Title Page

Full Title: Reducing public health costs with infant formulas: oral food challenge and misdiagnosed or outgrown cow's milk protein allergy

Authors*:* Ana Laura Mendes Becker Andrade (MD, MSc)[1,], Priscila da Silva Pereira (MD)[2]; Renan Marrichi Mauch (Ph.D)[1,3], Maria Angela Bellomo Brandão (MD, Ph.D)[2], Marcos Tadeu Nolasco da Silva (MD, Ph.D)[1], Adriana Gut Lopes Riccetto (MD, Ph.D)[1]

Affiliations of Authors:

1. Pediatric Allergy and Immunology, Center of Investigation in Pediatrics, Department of Pediatrics, School of Medical Sciences, University of Campinas. Campinas/SP, Brazil.
2. Pediatric Gastroenterology, Center of Investigation in Pediatrics, Department of Pediatrics, School of Medical Sciences, University of Campinas. Campinas/SP, Brazil.
3. Clinical Microbiology Department, Rigshospitalet (Copenhagen University Hospital). Copenhagen, Denmark.

Running Title: Reducing costs in cow's milk allergy

Corresponding author:

Renan Marrichi Mauch, Ph.D

Center of Investigation in Pediatrics, School of Medical Sciences, University of Campinas

Address: Rua Tessália Vieira de Camargo, 126 (FCM 04), Cidade Universitária "Zeferino Vaz", Barão Geraldo, Campinas, São Paulo, Brasil. CEP: 13083-887

E-mail: mauch@unicamp.br

Phone: +55 19 35218979

Word Count: Abstract: 240 words; Main Text: 2540 words

Number of Tables: 6

Abstract

Background: Accurate diagnosis and appropriate management of cow's milk protein allergy (CMPA) are crucial for avoiding unnecessary prescription of infant formulas. Here, we aimed to use the oral food challenge (OFC) for CMPA confirmation and for assessing development of natural tolerance to milk, in children with clinical CMPA diagnosis. We also assessed the economic impact in public health-care costs of reducing the prescription of infant formulas (provided by the São Paulo State's public health service, in Brazil, until two years of age) after ruling out CMPA diagnosis in children with negative OFC results. *Methods*: We reviewed medical records of 76 children [41 males, median age = 2.0 years (0.8-5.0)] who underwent OFC from January 2016 to June 2018, 30 of whom were ≤2 years old. *Results:* Before OFC, 52 (68.4%), 20 (26.3%) and five (5.3%) children were diagnosed with non-IgE-mediated, IgE-mediated and mixed CMPA, respectively. Most children were fed with aminoacid-based formulas (n=29, 38%). OFC was negative in 58 (76%) children, thus ruling out CMPA diagnosis. Out of 18 (24%) OFC-positive children, most (n=10, 56%) had gastrointestinal symptoms. After ruling out CMPA diagnosis, a mean of 152.3 formula cans (2,161.14 US dollars) were saved per children by the public health service. The total amount saved was 64,834.27 US dollars. *Conclusions:* OFC proved important not only for ruling out misdiagnosed CMPA, but also for preventing the indiscriminate use of infant formulas, which, in turn, had positive consequences for public health costs.

Keywords: public health costs; infant formulas; oral food challenge; milk allergy; food allergy; natural tolerance.

Main Text

Introduction

Cow's Milk allergy (CMPA) is one of the main food allergies in childhood, with a global prevalence of 2%-3% in the pediatric age group, and 1.8%-7.5% in the first year of life[1,2]. In Brazil, the incidence and prevalence of CMPA have been estimated at 2.2% and 5.4%, respectively[3], and the recent increases in incidence and prevalence make CMPA be considered a public health issue[4,5]. However, the currently reported prevalence rates are likely to be overestimated, as CMPA diagnosis mostly relies on medical history only.

