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Real-life management of gastrointestinal cow's milk protein allergy in Brazilian infants

Vanessa C. C. Rodrigues[a], Marcelo C. M. Fonseca[b], Dirceu Solé[c], Adiana Sanudo[d], Mauro B. Morais[e,*]

[a]*Postgraduation Program on Nutrition, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil*
[b]*Department of Gynecology, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil*
[c]*Division of Allergy, Clinical Immunology and Rheumatology, Department of Pediatrics, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil*
[d]*Department of Preventive Medicine, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil*
[e]*Division of Pediatric Gastroenterology, Department of Pediatrics, Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, Brazil*

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Abstract
Objective: To evaluate physicians' management of non-immunoglobulin E-mediated gastrointestinal cow's milk protein allergy (non-IgE-GI-CMPA) in Brazilian infants.
Methods: A total of 447 physicians from all the regions of Brazil answered an online questionnaire concerning their management of formula-fed infants with mild-to-moderate (Case 1) or severe (Case 2) clinical manifestations of non-IgE-GI-CMPA.
Results: In total, 95.3% and 86.0% of the interviewed physicians in cases 1 and 2 prescribed a cow's milk elimination diet ($p < 0.001$). In the initial management, the prescription rates of formulas based on extensively hydrolyzed protein and amino acid were 81.7% and 14.6% for Case 1 and 32.7% and 65.4% for Case 2 ($p < 0.001$); the percentages of answers for prescriptions of drugs or probiotics were 8.3% and 12.1% in cases 1 and 2 ($p < 0.001$); and requests for laboratory tests were 12.3% and 37.7 % ($p = 0.016$). The oral food challenge (OFC) test for the diagnosis of non-IgE-GI-CMPA was indicated by 55.1% and 42.7% of the physicians in cases 1 and 2 ($p < 0.001$). The OFC test was chosen to assess tolerance development by 92% of the interviewees. Performing the diagnostic OFC (D-OFC) test was positively associated with having board certification in pediatric gastroenterology and < 20 years of professional experience and negatively associated with using baked foods as a protein source in the oral tolerance OFC test.
Conclusions: Most interviewees followed the guidelines regarding prescribing an elimination diet; however, many should include the OFC test in diagnosing infants with non-IgE-GI-CMPA. Not performing the D-OFC may have negative consequences on patients and on the public healthcare system.

***Corresponding author**: Mauro B. Morais, Division of Pediatric Gastroenterology, Department of Pediatrics, Escola Paulista de Medicina, Universidade Federal de São Paulo. *Email address*: maurobmorais@gmail.com

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Introduction

Cow's milk protein allergy (CMPA) is an adverse and reproducible reaction to cow's milk proteins that occurs mainly in infants and is a consequence of immediate (immunoglobulin E [IgE]-mediated), late (non-IgE-mediated), or mixed immune reactions.[1-3] The clinical manifestations of non-IgE-mediated gastrointestinal CMPA (non-IgE-GI-CMPA) are unspecific, and its differential diagnosis includes functional gastrointestinal disorders, reflux gastroesophageal disease, and infections, among others,[1-5] as well as symptoms related to gastrointestinal development in infancy.[6] CMPA can cause poor growth, inadequate intake of energy and nutrients, micronutrient deficiencies, a predisposition to the development of feeding difficulties, and affect quality of life.[3,7-17]

The prevalence of CMPA is below 1%[3]; however, some infants have clinical manifestations similar to that of CMPA which are secondary to other disorders.[1-7] Hence, overdiagnosis is likely to occur more frequently than underdiagnosis.[3,4]

Several guidelines agree that the diagnoses of non-IgE-GI-CMPA must be performed in three stages:

1. Clinical evaluation that may eventually include additional laboratory tests
2. Assessment of the response to 2–4 weeks of cow's milk proteins elimination diet
3. If there is a clinical recovery under the diagnostic elimination diet, an oral food challenge (OFC) test must be performed to confirm the diagnosis.[1-4]

A positive OFC test is defined by the recurrence of symptoms after oral exposure to cow's milk proteins that could last for 2–4 weeks.[2,4] The diagnostic OFC (D-OFC) test is strongly recommended, as approximately 50% of infants who begin a cow's milk elimination diet do not have a positive D-OFC test.[7,18] In infants with suspected non-IgE-GI-CMPA, D-OFC test is of importance since the clinical manifestations are nonspecific and often secondary to causes other than food allergy. Furthermore, it is not possible to count on the support of the allergy tests available for patients with IgE-mediated CMPA, and the clinical manifestations are not immediate, making it difficult to establish the association between milk consumption and the occurrence of symptoms.[1-7]

Infants with non-IgE-GI-CMPA usually develop spontaneous oral tolerance (OT) to cow's milk proteins after 6–12 months of an elimination diet, which should be assessed using an OT-OFC test.[1-4]

Surveys performed in Brazil and other countries have shown gaps in knowledge[19-22] and adherence[23-25] of physicians to CMPA guidelines; however, to the best of our knowledge, no published study has focused specifically on diagnosing and treating infants with non-IgE-GI-CMPA in Brazil. Thus, this study aims at evaluating how physicians diagnose and treat non-IgE-GI-CMPA in infants. These results can be used to plan medical education activities, public healthcare programs, and economic studies.

Materials and Methods

Study design and subjects

This cross-sectional study included physicians recruited by email invitations sent to 26,814 Brazilian Society of Pediatrics (BSP) members. The Ethics Committee of the Federal University of São Paulo (CAAE 40956720.4.0000.5505) approved the project, and only those who signed the Informed Consent Form had access to the questionnaire. A sample size of 379 pediatricians was calculated according to Serdar et al. (2021) from a total of 26,814 members of the BSP.[26] We assumed that 50% of respondents would not indicate D-OFC performance, a 95% confidence level, and a 5% margin of error. With a 15% safety margin, the sample expectation was 435. Eligibility criteria included graduating from a medical program and handling babies with CMPA in Brazil, whereas the exclusion criterion was managing less than one infant with CMPA per month.

