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Research Article

# Diagnosis and Management of Cow's Milk Allergy (CMA) in Infants and Children: From Guidelines to Clinical Practice in Brazil

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## Abstract

**Background:** The diagnosis of non-IgE mediated cow's milk protein allergy (CMA) in infants is based on the elimination of cow's milk protein from the diet with clinical improvement, followed by reintroduction with relapse of symptoms. Given the potential for reactions to residual allergens in extensively hydrolyzed formula and the lack of real-world evidence on this subject in Brazil, this study aims to determine the role of amino acid formulas (AAFs), in the diagnosis and management of CMA in Brazil using a survey of experts.

**Methods:** Interviewees answered a survey regarding when AAF should be the first option in cases of suspected CMA, advantages and limitations of this approach, impact of delayed diagnosis and precautions when prescribing AAFs. Results were compiled and presented to validate responses and to collect additional information.

**Results:** Ten pediatric experts from Brazil participated. There was consensus that elimination of cow's milk from the diet and oral food challenges are key to diagnose CMA, and that AAF expedites diagnosis. Eighty percent agreed that i) AAF should be the first option for anaphylaxis, multiple food allergies or food protein-induced enterocolitis syndrome; ii) economic burden is the main disadvantage associated with the use of AAF. Most respondents agreed that there is a delay in CMA diagnosis in Brazil that may lead to faltering growth.

**Conclusions:** In line with current guidelines, this panel agreed that AAF should be recommended for complex presentations and for patients unresponsive to EHF. However, when the diagnosis is unclear, the use of AAF followed by oral challenge may shorten the time to confirm or exclude the diagnosis and to avoid unnecessary pharmacological and other nutritional managements or diagnostic tests. The panel pointed out that reducing psychological and social burdens must be considered when choosing the best approach for each patient.

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## ABBREVIATIONS

AAF: Amino Acid Formula; CMA: Cow's Milk Allergy; DBPCFC: Double-Blind, Placebo-Controlled Food Challenge; EHF: Extensive Hydrolyzed Formula; FPIES: Food Protein-Induced Enterocolitis Syndrome; SPT: Skin Prick Test

## INTRODUCTION

Food allergy is defined as an adverse immunologic response to a dietary protein [1]. Its prevalence has been increasing worldwide in recent decades in many western countries, appearing to result from environmental changes, urbanization, and biodiversity loss [2]. Early gut microbiome and gut integrity are implicated in the immune dysregulation associated with food allergy. The intestinal microbiome plays an essential role in the maintenance of the mucosal barrier and the immune response. Advances in the microbiome, metagenomics, proteomics, metabolomics, and systems biology are improving the prevention and treatment of chronic noncommunicable diseases, including allergy [3].

Cow's milk allergy (CMA), is one of the most common food allergies among children, affecting 1.9% to 4.9% [4]. According to data provided by the Brazilian Ministry of Health from 34 municipalities in the country, between 0.2% and 0.7% of children are treated for CMA in the public health system [2,3]. A survey conducted among 9,478 patients evaluated by 30 pediatric gastroenterologists in five geographical regions in Brazil in 2005 estimated an incidence and prevalence of suspected CMA of 2.2% and 5.7%, respectively [5].

Symptoms of CMA may include gastrointestinal, cutaneous, and respiratory reactions, such as vomiting, diarrhea, loose stools, urticaria, rhinitis, asthma, and growth failure [6,7]. Severe cases of anaphylaxis and food protein-induced enterocolitis syndrome (FPIES) may also occur [7]. Rapid-onset reactions are usually IgE-mediated and present shortly after milk ingestion. Slow-onset symptoms are non-IgE mediated and may take hours or days to start [8,9]. In most infants, CMA is usually non-IgE mediated. In contrast, IgE- mediated reactions are more frequent in children above the age of 6 months [9,10]. Gastrointestinal manifestations of CMA are also observed in other disorders (including infant colic, constipation, gastroesophageal reflux disease, and intestinal infections), with no pathognomonic signals [11,12], possibly resulting in over-diagnosis of CMA [10].