The variety of clinical manifestations and pathophysiological mechanisms makes it difficult to accurately diagnose CMPA. Regarding clinical and laboratory features, CMPA may be classified as: Non-IgE mediated (with presence of proctocolitis, enteropathy, enterocolitis); IgE-mediated (with presence of urticaria, angioedema, bronchospasm, anaphylaxis); and mediated by mixed mechanisms, that is both IgE- and T cell-mediated (with presence of atopic dermatitis, gastroenteritis and eosinophilic esophagitis)[2,6]. The gold standard for CMPA diagnosis, regardless of the underlying pathophysiology, is the Oral Food Challenge (OFC) test, which is useful both for confirming the diagnosis and for detecting the development of natural tolerance to milk[7]. OFC consists in administering progressive doses of the allergen to the patient at regular intervals, and is performed after a period of elimination diet and in a controlled manner[6,8,9]. Still, OFC is not routinely performed in the CMPA clinical setting in Brazil. Health insurance companies usually do not cover this procedure, which is carried out only in specialized clinics, private hospitals and university research centers.

The Public Health Service of the São Paulo State, in Brazil, provides patients diagnosed with CMPA with infant formulas on a monthly basis until they reach the age of two years[10]. A medical form stating the clinical diagnosis of CMPA is enough so patients can have access to this benefit, and an OFC result is not routinely required. Thus, a considerable number of children is likely to be misdiagnosed and prescribed restrictive and unnecessary diets, including the indiscriminate use of expensive infant formulas, which, in turn, can negatively impact public health-care costs. These facts clearly demonstrate the importance

of the accurate diagnosis and appropriate management of CMPA for public health-care costs. The aim of our study was to assess the usefulness and safety of OFC for confirmation of CMPA diagnosis in children and to assess the economic impact in the a public health service, regarding reduction in the prescription of infant formulas, after exclusion of MA diagnosis in children with negative OFC results.

Methods

Study Design

This was an observational, descriptive study. We reviewed medical records of 76 children aged 0-12 years who were diagnosed with CMPA based on clinical features. All patients were submitted to open OFC with cow's milk, at the University of Campinas Teaching Hospital (HC Unicamp), a tertiary-care hospital located in the city of Campinas, São Paulo State, Brazil, from January 2016 to June 2018. OFC was used both for confirming CMPA diagnosis and for detecting the development of tolerance to cow's milk.

Oral Food Challenge (OFC)

OFC was conducted according to our institutional protocol. A period of eight weeks of elimination diet was required before the OFC, either for confirming the CMPA diagnosis or for assessing development of natural tolerance to cow's milk. Type A pasteurized cow's milk (for children aged ≥1 year) and a milk formula containing intact milk protein (for children aged <1 year) were administered at increasing doses every 15 minutes, in five stages, with a total amount of 120 mL. During this time, patients were observed by a pediatric immunologist or pediatric gastroenterologist in order to verify objective or subjective adverse reactions to cow's milk, any of which were considered for stopping the OFC, if it was persistent or intense[11]. Objective signs and symptons of CMPA, such as skin, mucosal, gastrointestinal and respiratory manifestations, and anaphylaxis, were carefully monitored. One week after the OFC, the patients were evaluated for late adverse reactions. In case of any adverse reaction, either immediate or a week after OFC, the test was considered positive for CMPA.

Data collection and statistical analysis:

Medical records of patients submitted to OFC were assessed for variables of interest, such as sex, age at the onset of the symptoms, feeding at the onset of the symptoms, clinical manifestations of CMPA, mechanism of allergy, special milk formula used in the elimination diet period, age at which OFC was performed, reason for performing the test, and symptoms in patients with a positive result. The following data were used to assess the economic impact in public health-care costs after excluding CMPA diagnosis due to a negative OFC result: a) price per can of the infant formulas provided by the São Paulo State's Public Health Service , according to formula's type (aminoacid-based formula, extensively hydrolyzed formula, or soy-based formula); b) number of infant formula cans available each month for children clinically diagnosed with CMPA, according to their age (in months). For the latter, the following parameters were calculated: amount of money saved *(*Number of cans saved X price of the formula can); mean amount of money saved per month (total amount saved divided by the number of months without taking the formula); total amount of money saved (sum of the money saved per child). We considered the number of cans saved as the number of cans that would still be provided until the child reached 24 months old, in case they had not undergone OFC. Categorical variables were expressed as frequencies. Numerical variables were expressed as means and standard deviations, in case of normal distribution, or as medians and interquartile ranges, in case of non-normal distribution. Normality was assessed by the Shapiro-Wilk test. Analyses were performed using IBM® SPSS® Statistics software version 24 and Microsoft® Excel 365.