Questionnaire

To evaluate the applicability of the questionnaire, a pilot study was conducted with 28 physicians from five regions in Brazil. The questionnaire contained information on professional specialization and experience, state, whether physicians worked in public and/or private healthcare services, diagnostic and therapeutic management practices for infants with clinical manifestations of non-IgE-GI-CMPA, and the supply of hypoallergenic infant formulas by the public healthcare system. The Informed Consent Form and the questionnaire were hosted on Google Forms (Google, Menlo Park, CA, US).

Questions regarding the diagnosis and treatment of non-IgE-GI-CMPA were asked based on two clinical cases. The first (Case 1) was of an infant with mild-to-moderate clinical manifestations: "The infant received exclusive breastfeeding until 3 months of age, when an infant formula based on cow's milk proteins was introduced. At 3.5 months of age, the onset of gastrointestinal symptoms compatible with non-IgE-GI-CMPA (without malnutrition) was observed. At four months, the infant was evaluated by a physician and presented non-IgE-GI-CMPA symptoms, being fed with cow's milk infant formula and without the possibility of relactation." The questionnaire included the following possible gastrointestinal symptoms: regurgitation, vomiting, diarrhea, constipation, blood in the stool, food refusal, excessive colic/crying, and irritability.

The second clinical case (Case 2) was an infant with severe clinical manifestations—the clinical history was the same, but the symptoms were described as "severe" and associated with weight loss. The infant did not present with anaphylaxis or food protein-induced enterocolitis syndrome.

The same questions were asked for both clinical cases, including requests for tests, prescription of drugs, dietary management, referrals to specialists, and OFC performance.

In the instructions issued to respondents, they were encouraged to provide answers that reflected clinical practice with respect to their routine care activities and not knowledge obtained from guidelines or medical education

activities. To this end, it was ensured that the answers could not be linked to the identity of the respondent, and 11 highlighted alerts appeared reiterating that their answers should be based on their clinical practice.

Statistical analysis

Statistical analyses were performed using Jamovi version 2.3 (https://www.jamovi.org). Bivariate and multiple analyses were performed to identify factors associated with using the D-OFC test and a significance level of 5% was used for all the analyses.

Results

The questionnaire was completed by 478 participants between February and October 2022. However, 31 physicians were excluded because they had not managed any infants with CMPA per month. Table 1 presents the interviewees' characteristics and workplaces and Table 2 presents information on infants' access to hypoallergenic formulas.

Diagnosing infants with non-IgE-GI-CMPA

Table 3 presents the answers related to the management of non-IgE-GI-CMPA in cases 1 and 2. Detailed information on the statistical analyses is provided in Supplementary File 1, and Supplementary File 2 shows the requested laboratory tests and the prescribed drugs and probiotics.

If administering the elimination diet resulted in a lack of clinical recovery, 72.3% (311/430) of the physicians in Case 1 and 35.9% (133/370) in Case 2 reported that they would change the initially prescribed hypoallergenic formula. The most frequently reported formula change was from the extensively hydrolyzed formula (EHF) to the free amino acid formula (AAF) (91.6% [285/311] in Case 1 and 69.9% [93/133] in Case 2).

Another approach for addressing the lack of response to the elimination diet was the referral to another physician

Table 1 General data of the 447 surveyed physicians.

Characteristics	n (%)
Board certification or specialization	
Pediatrician (with or without additional board certification or specialization)	433 (96.9%)
Pediatrician without an additional board certification or specialization	221 (49.4%)
Pediatrician with certification in gastroenterology	51 (11.4%)
Pediatrician with certification in allergology	24 (5.4%)
Pediatrician with certification in nutrition	12 (2.7%)
Pediatrician with other certification or specialty	125 (28.0%)
Physician with another specialization or enrolled in a pediatric residency	10 (2.2%)
Information not available	4 (0.9%)
Professional experience	
0–4 years	36 (8.1%)
5–9 years	80 (17.9%)
10–20 years	104 (23.3%)
20–30 years	86 (19.2%)
> 30 years	141 (31.5%)
Brazilian regions of professional activity	
Southeast	226 (50.6%)
South	82 (18.3%)
Northeast	82 (18.3%)
Midwest	37 (8.3%)
North	20 (4.5%)
Number of infants assisted per month with suspected or diagnosed cow's milk protein allergy (CMPA)[a]	
1–3	263 (58.8%)
4–10	166 (37.1%)
> 10	18 (4.0%)
Assistance to infants with CMPA at public and/or private settings	
Only public setting (provided by the Unified Health System [SUS])	88 (19.7%)
Only private setting (out of pocket or provided by health insurance companies regulated by the National Regulatory Agency for Private Health Insurance [ANS])	180 (40.3%)
Both public and private settings	176 (39.4%)
Information not available	3 (0.6%)

ANS, Agência Nacional de Saúde Suplementar; CMPA, cow's milk protein allergy; SUS, Sistema Único de Saúde.
Values are expressed as numbers and percentages.
[a]The median number of infants assisted with CMPA per month was three (25th and 75th percentiles: 2 and 5).

Table 2 Reimbursement and access to hypoallergenic infant formulas prescribed for infants on a cow's milk elimination diet.