The detection of serum milk specific IgE, skin prick test (SPT), and atopy patch tests have been used as diagnostic tools. However, there are limitations, because, although they can reliably identify negative cases, their high sensitivity results in false positive results [8,11,13,14]. The double-blind, placebo-controlled food challenge (DBPCFC), is considered the gold standard for confirming the diagnosis of CMA [9,13,15,16]. Nevertheless, DBPCFC is an expensive and time-consuming test, requiring careful medical supervision. Thus, the majority of the guidelines accept an open challenge in infants suspected of CMA [8,9,13,15]. In clinical practice, the open challenge is the first option when negative results are expected [17-19], and in infants younger than three years of age with an objective set of symptoms [19]. In fact, a recent study with 415 Brazilian pediatricians showed low adherence to international food allergy guidelines due mainly to lack of resources, but possibly also to lack of awareness [20].

The diagnosis of non-IgE mediated CMA in exclusively breastfed infants is based on the elimination of cow's milk protein from the maternal diet for 2–4 weeks with clinical improvement, followed by reintroduction with relapse of symptoms. For bottle-fed and partially bottle-fed infants, the appropriate choice of a hypoallergenic formula is crucial [21]. It is accepted that most children with CMA will improve on an extensively hydrolyzed formula (EHF) [22]. Nevertheless, some infants may react to residual allergens [15,23], and will benefit from an amino acid formula (AAF) [9,24].

A review of the United Kingdom's resource use for CMA diagnosis and treatment found inconsistencies in the choice of formulas, in referral decisions and with respect to issues such as delayed diagnoses, incorrect diagnoses, and underdiagnoses [7]. A survey in the United Kingdom showed that diagnostic and therapeutic pathway differs according to the physician's or the parent's perspective [25]. Given the lack of real-world evidence on this subject in Brazil, a panel survey was conducted to obtain the views and experience of experts regarding the role of AAFs in CMA diagnosis and management in Brazil and to generate additional insights in this area.

## MATERIALS AND METHODS

This study was divided into two steps: an online survey, answered by experts in the area, followed by a panel discussion. A survey with seven questions was developed to understand strategies used by the experts to diagnose and manage CMA in their practices. The survey was reviewed by the lead author. The questionnaire containing multiple- choice and open-ended questions [see Additional file 1] was sent to all participants of the study who were instructed to answer according to their experience.

Descriptive statistics were used to analyze the results. The responses were extracted with counting/ranking for multiple-choice questions and categorization for open-ended questions. Subsequently, the results from all responses were summarized using frequency analyses, with descriptive purposes only. Results were reported as the frequency of each response.

Subsequently, experts were invited to participate in a face-to-face meeting in September 2019 in Sao Paulo. Following the presentation of the survey results, the experts participated in a panel discussion to validate their opinions, elaborate on their views, share their experience and comment on the differences between distinct Brazilian scenarios (public versus private healthcare system; wealthier and poorer regions), assess consensus and gather possible insights and limitations of various strategies used for the diagnosis and treatment of CMA. During the meeting, the participants addressed issues related to treatment patterns, difficulties, and barriers for the diagnosis and treatment of patients with CMA and the availability of published evidence and possible measures to improve their scenarios.

No ethics approval or informed consent to participate were necessary and authors reported their own knowledge and experience.

## RESULTS AND DISCUSSION

Ten specialists in pediatric allergy, immunology, gastroenterology and nutrition from the private and public healthcare systems, working at referral centers for food allergy and with extensive experience in the diagnosis and treatment of CMA were invited to participate in the study. The participants were from the South, Southeast, Northeast, and Central-west regions of Brazil. The participants are authors of this paper. Figure 1 presents the experts' responses regarding situations in which they agree with using AAF as the first option in cases of suspected CMA. Anaphylaxis, multiple allergies, and FPIES were the responses with the highest concordance, with 80% (8/10) or more of the responses. Most experts also selected the option "other" and described additional situations as follows: blood in stool, enteropathy with profuse diarrhea blood loss-induced anemia, signs and symptoms of non-IgE mediated food allergy, a combination of gastroesophageal reflux disease with irritability and feeding difficulties, association of malnutrition with relevant skin and gastrointestinal conditions, and multiple dietary exclusions.

Figure 2 presents an agreement on advantages in recommending AAF in cases of suspected CMA. The experts were unanimous in pointing out the speed of CMA diagnosis or exclusion as the advantage of recommending the amino acid formula to be the first option. Eighty percent (8/10), of the experts pointed to cost-effectiveness and precision of non-IgE mediated CMA diagnosis, as well as the speed of symptom relief for patients as advantages.

Figure 3 presents an agreement on the limitations of recommending AAF as the first option in the case of suspected CMA. "Pricing" was selected by most of the experts, while only a minority mentioned lack of scientific support. Two experts also selected the option "Other" and mentioned one additional limitation each, as follows: difficulty in palatability and non-compliance with dispensation rules in public services.