Ethical approval:

The study was approved by the Research Ethics Committee of the University of Campinas (Unicamp, #2932486, 10/02/2018).

Results

Patients´ characteristics

The characteristics of the 76 evaluated patients are described in **Table 1**. Most patients were male and started to present clinical symptoms before the age of one year. Upon identification of CMPA symptoms, most infants were fed

with a standard cow's milk-based formula containing intact milk protein, while 16 (21.1%) children were exclusively breastfed and 29 (38.2%) patients were fed with whole milk (or derivates) or with both breast milk and infant formulas. Non-IgE mediated CMPA was the most commonly CMPA type diagnosed in the study population. As for prescribed infant formulas, aminoacid-based formulas were most commonly used during the elimination diet period, before OFC was performed. Some patients had the extensively hydrolyzed formula replaced with the aminoacid-based formula due to symptom persistence. Twelve children used more than one type of infant formula during the elimination diet period.

OFC results

The median age of the children when OFC was performed was 2.0 years [0.8-5.0]. In most cases, OFC was carried out to evaluate the development of tolerance to cow's milk. OFC results, along with symptoms presented by patients with positive results are shown in **Table 2**. Out of the OFC-positive patients, eight (44.4%) had symptoms of IgE-mediated CMPA and were treated with antihistamines, corticosteroids and bronchodilators. Out of these, seven patients had a good response to treatment and one patient had an anaphylactic reaction, requiring treatment with adrenalin. The symptoms of anaphylaxis were rapidly reversed, and this patient was discharged after a 48-hour observation period. Overall, 10 patients had gastrointestinal symptoms during OFC, out of whom eight had late symptoms, as diarrhea or bloody stools, and two had acute Food Protein-Induced Enterocolitis Syndrome (FPIES), including protracted vomiting, requiring hospital admission. These patients progressed well and were discharged within a few days. Most patients had no immediate or late symptoms after OFC, and were considered OFC-negative, thus having the elimination diet suspended.

Among children who tested negative for OFC, 30 had less than 24 months of age, most of whom had clinical diagnosis of non-IgE-mediated CMPA, and aminoacid-based formula was mostly used during their elimination diet period (**Table 3**). After ruling out CMPA, the mean number of cans saved per children by the public health service was 152.3 cans (40 – 226) (**Table 4**). The mean amount saved per child was 2,161.14 US dollars (225.82 – 3,509.78) (**Table 5**). The total amount of money saved in the study population was 64,834.27 US dollars (**Table 6**).

Discussion

Although CMPA is very common in childhood, concerns have been risen about overdiagnosis, both in Brazil[10] and abroad[12,13]. Our results give reason for such concerns, since an extense majority of children with clinical diagnosis of CMPA referred to our hospital turned out to be misdiagnosed, as shown by negative OFC results. Such misdiagnoses can have serious consequences not only for patients' growth and nutrition, but also for public health-care costs. With a low number of patients evaluated, we could show a considerable amount of money saved by a state public health system by avoiding provision of expensive and unnecessarily prescribed infant formulas. Such outcome highlights the importance of a complete diagnostic approach for CMPA and how relying only on clinical criteria can be problematic.