Reimbursement and access to hypoallergenic formulas	
Reimbursement	**n = 447**
Out of pocket, which could be followed by a lawsuit	38 (8.5%)
Public reimbursement via an administrative request (no need to file a lawsuit)	403 (90.2%)
Information not available	6 (1.3%)
Deadline for availability of the formula by the public healthcare system (SUS) via an administrative request	**n = 403**
Immediate availability	95 (23.6%)
No immediate availability (out of pocket in the first weeks of the elimination diet)	307 (76.2%)
Information not available	1 (0.2%)
Requirements for obtaining formulas with public reimbursement via an administrative request	**n = 403**
Only present medical prescription and other required documents	183 (45.4%)
An approval from a physician from the Department of Health is required upon evaluation of the prescription and other documents	66 (16.4%)
A medical evaluation of the infant in a reference center from the Department of Health is required	143 (35.5%)
Information not available	11 (2.7%)

SUS, Unified Health System (Sistema Único de Saúde).
Values are expressed as numbers and percentages.

with an additional board certification: 21.9% (94/430) in Case 1 and 50.8% in Case 2 (188/370). For both the cases, most referrals were to pediatricians with certification in gastroenterology (73/94 [77.7%] and 140/188 [74.5%]) and allergology (19/94 [20.2%] and 39/188 [20.7%]).

The third most common approach by physicians for addressing the lack of response to the elimination diet was to rule out the diagnosis of CMPA in infants fed with AAF; however, only 21.0% (13/62) and 15.4% (36/224) of the physicians who indicated AAF in both the cases ruled out the diagnosis of CMPA. The number of participants who did not choose to prescribe a D-OFC test was relevant (Table 3).

Treating infants with non-IgE-GI-CMPA

During the follow-up of infants with CMPA, the practice of switching the hypoallergenic formula with a cheaper one or one with another type of protein was reported by 47.9% (206/430) physicians in Case 1 and 31.9% (118/370) in Case 2 ($p < 0.001$).

In Case 1, the most frequently reported changes were:

1. AAF to EHF: 65.1% (134/206)
2. EHF to partially hydrolyze protein-based infant formula (PHF): 37.9% (78/206)
3. EHF to soy protein-based infant formula (soy formula [SF]): 13.1% (27/206).

For Case 2, the same changes were observed:

1. AAF to EHF: 86.4% (102/118)
2. EHF to PHF: 15.3% (18/118)
3. EHF to SF: 7.6% (9/118).

More than 90% of the physicians recommended the OT-OFC (Table 3), and the most frequent milk protein sources used in the OT-OFC were cow's milk infant formula in Case 1 and baked foods in Case 2.

Factors associated with the performance of the D-OFC test

Table 4 presents the bivariate and multivariate analyses performed to evaluate the variables associated with using the D-OFC test (complete data in Supplementary File 3). The multiple regression analyses included variables with p values < 0.20 as independent variables. For both cases, performing the D-OFC presented a positive association with having a certification in pediatric gastroenterology and < 20 years of professional practice, and was negatively associated with using baked foods as a protein source in the OT-OFC. Only in Case 1 did certification in nutrition present a negative association with the practice of performing the D-OFC.

Discussion

We evaluated the practices of 447 physicians with respect to the diagnostic and therapeutic management of non-IgE-GI-CMPA in infants. In general, the initial management, prescription of an elimination diet, and frequency of indication of the OT-OFC test followed the guidelines. Access to hypoallergenic formulas subsidized by the public healthcare system was reported by > 90% of the physicians. In contrast, the D-OFC was performed by approximately half of the physicians, > 90% indicating that a good response to diet does not require this test. The D-OFC was most frequently performed by physicians specializing in pediatric gastroenterology and with < 20 years of professional experience. The use of baked foods as a protein source in the OT-OFC test was reported by more than one-third of physicians and was associated with not performing the D-OFC.

Table 3 Diagnostic and therapeutic management of infants with mild-to-moderate (Case 1) or severe clinical manifestations (Case 2) of non-IgE-mediated gastrointestinal cow's milk protein allergy (non-IgE-GI-CMPA).

Diagnostic and therapeutic management	Clinical manifestations		p
	Mild to moderate (Case 1)	Severe (Case 2)	
First approach	**n = 447**	**n = 430**	
Prescription of a cow's milk elimination diet with/without other interventions[a]	426 (95.3%)	370 (86.0%)	< *0.001*
Only prescription of an elimination diet	336 (75.2%)	181 (42.1%)	
Prescription of an elimination diet and other interventions[a]	90 (20.1%)	189 (44.0%)	
Referral to a specialist with/without other interventions[b,c]	17 (3.8%)	60 (15.4%)	< *0.001*
Information not available or other approaches[d]	4 (0.9%)	0 (0.0%)	
First prescribed formula	**n = 426**	**n = 370**	
Extensively hydrolyzed protein-based infant formula	348 (81.7%)	121 (32.7%)	< *0.001*
Amino acid-based infant formula	62 (14.6%)	242 (65.4%)	< *0.001*
Soy protein-based infant formula	13 (3.1%)	7 (1.9%)	< *0.001*
Partially hydrolyzed protein-based infant formula	2 (0.5%)	0 (0.0%)	
Information not available	1 (0.2%)	0 (0.0%)	
Time for assessment of the initial response to the diet (days)	13.6 ± 6.7[e]	13.6 ± 11.0[e]	*0.113*
Oral food challenge (OFC) test for diagnosing non-IgE-GI-CMPA	**n = 430**	**n = 370**	
Yes	237 (55.1%)	158 (42.7%)	< *0.001*
Duration of the elimination diet prior to the OFC (days)	47.3 ± 48.5[e]	59.4 ± 54.2[e]	< *0.001*
No	174 (40.5%)	197 (53.2%)	< *0.001*
Refers to specialist to evaluate or do the OFC for diagnosing non-IgE-GI-CMPA	5 (1.2%)	8 (2.2%)	
Information not available	14 (3.3%)	7 (1.9%)	
Main reasons for not indicating the OFC test	**n = 174**	**n = 197**	
The positive response to the elimination diet is enough for the diagnostic confirmation of CMPA	165 (94.8%)	178 (90.4%)	*0.058*
Use of lab tests to confirm the diagnosis of CMPA	4 (2.3%)	13 (6.6%)	*0.102*
Lack of setting or conditions to perform the OFC	3 (1.7%)	1 (0.5%)	*0.317*
Cow's milk protein source used in the OFC test	**n = 237**	**n = 158**	
Cow's milk-based infant formula	185 (78.1%)	107 (67.7%)	*0.012*
Lactose-free infant formula or cow's milk	38 (16.0%)	32 (20.3%)	*0.092*
Baked foods containing cow's milk protein	8 (3.4%)	15 (9.5%)	*0.219*
Partially or extensively hydrolyzed protein-based infant formulas	2 (0.8%)	3 (1.9%)	*1.000*
Information not available	4 (1.7%)	1 (0.6%)	
Setting for performance of the OFC	**n = 237**	**n = 158**	
Domicile	145 (61.2%)	40 (25.3%)	< *0.001*
Healthcare service	80 (33.8%)	110 (69.6%)	< *0.001*
Information not available	12 (5.1%)	8 (5.1%)	
Healthcare service where the physician performs the OFC	**n = 80**	**n = 110**	
Outpatient unit or medical office	51 (63.8%)	42 (38.2%)	< *0.001*
Hospital setting (emergency room, inpatient unit, day hospital)	28 (35.0%)	68 (61.8%)	< *0.001*
Information not available	1 (1.3%)	0 (0.0%)	
Assessing the development of oral tolerance to cow's milk proteins via the OFC test	**n = 430**	**n = 370**	
Yes	397 (92.3%)	338 (91.4%)	*1.000*
No (awaits accidental exposure to cow's milk proteins)	27 (6.3%)	19 (5.1%)	*1.000*
Refers to a specialist to evaluate or do the OFC for oral tolerance assessment	4 (0.9%)	10 (2.7%)	
Information not available	2 (0.5%)	3 (0.8%)	
Criteria adopted to define the timing of performing the OFC	**n = 397**	**n = 338**	
Age of the infant[f]	101 (25.4%)	88 (26.0%)	*0.572*
Duration of the elimination diet[g]	105 (26.4%)	80 (23.7%)	*0.078*
Combination of age of the infant and duration of the elimination diet[h]	186 (46.9%)	166 (49.1%)	*0.133*
Information not available	5 (1.3%)	4 (1.2%)	