When asked if it is possible and how to differentiate the CMA-related gastrointestinal symptoms and those associated with discomfort or functional gastrointestinal disorders, 60% (6/10), of the experts highlighted the importance of excluding cow's milk from the diet and 67% (4/6), also mentioned the oral food challenge. Twenty percent (2/10), of the responses referred only to the clinical presentation as a means of diagnosis. During the panel discussion, there was a consensus that the elimination of cow's milk from the diet, followed by the oral food challenge is the gold standard method to diagnose CMA. Ninety percent (9/10), of the experts agreed that there are delays in CMA diagnosis in Brazil. While the ideal timeline was generally agreed to be between 2 and 4 weeks for cases of clearer symptomatology and up to 9 weeks for more complex cases, the timeline reported by the experts for the private and the public settings was one month and from 2 to 6 months, respectively. Timelines were reportedly shorter for IgE-mediated allergies than for non-IgE mediated ones.

When asked about the main impacts of delayed CMA diagnosis, malnutrition was mentioned by 50% (5/10), of the experts, a combination of psychological, clinical, economic, and social impacts were mentioned by 30% (3/10), and loss of breastfeeding was mentioned by 20% (2/10). Other responses included lower height-for-age, social exclusion, impact on the parent's professional life and family dynamic, the cost of trying out new formulas, medications, exams, and medical appointments, as well as repercussions of continued symptoms.

When asked about primary cautions physicians should have in mind when prescribing AAF, 50% (5/10), of the experts raised guiding and educating the family, with emphasis on the importance of regular follow-up to confirm the diagnosis. While the importance of the oral challenge test for diagnosis confirmation was spontaneously raised by 30% (3/10), of the experts when responding to the survey, all physicians agreed to it in the panel discussion. Nevertheless, most experts mentioned

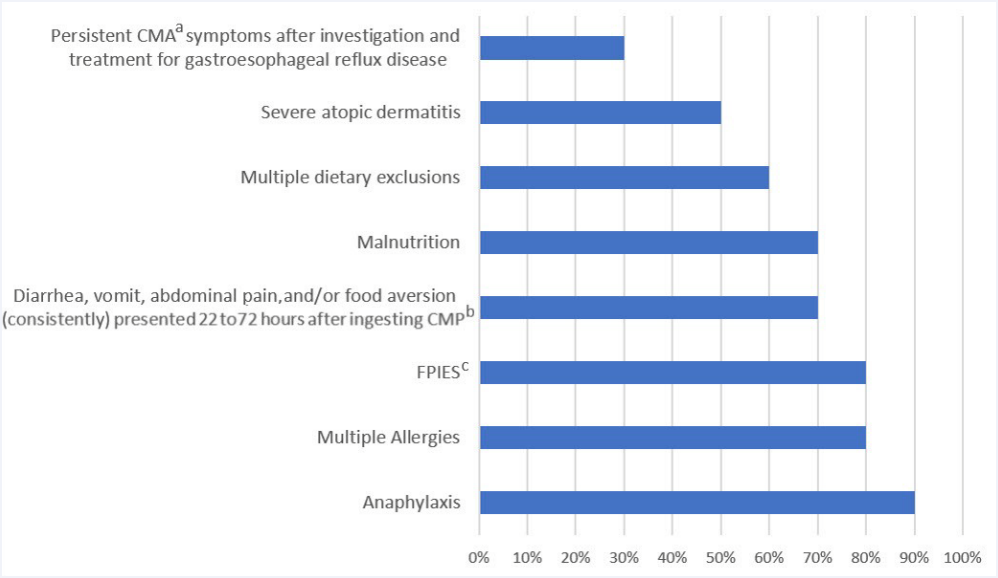


**Figure 1** Agreement levels: Reasons for using amino acid formula as the first option for suspected CMA.
[a]CMA, cow's milk protein allergy; [b]CMP, cow's milk protein; [c]FPIES, food protein- induced enterocolitis syndrome.