Notably, most children assessed in the present study were clinically diagnosed with non-IgE-mediated CMPA, which is worrisome, as symptoms in this condition are set more slowly and are not specific of CMPA or other food allergies. For this reason, the diagnosis can only be made after elimination diet followed by reintroduction[14]. Recently, allergy specialists raised concern about the possibility that patients with non-IgE-mediated CMPA can be more vulnerable to unnecessary ingestion of infant formulas, due to these confounders[15]. A population-based study found that 243 out of 381 children with possible adverse reactions to cow's milk were misdiagnosed with CMPA, whose symptoms were different when compared to children with IgE-mediated CMPA[16]. In this scenario, most patients assessed in our study had CMPA ruled out after OFC, and less than a half of patients with a positive OFC result had symptoms of IgE-mediated CMPA. Immunoassays based on detection of serum allergen-specific IgE could be an interesting complement for screening patients with this condition and for guiding a more suitable clinical management. These assays have good sensitivity and specificity[2,17–19], are easy to run and several samples can be analyzed simultaneously. However, it should be considered that many tests can present inconclusive results, given the physiological immaturity of the immune system in children. Atopy cases, in which IgE is elevated, may also bias the serological results[5]. As for children with non-IgE-mediated CMPA, OFC proved particularly crucial, as these children can reinclude cow's milk more easily, and in tolerable amounts, in their diets. Still,

OFC is not commonly performed in public health services in Brazil. Most patients in the present study were referred to HC Unicamp by other public primary or secondary care units. Increasing the access to OFC in secondary care units may help to identify more misdiagnosed children.

There was a substantial reduction in the costs of infant formula provision by the São Paulo State's public health service after exclusion of 58 (76.3%) misguided CMPA diagnoses (**Tables 4-6**), which is impressive, given the low number of patients seen in a single center. CMPA overdiagnosis and exaggerated spending on infant formula is a problem also for the English National Health System, which has faced a nearly 500% increase in the prescriptions of these products between 2006 and 2016, while NHS spending on them increased by nearly 700%, from 8.1m to 60m British pounds annualy[15]. Other study found that in performing OFC was associated with a mean cost estimated at 4184,00 dollars per child, per year of delay in testing[20]. In our study, aminoacid-based formula was the first therapeutic option in most patients, despite the lack of characterization for its indication. This is the most expensive choice of infant formula and it is not always the best option available for allergic children[2,4,5,17,18]. Importantly, a recent Cochrane review of 16 studies did not find evidence to support short- or long-term feeding with extensively hydrolyzed formula for preventing CMPA in children, when compared with both maternal breastfeeding and feeding with milk-based formula[21]. It is worth mentioning that, although there are evidences of mother-child transfer of cow's milk protein via maternal breastfeeding, the transferred amounts are not likely enough to cause CMPA symptoms, and the evidences for prescribing maternal elimination diets for treating unspecific symptoms is weak[22]. Also, CMPA misdiagnosis may cause mothers to worry about the possibility that CMPA is caused by breastfeeding, ending up to interrupting it and switching to a formula-based feeding. This may bring serious consequences for the infant, who may not tolerate the formula feeding, which, in turn, can impact the their growth and nutrition, and also for the mother, as breastfeeding cessation is a cause of postpartum depression[15,23]. Altogether, these findings are particularly important, when it comes to a country like Brazil, where about 11 million individuals are diagnosed with CMPA, with four million new cases per year[3]. Given that most of Brazilian individuals are diagnosed with basis on their clinical features, the

amount of money spent by public health services with provision of infant formulas, as well as impacts in health of both mothers and children may have a significant reduction, if measures for more accurate diagnosis of CMPA are implemented nationwide.

Although the OFC importance is evident here, and in the literature, this test is not devoid of risks[7]. In our study, reactions (including one case of anaphylaxis) occurred in a considerable number of OFC-positive children, and most were restricted to a single organ (**Table 2**). All these cases were managed rapidly and appropriately, without any further complication. There are few studies in the literature addressing the OFC's safety. Anagnostou et al.[24] assessed the safety of performing OFC in children up to two years of age and found that symptoms, when occurring, were mostly limited to the skin. The authors concluded that OFC in infants has acceptable risks. Since symptoms caused by OFC are not difficult to treat, and OFC is an easy, low-cost and feasible method, with proven benefits for CMPA screening, we also think that its risks are acceptable, if the test is carried out by strictly following the appropriate protocol.