(*continues*)

Table 3 Continued.

Diagnostic and therapeutic management	Clinical manifestations		p
	Mild to moderate (Case 1)	Severe (Case 2)	
Cow's milk protein source used in the OFC test	**n = 397**	**n = 338**	
Cow's milk-based infant formula	184 (46.3%)	115 (33.9%)	< *0.001*
Lactose-free infant formula or cow's milk	66 (16.6%)	55 (16.2%)	*1.000*
Baked foods containing cow's milk proteins	137 (34.5%)	150 (44.2%)	< *0.001*
Partially or extensively hydrolyzed protein-based infant formulas	2 (0.5%)	9 (2.7%)	*0.065*
Information not available	8 (2.0%)	9 (2.7%)	
Setting for performance of the OFC	**n = 397**	**n = 338**	
Domicile of the infant	228 (57.4%)	115 (34.0%)	< *0.001*
Healthcare service	146 (36.8%)	217 (64.2%)	< *0.001*
Information not available	23 (5.8%)	6 (1.8%)	
Healthcare service where the physician performs the OFC	**n = 146**	**n = 217**	
Outpatient or medical office	91 (62.3%)	95 (43.8%)	< *0.001*
Hospital (emergency room, inpatient unit, day hospital)	55 (37.7%)	121 (55.8%)	< *0.001*
Information not available	0 (0.0%)	1 (0.5%)	

Values are expressed as numbers and percentages (McNemar test, including only the data of the professionals who answered the questions of the two clinical cases [complete data are shown in Supplemental File 1]).
Non-IgE-GI-CMPA, non-IgE gastrointestinal cow's milk protein allergy; OFC, oral food challenge test.
[a]Other interventions—requests for lab tests and/or prescription of medications, probiotics and/or vitamins and mineral supplements, and/or referral to a specialist.
[b]Other interventions—requests for lab tests and/or prescription of medications, probiotics, and/or vitamins and mineral supplements.
[c]The 17 referrals in Case 1 were to pediatricians with certification in gastroenterology (14/17), allergology (2/17), and both gastroenterology and allergology (1/17). The 60 referrals in Case 2 were to pediatricians with certifications in gastroenterology (43/60), gastroenterology and allergology (11/60), allergology (4/60), gastroenterology and nutrition (1/60), and gastroenterology, allergology, and nutrition (1/60).
[d]Other approaches—management of the volume of cow's milk-based infant formulas and/or complementary feeding.
[e]Values are expressed as mean ± standard deviation (SD) (paired t-test).
[f]The mean ages (± SD) reported for tolerance OFC were 14.6 ± 7.1 months (n = 100) for Case 1 and 15.0 ± 7.0 months (n = 87) for Case 2. The age of 12 months was reported by 56.0% (56/100) in Case 1 and 58.6% (51/87) in Case 2.
[g]The mean duration of the diet (± SD) reported was 4.2 ± 2.6 months (n = 105) for Case 1 and 4.9 ± 3.1 months (n = 77) for Case 2. The most frequently reported therapeutic elimination diet duration was 6 months: 37.1% (39/105) in Case 1 and 40.3% (31/77) in Case 2.
[h]The most frequent combination was 12 months of age plus 6 months of elimination diet: 17.7% (33/186) for Case 1 and 18.1% (30/166) for Case 2.

