó and Sanofi.

ERR has participated in educational activities funded by Casen Fleet, Ferrer Internacional, Ferring, Mead Johnson, and Nestlé.

RVF has received funds to attend congresses, has received fees for speaking at Nestlé and Sanofi, and has received fees as a speaker for Carnot, BioGaia, and Nutricare.

MBdM has received fees for being a speaker and for developing scientific material for Danone, Nestlé, Biolab, and Ache/BioGaia.

PS has received fees for speaking at and advising Nutricia Medical Care.

CBM has received funds to attend congresses and has received fees for lectures as a KOL for Nutricia, Mead Johnson, Nestlé, Sanofi, and Biocodex.

The remaining authors declare they have no conflict of interest.

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