Naturally, our study has limitations. First, the low number of patients seen in a single center is a cause of selection bias. Including a greater population and other centers would allow more reliable statistical analyses. Also, we were able to perform only the open OFC, and not the double-blinded OFC, which is the most reliable one[2,17,18].. Still, even with a small sample size, we show that OFC application could identify a considerable fraction of patients who were misdiagnosed with CMPA, allowing our clinical staff to stop several expensive and unnecessary formula-based diets, which had a direct economic impact for the São Paulo State's public health service.

Conclusion

We conclude that OFC was crucial for identifying misdiagnosed CMPA cases, especially when it comes to patients with non-IgE-mediated CMPA, for whom milk reintroduction (in tolerable amounts) in the diet is easier. Ruling out CMPA meant a substantial reduction in the prescription of infant formulas, which can bring positive outcomes for growth, nutrition, and development of children, as well as for the quality of life of both children and mothers. We show

that stopping unnecessary formula-based diets can have a positive economic impact for public health systems by causing them to save great amounts of money that are spent on providing these formulas. OFC should be more spread through secondary healthcare units to increase the public access to this test.

Conflict of interest

On behalf of all authors, the corresponding author states that there is no conflicts of interest to declare.

References

1. Warren CM, Jhaveri S, Warrier MR, Smith B, Gupta RS. The epidemiology of milk allergy in US children. *Ann Allergy, Asthma Immunol*. 2013;110(5):370-374. doi:10.1016/j.anai.2013.02.016
2. Luyt D, Ball H, Makwana N, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. *Clin Exp Allergy*. 2014;44(5):642-672. doi:10.1111/cea.12302
3. Vieira MC, Morais MB, Spolidoro JVN, et al. A survey on clinical presentation and nutritional status of infants with suspected cow' milk allergy. *BMC Pediatr*. 2010;10(1):25. doi:10.1186/1471-2431-10-25
4. Solé D, Silva LR, Cocco RR, et al. Consenso Brasileiro sobre Alergia Alimentar: 2018 - Parte 1 - Etiopatogenia, clínica e diagnóstico. Documento conjunto elaborado pela Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunologia. *Arq Asma, Alerg e Imunol*. 2018;2(1):7-38. doi:10.5935/2526-5393.20180004
5. Solé D, Silva LR, Cocco RR, et al. Consenso Brasileiro sobre Alergia Alimentar: 2018 - Parte 2 - Diagnóstico, tratamento e prevenção. Documento conjunto elaborado pela Sociedade Brasileira de Pediatria e Associação Brasileira de Alergia e Imunologia. *Arq Asma, Alerg e Imunol*. 2018;2(1):39-82. doi:10.5935/2526-5393.20180005
6. Burks AW, Tang M, Sicherer S, et al. ICON: Food allergy. *J Allergy Clin Immunol*. 2012;129(4):906-920. doi:10.1016/j.jaci.2012.02.001
7. Bird JA, Leonard S, Groetch M, et al. Conducting an Oral Food Challenge: An Update to the 2009 Adverse Reactions to Foods Committee Work Group Report. *J Allergy Clin Immunol Pract*.