Evidence shows that 20 years ago, the most commonly used formulas in Brazil were soy-based, in addition to inadequate options such as plant-based drinks, goat's milk, lactose-free milk, and PHF or even the nonprescription of breast milk substitutes.[7,8,19,20] In the past 20 years, several guidelines have been published for CMPA,[1–4,27,28] and several scientific events have been held with the focus on this disease. Simultaneously, the public healthcare system established municipal and state protocol for the supply of hypoallergenic formulas. Based on data collected from 2014, a preference for EHF and AAF has been observed.[11,13,14,22,24,29]

This study complements the published data, demonstrating temporal adherence to the guidelines regarding the choice of formulas according to the severity of the clinical condition. Increasing access to hypoallergenic formulas is essential for the implementation of these guidelines. Various studies that have evaluated the nutritional status and food intake of patients with CMPA have shown a positive change, which could have resulted from adopting appropriate elimination diets. In addition to the lower than recommended daily intake of energy, calcium, and phosphorus in half of the children and vitamins A and D in 38%,[8] studies conducted 20 years ago identified underweight in 15–23% and stunting in 12–24% of infants.[8,9] However, recent studies have shown an improvement in nutrition with a decrease in the rates of underweight (0.0–6.7%) and stunting (6.7–16.7%).[11,12,14,29] Additionally, more than 90% of formula-fed infants were fed EHF or AAF[11,13,14,29] associated to a significant reduction in the frequency of intake below the daily recommendations for energy and macro- and micronutrients.[11,13]

Regarding the formulas, adherence to the guidelines was observed in initial management and in the management of infants with a lack of response to the diet, where exchange of EHF for AAF or referral of the infant for management by a specialist predominated. Nevertheless, many interviews revealed a frequent misconception regarding

Table 4 Bivariate and multivariate analyses to evaluate factors associated with performing the oral food challenge test to diagnose non-IgE-GI-CMPA in infants with mild-to-moderate (Case 1) or severe (Case 2) clinical manifestations.

	Case 1 (mild-to-moderate clinical manifestations)		Case 2 (severe clinical manifestations)	
	Bivariate analysis ORcrude (95% CI); p-value	Multiple logistic regression Final model ORadj (95% CI); p-value	Bivariate analysis ORcrude (95% CI); p-value	Multiple logistic regression Final model ORadj (95% CI); p-value
Board certification or specialty	**< 0.001**		**0.015**	
Pediatrician without a subspecialty	ref.a	ref.a	ref.a	ref.a
Pediatrician with certification in gastroenterology	7.20 (2.94, 17.65); < 0.001	6.24 (2.47, 15.75); < 0.001	2.93 (1.51, 5.66); 0.001	2.94 (1.45, 5.95); 0.003
Pediatrician with certification in allergology	1.34 (0.57, 3.17); 0.525	1.22 (0.47, 3.15); 0.677	0.88 (0.36, 2.12); 0.827	0.75 (0.29, 1.98); 0.561
Pediatrician with certification in nutrition	0.32 (0.08, 1.22); 0.135	0.21 (0.05, 0.81); 0.023	0.73 (0.21, 2.53); 0.765	0.53 (0.15, 1.92); 0.332
Pediatrician or physician with other certifications or enrolled in a pediatric residency	1.43 (0.91, 2.26); 0.134	1.17 (0.71, 1.93); 0.526	1.08 (0.65, 1.79); 0.797	1.12 (0.64, 1.95); 0.700
Professional experience	**0.036**		**0.043**	
< 20 years	1.53 (1.03, 2.27); 0.036	1.83 (1.17, 2.87); 0.009	1.55 (1.02, 2.36); 0.043	1.69 (1.05, 2.71); 0.031
≥ 20 years	ref.b	ref.b	ref.b	ref.b
Assistance to infants with CMPA at public and/or private settings	**0.130**		**0.094**	
Only private settings (out of pocket or provided by health insurance companies regulated by the ANS)	0.65 (0.42, 1.01); 0.059		0.60 (0.38, 0.96); 0.043	
Only public settings (provided by SUS)	0.69 (0.40, 1.19); 0.206		0.69 (0.38, 1.24); 0.239	
Both public and private settings	ref.a		ref.a	
First prescribed formula	**0.073**		**0.049**	
Extensively hydrolyzed protein-based infant formula	ref.b		0.99 (0.64, 1.55); 1.000	
Amino acid-based infant formula	0.58 (0.33, 0.10); 0.050		ref.b	
Other (soy protein-based or partially hydrolyzed protein-based infant formulas)	0.49 (0.17, 1.45); 0.266		Undefined OR; p=0.019[c]	
Cow's milk protein source used in the OFC to assess tolerance development	**0.003**		**< 0.001**	
Cow's milk-based infant formula	ref.b	ref.b	ref.b	ref.b
Lactose-free infant formula or cow's milk	1.17 (0.64, 2.17); 0.646	0.95 (0.49, 1.85); 0.877	0.98 (0.51, 1.88); 1.000	0.90 (0.45, 1.83); 0.774
Baked foods containing cow's milk proteins	0.48 (0.30, 0.76); 0.002	0.42 (0.26, 0.69); < 0.001	0.36 (0.22, 0.60); < 0.001	0.32 (0.19, 0.55); < 0.001
Partially or extensively hydrolyzed protein-based infant formulas	1.04 (0.09, 11.76); 1.000	0.57 (0.05, 6.89); 0.654	0.76 (0.21, 2.77); 0.746	0.80 (0.21, 2.99); 0.741

a, reference according to the numeric relevance; ref.b, reference according to the variable that suggests higher adherence to guidelines.
c In Case 2, the use of soy protein-based formulas could not be included in the model because it would cause instability in the estimates.
ANS, National Regulatory Agency for Private Health Insurance (Agência Nacional de Saúde Suplementar); CI, confidence interval; OFC, oral food challenge test; ORadj, adjusted Odds Ratio; ORcrude, crude Odds Ratio; SUS, the Unified Health System (Sistema Único de Saúde); non-IgE-GI-CMPA, non-IgE-mediated gastrointestinal cow's milk protein allergy.
The complete data are presented in Supplementary File 3.

the exchange of EHF for PHF after the confirmation of CMPA diagnosis. PHF is not recommended for the therapeutic management of CMPA[1-4] and tolerance to this type of product may indicate that the infant has already developed tolerance to cow's milk proteins.