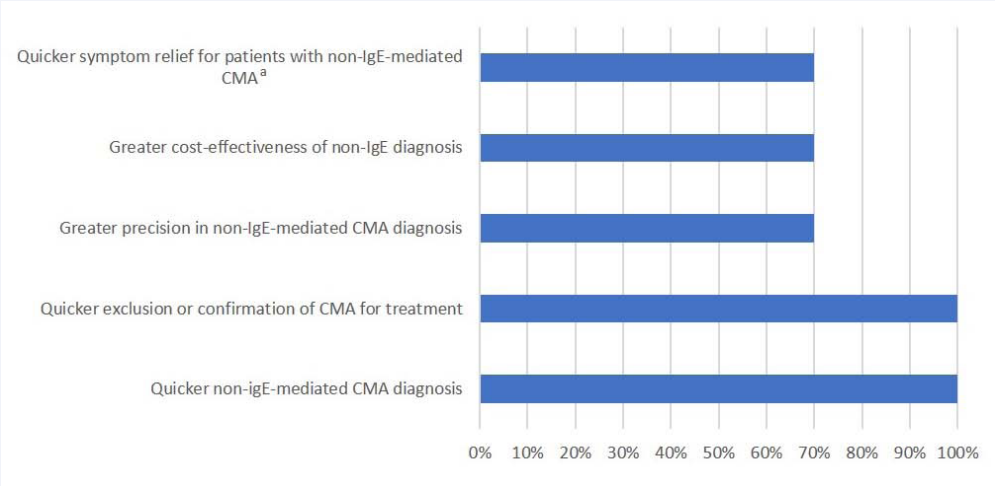


**Figure 2** Agreement on advantages in recommending AAF in cases of suspected CMA.
[a]CMA, cow's milk protein allergy

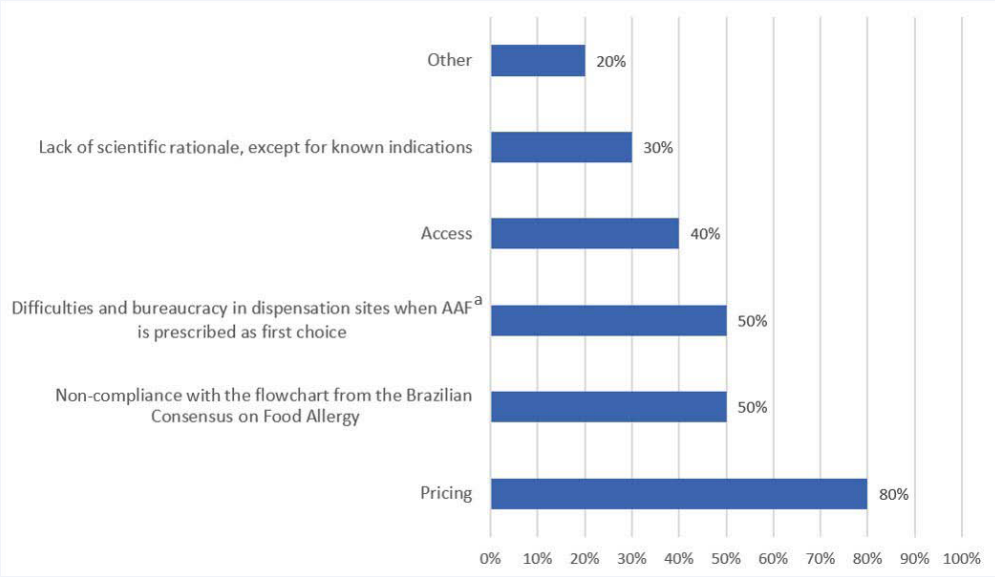


**Figure 3** Agreement levels: Limitations of use of amino acid formula (AAF) in cases of suspected CMA.
CMA, cow's milk protein allergy; [a]AAF, amino acid formula

difficulties in performing the oral challenge, including technical difficulties and reluctance by many parents in subjecting their children to the test. According to the experts, low-income families may fear losing their right to receive the formula provided by the public health system depending on the results of the oral food challenge. Two interviewees mentioned that transitioning to an EHF may help develop tolerance, despite the need for well-designed studies to determine whether the choice between EHF and AAF formula influences the development of tolerance.

Early diagnosis of CMA is essential. For the diagnosis of IgE-mediated CMA, the use of specific serum IgE tests or SPTs are recommended; nevertheless, it is important to recognize that these methods simply identify sensitization (i.e. presence of IgE antibodies) to a food allergen, and do not confirm allergy. There are no validated laboratory tests for the diagnosis of non-IgE CMA, apart from evaluating clinical responses to an elimination diet followed by a cow's milk challenge. As a result, CMA diagnosis and treatment are closely connected and are largely dependent on clinical responses to dietary modifications [22]. Moreover, while a change to a specific diet may be necessary from a treatment perspective and considering the patient's history and risk avoidance, the response can only be evaluated after a few weeks of its implementation, hampering rapid diagnosis. Comprehensive guidelines have been developed in

this area in several countries, including one by the World Allergy Organization (WAO) [26], and others in the UK (Milk Allergy in Primary care, MAP) [12], Australia [27], and Brazil [22].