2020;8(1):75-90.e17. doi:10.1016/j.jaip.2019.09.029

8. Mendonça RB, Rodrigues Cocco R, Oselka R, et al. Teste de provocação oral aberto na confirmação de alergia ao leite de vaca mediada por IgE: qual seu valor na prática clínica? *Rev Paul Pediatr*. 2011;29(3):415-437.
9. Ballmer-Weber BK, Beyer K. Food challenges. *J Allergy Clin Immunol*. 2018;141(1):69-71. doi:10.1016/j.jaci.2017.06.038
10. Estado de São Paulo. Secretaria de Saúde. *Resolução No. 336, de 27 de Novembro de 2011. Diário Oficial Da União. 223a. Ed 28 de Novembro de 2007.*; 20107.
11. Lins MDGM, Horowitz MR, Da Silva GAP, Motta MEFA. Oral food challenge test to confirm the diagnosis of cow's milk allergy. *J Pediatr (Rio J)*. 2010;86(4):285-289. doi:10.2223/JPED.2011
12. Dambacher WM, De Kort EHM, Blom WM, Houben GF, De Vries E. Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: Prevention of unnecessary elimination diets and determination of eliciting doses. *Nutr J*. 2013;12(1):1-9. doi:10.1186/1475-2891-12-22
13. Bird JA, Crain M, Varshney P. Food allergen panel testing often results in misdiagnosis of food allergy. *J Pediatr*. 2015;166(1):97-100.e1. doi:10.1016/j.jpeds.2014.07.062
14. Venter C, Brown T, Meyer R, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: IMAP - An international interpretation of the MAP (Milk Allergy in Primary Care) guideline. *Clin Transl Allergy*. 2017;7(1):26. doi:10.1186/s13601-017-0162-y
15. Van Tulleken C. Overdiagnosis and industry influence: How cow's milk protein allergy is extending the reach of infant formula manufacturers. *BMJ*. 2018;363(December):1-5. doi:10.1136/bmj.k5056
16. Elizur A, Cohen M, Goldberg MR, Rajuan N, Katz Y. Mislabelled cow's milk allergy in infants: a prospective cohort study. *Arch Dis Child*. 2013;98(6):408-412. doi:10.1136/archdischild-2012-302721
17. NIDAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: Report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol*.

2010;126(6 SUPPL.):S1-S58. doi:10.1016/j.jaci.2010.10.007

18. Fiocchi A, Brozek J, Schünemann H, et al. World allergy organization (WAO) diagnosis and rationale for action against cow's milk allergy (DRACMPA) guidelines. *Pediatr Allergy Immunol*. 2010;21(SUPPL. 21):1-125. doi:10.1111/j.1399-3038.2010.01068.x
19. Martorell-Aragonés A, Echeverría-Zudaire L, Alonso-Lebrero E, et al. Position document: IgE-mediated cow's milk allergy. *Allergol Immunopathol (Madr)*. 2015;43(5):507-526. doi:10.1016/j.aller.2015.01.003
20. Couch C, Franxman T, Greenhawt M. The economic effect and outcome of delaying oral food challenges. *Ann Allergy, Asthma Immunol*. 2016;116(5):420-424. doi:10.1016/j.anai.2016.02.016
21. Osborn DA, Sinn JK, Jones LJ. Infant formulas containing hydrolysed protein for prevention of allergic disease. *Cochrane database Syst Rev*. 2018;10(10):CD003664. doi:10.1002/14651858.CD003664.pub6
22. Gordon M, Biagioli E, Sorrenti M, et al. Dietary modifications for infantile colic. *Cochrane database Syst Rev*. 2018;10:CD011029. doi:10.1002/14651858.CD011029.pub2
23. Sha T, Gao X, Chen C, et al. A prospective study of maternal postnatal depressive symptoms with infant-feeding practices in a Chinese birth cohort. *BMC Pregnancy Childbirth*. 2019;19(1):388. doi:10.1186/s12884-019-2559-1
24. Anagnostou K. Safety of Oral Food Challenges in Early Life. *Children*. 2018;5(6):65. doi:10.3390/children5060065

Authorship

1) *Ana Laura Mendes Becker Andrade*: Substantial contributions to conception and design, acquisition of data, analysis and interpretation of data; involved in drafting the manuscript.

2) *Priscila da Silva Pereira*: Substantial contributions to acquisition of data

3) *Renan Marrichi Mauch*: Involved in drafting and revising the manuscript critically for important intellectual content; gave final approval of the version to be published.

3) *Maria Angela Bellomo Brandão:* Substantial contributions to conception and design and acquisition of data

4) *Marcos Tadeu Nolasco da Silva*: Substantial contributions to conception and design, analysis and interpretation of data; involved in revising the manuscript critically for important intellectual content; gave final approval of the version to be published.