Regarding the duration of the diagnostic elimination diet, the most recent guidelines recommend 2–4 weeks for patients with non-IgE-GI-CMPA.[2-4] This period may be too short for patients with severe conditions to achieve complete clinical and nutritional recovery. In this study, the mean duration of the diagnostic diet was 6 weeks in Case 1 and 8 weeks in Case 2, which are consistent with those recommended in the Brazilian guideline.[1] Another highlight is that 76% of the physicians reported that access to formulas subsidized by the public system was not immediate and that the family needed to pay for the formulas at the beginning of the elimination diet. This can lead to the use of cheaper and inadequate milk substitutes such as plant-based milks, thereby extending the period required for clinical and nutritional recovery. Recommending D-OFC test 2 weeks after clinical and nutritional recovery would be a personalized and assertive strategy, respecting each patient's severity and recovery speed.[30]

In this study, 12.3% and 37.7% of the participants reported requesting tests and 8.3% and 12.1% reported prescribing drugs and/or probiotics, respectively, for cases 1 and 2 (Supplementary File 2). Most of these tests were probably requested for differential diagnosis or investigation of symptoms related to other conditions. The substantial diversity of tests requested suggests that different prior experiences of the respondents may influence the lab tests requested for differential diagnosis. Notably, the frequencies of lab tests requested and prescribed drugs were lower than those reported in an older study,[20] again demonstrating progress in the Brazilian medical practice.

The D-OFC test has the potential to rule out suspicion of CMPA in approximately half of the children,[7,18] provide several nutritional and quality of life benefits, and avoid unnecessary costs associated with formulas, special foods, consultations, and exams.[3,4,15,23,31-34] This diagnostic option was reported by 31% of the physicians in a Brazilian study conducted more than 10 years ago[20] and by only half of the participants in this study. Another study conducted in 2017 reported a notable result, as only 18% of pediatricians adhered to the use of the OFC test with 20% aware of this recommendation.[24] An analysis of the national medical prescription databases of the United Kingdom, Norway, and Australia confirmed that the prescription of hypoallergenic formulas has been much higher than expected, given the prevalence of CMPA.[35] In this study, the types of formulas prescribed by the physicians complied with the guidelines, highlighting the lack of D-OFC test as a critical negative factor for unnecessary prescription of hypoallergenic formula. The provision of more public services for OFC performance may also contribute to avoiding overdiagnosis.

In this study, the parent's refusal to perform the OFC and the difficulties in its implementation and evaluation were not assessed, such as possible false-negative and false-positive OFC tests, secondary, respectively, to a delay in performing the D-OFC or viral infections and other symptoms during the OFC test, suggesting the recurrence of reactions to cow's milk proteins. Brazilian guidelines[1] advocate the use of the D-OFC test; however, additional modifications are necessary to ensure its comprehensive implementation. The OFC test was officially incorporated into the country's public and private health systems in 2022, as stated in the Ordinance SCTIE/MS No. 32 dated 03/31/2022 and ANS Normative Resolution No. 536/22. Nevertheless, prior to the submission of this article for publication, we could not ascertain from the SIA/SUS (Ambulatory Information Systems of the Unified Health System) website the total number of OFC tests conducted from the time of the publication of the ordinance as well as the amount of reimbursement.

However, over 90% of physicians have reported indicating OT-OFC test predominantly after 6 months of an elimination diet or when the infant reaches the age of 12 months, as established by the guidelines.[1-4]

This study revealed that for the most part, the physicians opted to conduct the OFC test at home for Case 1 and in a health service for Case 2, which is consistent with the latest guidelines.[2-4] The low availability of public and private services structured for the performance of the OFC may have contributed to these practices. However, it is essential to point out that the OFC test is not completely risk-free. Besides, fear and anxiety may cause parents to mistake a nonspecific manifestation to be secondary to a reaction to the milk. Thus, performing the test at home does not exempt the physician from interpreting the result[3] and whenever possible, the OFC should be performed under medical supervision.[1]

Regarding the food used in the OFC test, milk formulas predominated in the D-OFC test, whereas baked foods had a relevant frequency in the OT-OFC test. The use of baked foods in the OT-OFC test is not a substitute for a D-OFC test and is not recommended for confirming the diagnosis of CMPA.[3,4] Thus, although the use of baked foods in the OT-OFC test is an option in the most recent guidelines,[3,4] the association of this practice with the nonperformance of the D-OFC suggests a misunderstanding of the role of the use of baked foods.

Another point observed in this study was that the D-OFC test was used most frequently by physicians who had less professional experience (< 20 years). In Brazil, the OFC test has been recommended for the last 20 years; hence, more likely to be part of the practices of professionals with academic training during this period. Specialization in gastroenterology was also associated with the indication for the D-OFC test, possibly because of the nonspecific characteristics of non-IgE-mediated gastrointestinal manifestations compared to IgE-mediated reactions.

One limitation of this study was that the recruitment and data collection were done online; however, this had the advantage of having a low cost and ample coverage by including professionals from all regions of Brazil. Although the absolute number of respondents working in the Southeast was higher, the distribution across all regions was similar to that of the workplaces of members of the BSP and the medical demography of Brazil.[36] Notably, the aim of this study was to evaluate real-life medical practices; hence the strategies adopted to encourage responses that pertained to these care practices. These data should be confirmed in future studies with data collection from records of care provided by public health services. Additionally, to our knowledge, this is the first study to

assess access to formulas, which is critical for the adequate treatment of CMPA.

Conclusion

Finally, unlike in the past, most participants followed the guidelines regarding the type of hypoallergenic formulas that should be used in the elimination diet according to the severity of clinical manifestations. This progress in pediatric practice in Brazil is likely the result of improvements in guidelines adherence, medical education campaigns, and access to hypoallergenic formulas subsidized by the public healthcare system. Administering the OT-OFC test was a common practice; however, the D-OFC test was done by only half of the physicians, indicating the need to promote this practice to avoid the negative impacts of unnecessary restrictive diets and provide better outcomes for individuals and society. Studies need to be carried out on the practices of physicians from other countries in performing the OFC for diagnosing CMPA in infants.