In this panel, ten experts provided real-world data and region-specific recommendations considering existing evidence, challenges, and opportunities for the use of AAF in CMA management. The findings about the use of AAF as the first option in cases of suspected CMA accompanied by severe conditions (such as anaphylaxis, FPIES, and malnutrition) are in line with national and international guidelines [1,12,22-24,28]. There was also considerable consensus regarding the advantage of this strategy with respect to time from start of treatment to diagnosis confirmation, and greater cost-effectiveness by allowing earlier oral challenge test.

Regarding the drawbacks and limitations of prescribing AAF as first-line treatment, the number one response was its high price. As observed in other countries, the AAF average price is higher (around 1.6 times in Brazil) than that of EHF, considering data from five Brazilian states (public state health secretaries) [29]. Comprehensive studies considering whole CMA treatment and health resource use in patients with CMA with or without complications are lacking, as are studies on cost-effectiveness. These data would be important to inform use and outcomes from incorporation by the public healthcare system in Brazil, where the public health system provides the EHF and AAF for free. In fact, roughly half of the experts mentioned access issues and lack of compliance with current Brazilian and international guidelines.

Lozinsky et al., found that the burden of CMA on families includes exhaustion in 46.7% of parents and stress or anxiety regarding the child's health in 55.7%; moreover, 33% of fathers delayed going back to work due to the child's health problems and the time required for diagnosis [25]. In this panel, physicians also raised the issue of the psychological, economic, and social burden related to the delay in diagnosis. Their role in alleviating this burden, educating and comforting the family, was also emphasized. Proper guidance to families was considered to contribute to timely follow-up and improved rates of diagnosis confirmation and testing for tolerance development.

This panel found that the diagnosis timelines in private institutions met the expected timeframe of 2 to 4 weeks; for complex cases, particularly in public institutions, the timeframe for diagnosis may extend considerably up to 6 months, which may be aggravated by recent developments in the country's financing of public healthcare [30]. Of note, according to a Brazilian cost-effectiveness study, the use of AAF in the elimination diet of infants with suspected CMA has lower cost and results in an increased number of symptom-free days as compared to the current diagnostic recommendations of the Brazilian Food Allergy Guidelines (based on EHF or soy milk) [6].

This paper intends to present real-world evidence regarding the challenges of implementing guidelines and highlighting the lack of scientific support for cases of greater urgency or harder diagnosis. As a first step, it is important to emphasize that breastfeeding should be the first option whenever possible. The maternal elimination diet of cow's milk should be implemented when there are symptoms of suspected CMA, allowing the infant to continue breastfeeding. Policies to encourage and support breastfeeding should be prioritized.

Potential conflicts of interest with different companies including manufacturers of infant formula have been declared by authors of this study. Although the authors are specialists working at referral centers with large experience in the diagnosis and treatment of food allergies, there is a risk of unconscious bias.

## CONCLUSION

This panel considered that AAF could significantly contribute to the diagnosis and treatment of CMA in the real-world setting. Particularly in severe, unclear, and/or non- IgE mediated cases and in those unresponsive to EHF, the use of AAF followed by oral food challenge may shorten the time to confirm or exclude the diagnosis, avoiding unnecessary pharmacological treatments or diagnostic tests. This may also help to reduce parental anxiety and relieve the economic burden, which should be seriously considered by the physician, along with educating parents and caregivers. While current national and international guidelines provide a general roadmap for CMA management, the availability of more data and guidance on these aspects may improve the care of patients with suspected CMA.

## CONFLICT OF INTEREST

MCV has produced educational materials, received research funding and consultancy and/or educational lecture fees from Danone Nutricia, Nestlé Nutrition, Biolab and Aché laboratories.

CPB has produced educational materials and received lecture fees from Danone Nutricia and Mead-Johnson.

MBM has produced educational materials, received research funding and consultancy and/or educational lecture fees, and supported the development of research projects from Danone Nutricia, Ach laboratories, Biolab, Laboratório Bago, and Nestlé Nutrition.

APC received fees for services performed for Danone Nutricia, Sanofi and Aché.

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