5) *Adriana Gut Lopes Riccetto:* Substantial contributions to conception and design, analysis and interpretation of data; had been involved in drafting the manuscript and revising it critically for important intellectual content; gave final approval of the version to be published.

Table 1. Characteristics of the 76 patients with diagnosis of Cow's Milk Protein Allergy (CMPA).

Characteristic	**N (%)**
Sex	
Male	41 (53.9)
Clinical symptoms in early diagnosis of CMPA	
Median age at onset of symptoms; months [range]	2.0 [0.8–5.0]
Gastrointestinal tract (vomiting, diarrhea, bloody stools)	52 (68.4)
Anaphylaxis	13 (17.1)
Urticaria/angioedema	7 (9.2)
Worsening of atopic dermatitis	4 (5.3)
Feeding at onset of symptoms of MA	
Common milk formula (intact protein)	31 (40.8)
Maternal milk	16 (21.1)
Whole milk/derivatives	15 (19.7)
Formula + maternal milk	14 (18.4)
Mechanism of Allergy (MA)	
Non-IgE mediated	52 (68.4)
IgE- mediated	20 (26.3)
Mixed	4 (5.3)
Elimination diet, before Oral Food Challenge (OFC)	
Aminoacid-based formula	29 (38.2)
Extensively hydrolyzed formula	26 (34.2)
Soy-based formula	18 (23.7)
More than one type of Infant Formula	12 (15.8)
Maternal milk	12 (15.8)
Non-use of maternal milk, formula or vegetable milk	5 (6.6)

Table 2. Characteristics of 76 patients with Cow's Milk Protein Allergy (CMPA), at the time of Oral Food Challenge (OFC).

Characteristic	**N (%)**
Median age at the time of OFC; years [range]	2.0 [0.8–5.0]
Aim of OFC	
Evaluate tolerance	62 (81.6)
Confirm diagnosis	14 (18.4)
OFC result	
Negative	58 (76.3)
Positive	18 (23.7)
Symptoms exhibited upon positive OFC (N=18)	
Gastrointestinal tract	*10 (55.6)*
Food Protein Induced Enterocolitis Syndrome (FPIES)	*2 (11.1)*
Ocular pruritus/nasal congestion/tongue pruritus	*3 (16.7)*
Urticária/angioedema	*4 (22.2)*
Anaphylaxis	*1 (5.5)*

Table 3. Children aged <24 months who used infant formulas during the elimination diet period and tested negative for Oral Food Challenge (OFC) (n = 30/76). Mechanism of Cow's Milk Protein Allergy (CMPA) diagnosed before OFC and infant formulas used during the elimination diet.

CMPA mechanism diagnosed before OFC	**N (%)**
Non-IgE mediated	29 (96.7)
IgE- mediated	1 (3.3)
Infant formula used during the elimination diet, before OFC	
Aminoacid-based formula	17 (56.7)
Extensively hydrolyzed formula	12 (40.0)
Soy-based formula	1 (3.3)

Table 4. Children aged <24 months who used infant formulas during the elimination diet period and tested negative for Oral Food Challenge (OFC) (n = 30/76). Number of cans saved per child, according to patient's age after negative OFC.

P	Age at OFC (months)	Number of cans saved*	Number of cans received until OFC	Number of cans saved after negative OFC	Infant formula used before OFC
1	2	255	29	226	AA-based
2	2	255	29	226	AA-based
3	3	255	44	211	AA-based
4	3	255	44	211	AA-based
5	3	255	44	211	AA-based
6	4	255	60	195	AA-based
7	5	255	76	179	AA-based
8	5	255	76	179	AA-based
9	6	255	92	163	AA-based
10	6	255	92	163	AA-based
11	7	255	105	150	AA-based
12	9	255	131	124	AA-based
13	10	255	141	114	AA-based
14	12	255	159	96	AA-based
15	13	255	167	88	AA-based
16	15	255	183	72	AA-based
17	19	255	215	40	AA-based
18	3	255	44	211	EHF
19	4	255	60	195	EHF
20	4	255	60	195	EHF
21	5	255	76	179	EHF
22	5	255	76	179	EHF
23	6	255	92	163	EHF
24	6	255	92	163	EHF
25	8	255	118	137	EHF
26	8	255	118	137	EHF
27	10	255	141	114	EHF
28	11	255	151	104	EHF
29	13	255	167	88	EHF
30	17	255	199	56	Soy-based