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Authors Contribution

Conception and study design (VCCR, MCMF, MBM); recruitment strategy (MBM, DS); data collection (VCCR); data analysis and interpretation (VCCR, MCMF, AS, MBM); article writing (VCCR, MBM); critical review and final approval of the article (VCCR, MCMF, AS, DS, MBM).

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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References

1. Solé D, Silva LR, Cocco RR, Ferreira CT, Sarni RO, Oliveira LC, et al. Brazilian consensus on food allergy: 2018 – Part 2 – Diagnosis, treatment, and prevention. Joint position paper of the Brazilian Society of Pediatrics and the Brazilian Association of Allergy and Immunology. Arq Asma Alerg Imunol. 2018;2:39–82. http://doi.org/10.5935/2526-5393.20180005
2. Toca MC, Morais MB, Vásquez-Frias R, Becker-Cuevas DJ, Boggio-Marzet CG, Delgado-Carbajal L, et al. Consensus on the diagnosis and treatment of cow milk protein allergy by the Latin American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Rev Gastroenterol Mex (Engl Ed). 2022;87(2):235–50. https://doi.org/10.1016/j.rgmxen.2022.01.002
3. Vandenplas Y, Broekaert I, Domellöf M, Indrio F, Lapillonne A, Pienar C, et al. An ESPGHAN position paper on the diagnosis, management, and prevention of cow's milk allergy. J Pediatr Gastroenterol Nutr. 2024 Feb;78(2):386-413. https://doi.org/10.1097/MPG.0000000000003897
4. Meyer R, Venter C, Bognanni A, Szajewska H, Shamir R, Nowak-Wegrzyn A, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guideline update – VII – Milk elimination and reintroduction in the diagnostic process of cow's milk allergy. World Allergy Organ J. 2023;16(7):100785. https://doi.org/10.1016/j.waojou.2023.100785
5. Sissoko NDN, Chen W, Wang C, Wu Y, Zheng X, Dong X, et al. Associations between functional constipation and non-IgE-mediated food allergy in infants and children. Allergol Immunopathol (Madr). 2023;51(3):163-73. https://doi.org/10.15586/aei.v51i3.738. PMID: 37169574
6. Morais MB, Toporovski MS, Tofoli MHC, Barros KV, Silva LR, Ferreira CHT. Prevalence of functional gastrointestinal disorders in Brazilian infants seen in private pediatric practices and their associated factors. J Pediatr Gastroenterol Nutr. 2022;75(1):17-23. https://doi.org/10.1097/MPG.0000000000003469
7. Lins MG, Horowitz MR, Silva GAP, Motta ME. Oral food challenge test to confirm the diagnosis of cow's milk allergy. J Pediatr (Rio J). 2010;86:285–9. https://doi.org/10.2223/jped.2011
8. Medeiros LC, Speridião PG, Sdepanian VL, Fagundes-Neto U, Morais MB. Nutrient intake and nutritional status of children following a diet free from cow's milk and cow's milk by-products. J Pediatr (Rio J). 2004;80:363-70. https://doi.org/pubmed.ncbi.nlm.nih.gov/15505731/
9. 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. https://doi.org/10.1186/1471-2431-10-25
10. Meyer R. Nutritional disorders resulting from food allergy in children. Pediatr Allergy Immunol. 2018;29:689–704. https://doi.org/10.1111/pai.12960
11. Augusto EO, Bonucci VG, Cardoso RV, Morais MB. Complementary feeding and nutritional status of infants on cow's milk proteins elimination diet. Rev Paul Pediatr. 2022;40:e20200429. https://doi.org/10.1590/1984-0462/2022/40/2020429IN
12. Rodrigues VCC, Speridião PGL, Sanudo A, Morais MB. Feeding difficulties in children fed a cows' milk elimination diet. Br J Nutr. 2022;128(6):1190–9. https://doi.org/10.1017/S0007114521004165
13. Frizzo J, Rodrigues VCC, Speridião PGL, Morais MB. Evaluation of the complementary feeding practices, dietary intake, and nutritional status of infants on a cow's milk protein elimination diet. J Pediatr (Rio J). 2022;98:256–63. https://doi.org/10.1016/j.jped.2021.06.005
14. Jardim-Botelho A, Martins TG, Motta-Franco J, Meyer R, Fontes Vieira SC, Protásio BF, et al. Growth and nutritional biomarkers in Brazilian infants with cow's milk allergy at diagnosis and 18-month follow-up: A prospective cohort

study. Pediatr Gastroenterol Hepatol Nutr. 2023;26(6):355-69. https://doi.org/10.5223/pghn.2023.26.6.355
15. Fakih-Botero I, Cerchiaro-Mejia MC, Rusinque MJ, Palacios-Ariza MA, Plata-Garcia CE, Peña-Hernández S. Out-of-pocket expenses and parent reported quality of life in children with cow's milk protein allergy in Bogotá, Colombia. J Pediatr Gastroenterol Nutr. 2024. https://doi.org/10.1002/jpn3.12203 PMID: 38587147.
16. Rodrigues VCC, Cezar TM, Abreu CLM, Sanudo A, Morais MB. A real-world cross-sectional study evaluating the role of an oral amino acid-based supplement in nutrient intake by preschoolers on a cow's milk elimination diet. Allergol Immunopathol (Madr). 2024;52(3):42-52. https://doi.org/10.15586/aei.v52i3.1053. PMID: 38721954.
17. Dziechciarz P, Stróżyk A, Horvath A, Cudowska B, Jedynak-Wąsowicz U, Mól N, et al. Nutritional status and feeding difficulties in children up to 2 years of age with cow's milk allergy. J Pediatr Gastroenterol Nutr. 2024;79(1):131-9. https://doi.org/10.1002/jpn3.12139. PMID: 38291802.
18. Petrus NC, Schoemaker AF, van Hoek MW, Jansen L, Jansen-van der Weide MC, van Aalderen WM, et al. Remaining symptoms in half the children treated for milk allergy. Eur J Pediatr. 2015;174(6):759-65. https://doi.org/10.1007/s00431-014-2456-6
19. Cortez APB, Medeiros LCS, Speridião PGL, Mattar RHGM, Fagundes Neto U, Morais MB. Pediatricians and nutritionists knowledge about treatment of cow milk allergy in infants. Rev paul pediatr. 2007;25(2):106-13. https://doi.org/10.1590/S0103-05822007000200002
20. Sole D, Jacob CMA, Pastorino AC, Porto Neto A, Burns DA, Sarinho ESC, et al. O conhecimento de pediatras sobre alergia alimentar: Estudo piloto. Rev Paul Pediatr. 2007; 25(4):311-6. https://doi.org/10.1590/S0103-05822007000400003
21. Yüce A, Dalgıç B, Çullu-Çokuğraş F, Çokuğraş H, Kansu A, Alptekin-Sarıoğlu A, et al. Cow's milk protein allergy awareness and practice among Turkish pediatricians: A questionnaire-survey. Turk J Pediatr. 2017;59(3):233-43. https://doi.org/10.24953/turkjped.2017.03.002
22. Faria DPB, Cortez APB, Speridião PGL, Morais MB. Knowledge and practice of pediatricians and nutritionists regarding treatment of cow's milk protein allergy in infants. Rev Nutr. 2018;31(6):535-46. http://doi.org/10.1590/1678-98652018000600003
23. van den Hoogen SCTA, van de Pol AC, Meijer Y, Toet J, van Klei C, de Wit NJ. Suspected cow's milk allergy in everyday general practice: A retrospective cohort study on health care burden and guideline adherence. BMC Res Notes. 2014;7:507. https://doi.org/10.1186/1756-0500-7-507
24. Vieira SCF, Santos VS, Franco JM, Nascimento-Filho HM, Barbosa KdOeSS, Lyra-Junior DPd, et al. Brazilian pediatricians' adherence to food allergy guidelines—A crosssectional study. PLoS One. 2020;15(2):e0229356. https://doi.org/10.1371/journal.pone.0229356
25. Granot M, Machnes Maayan D, Weiss B, Haberman Y, Agmon-Levin N, Shouval DS. Practice variations in the management of infants with non-IgE-mediated cow's milk protein allergy. J Pediatr Gastroenterol Nutr. 2022;75(4):444-9. https://doi.org/10.1097/MPG.0000000000003556. PMID: 35797449.
26. Serdar CC, Cihan M, Yücel D, Serdar MA. Sample size, power and effect size revisited: simplified and practical approaches in pre-clinical, clinical and laboratory studies. Biochem Med (Zagreb). 2021;31(1):010502. https://doi.org/10.11613/BM.2021.010502. PMID: 33380887; PMCID: PMC7745163.
27. Fiocchi A, Brozek J, Schünemann 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. Pediatr Allergy Immunol. 2010;21(Suppl 21):1-125. https://doi.org/10.1111/j.1399-3038.2010.01068.x
28. 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. https://doi.org/10.1097/MPG.0b013e31825c9482
29. Taveira GR, Fernandes CDR, Silva YFR, Aquino MCB, Silva ACMV, Faria CP, et al. Evolution of nutritional status and associated factors among formula-fed infants with cow's milk protein allergy in a government program. Arch Public Health. 2023;81(1):90. https://doi.org/10.1186/s13690-023-01094-3
30. Morais MB. Definição e diagnóstico. In: ILSI Brasil International Life Sciences Institute do Brasil. Alergia à proteína do leite de vaca: Uma abordagem prática: Volume 11. 1st ed. São Paulo: ILSI Brasil; 2021 (Série de publicações ILSI Brasil). Pp. 8-26.
31. Meyer R, Godwin H, Dziubak R, Panepinto JA, Foong RM, Bryon M, et al. The impact on quality of life on families of children on an elimination diet for non-immunoglobulin E mediated gastrointestinal food allergies. World Allergy Organ J. 2017;10(1):8. https://doi.org/10.1186/s40413-016-0139-7
32. Kansen HM, Le TM, Meijer Y, Flokstra-de Blok BMJ, Welsing PMJ, van der Ent CK, et al. The impact of oral food challenges for food allergy on quality of life: A systematic review. Pediatr Allergy Immunol. 2018;29:527-37. https://doi.org/10.1111/pai.12905
33. Alsaggaf A, Murphy J, Leibel S. Estimating cost-effectiveness of confirmatory oral food challenges in the diagnosis of children with food allergy. Glob Pediatr Health. 2019;6:2333794X19891298. https://doi.org/10.1177/2333794X19891298
34. de Faria DPB, Sillos MD, Speridião PGL, Morais MB. Outcome of food intake and nutritional status after discontinuation of a cow's-milk-free diet post negative oral food challenge in infants and children. Allergol Immunopathol (Madr). 2022;50:1-8. https://doi.org/10.15586/aei.v50i1.471
35. Mehta S, Allen HI, Campbell DE, Arntsen KF, Simpson MR, Boyle RJ. Trends in use of specialized formula for managing cow's milk allergy in young children. Clin Exp Allergy. 2022;52(7):839-47. https://doi.org/10.1111/cea.14180
36. Scheffer M, Biancarelli A, Cassenote A, Guilloux AGA, Miotto BA, Mainardi GM. Demografia Médica no Brasil 2018. São Paulo, SP: FMUSP, CFM, Cremesp, 2018. p.118. ISBN: 978-85-87077-55-4.