P (patient); OFC (Oral Food Challenge); AA (aminoacid); EHF (Extensively hydrolyzed formula);

**Number of cans that would be provided by the Public Health System if CMPA was not ruled out.*

Table 5. Children aged <24 months who used infant formulas during the elimination diet period and tested negative for Oral Food Challenge (OFC) (n = 30/76). Total amount of money* saved per child according to patient's age upon negative OFC and number of cans that would be provided by the Public Health system up to 24 months of age.

Patient	Age at test (months)	Nº of cans saved after OFC	Infant formula used	Price of can (BRL)	Total amount of money saved (BRL)	Money saved per month (BRL)
1	2	226	AA-based	62.12	14,039.12	638.14
2	2	226	AA-based	62.12	14,039.12	638.14
3	3	211	AA-based	62.12	13,107.32	624.16
4	3	211	AA-based	62.12	13,107.32	624.16
5	3	211	AA-based	62.12	13,107.32	624.16
6	4	195	AA-based	62.12	12,113.40	605.67
7	5	179	AA-based	62.12	11,119.48	585.24
8	5	179	AA-based	62.12	11,119.48	585.24
9	6	163	AA-based	62.12	10,125.56	562.53
10	6	163	AA-based	62.12	10,125.56	562.53
11	7	150	AA-based	62.12	9,318.00	548.12
12	9	124	AA-based	62.12	7,702.88	513.53
13	10	114	AA-based	62.12	7,081.68	505.83
14	12	96	AA-based	62.12	5,963.52	496.96
15	13	88	AA-based	62.12	5,466.56	496.96
16	15	72	AA-based	62.12	4,472.64	496.96
17	19	40	AA-based	62.12	2,484.80	496.96
18	3	211	EHF	50.37	10,628.07	506.10
19	4	195	EHF	50.37	9,822.15	491.11
20	4	195	EHF	50.37	9,822.15	491.11
21	5	179	EHF	50.37	9,016.23	474.54
22	5	179	EHF	50.37	9,016.23	474.54
23	6	163	EHF	50.37	8,210.31	456.13
24	6	163	EHF	50.37	8,210.31	456.13
25	8	137	EHF	50.37	6,900.69	431.29
26	8	137	EHF	50.37	6,900.69	431.29
27	10	114	EHF	50.37	5,742.18	410.16
28	11	104	EHF	50.37	5,238.48	402.96
29	13	88	EHF	50.37	4,432.56	402.96

30	17	56	EHF	16.13	903.28	129.04

BRL (Brazilian Reals); AA (Aminoacid); EHF (Extensively hydrolyzed formula).

** Considering the amount subsidized by the high-cost pharmacy of the University of Campinas Teaching Hospital (July 2018) - EHF: R$50.37/can; AA-based formula: R$62.12/Can; Soy-based formula: R$16.13/can.*

Table 6. Total amount of money* saved per child who used infant formula during the elimination diet, according to patient's age upon negative Oral Food Challenge (OFC) and number of cans that would be provided by the Public Health system up to 24 months of age (n = 30/76).

Analysis	*Amount in BRL*	*Amount in USD*
Mean amount saved per child	8,644.57 ± 3,394.60	2,161.14 ± 848.65
Total amount saved per month	15,162.63	3,790.65
Total amount saved per year	181,951.54	45,487.89
Total amount saved	259,337.09	64,834.27

* July 2018; *BRL (Brazilian Reals); USD (United States Dollars).*