

## Tolerability Study of a Free Amino Acid-based Formula in Children with Cow's Milk Allergy

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### Abstract

**Background:** The prevalence of food allergy has increased worldwide. Cow's milk allergy is a very common type of allergy in childhood. In non-breast-fed infants, with extremely severe or life-threatening symptoms, an amino acid-based formula may be considered the first choice for the dietary treatment. This study aimed to assess the tolerance to a new Brazilian amino acid-based formula and the nutritional status in children affected by cow's milk allergy fed with this formula.

**Objective:** To assess the tolerance to an amino acid-based formula and its nutritional status impact on children affected by cow's milk allergy.

**Method:** This is a clinical study conducted with a sample of 15 children, less than 5 years old with a clinical cow's milk allergy diagnosis. The children were followed-up, in a Pediatric Outpatient Clinic. Anthropometric, clinical, epidemiological data were collected at the baseline and it was also prescribed the amino acid-based formula. Throughout the treatment, which lasted five months, the clinical response was assessed based on the remission of symptoms initially presented and the evolution of nutritional status, using the WHO child growth standards charts.

**Results:** The sample included predominantly boys with a mean age of 28.1 months and 66.7% IgE-mediated. The average age of onset of the allergic symptoms was  $2.15 \pm 2.33$  months. Symptoms were reported in different systems (cutaneous, gastrointestinal and respiratory). In every child, there was complete remission of allergy symptoms initially presented and proper evolution of nutritional status.

**Conclusion:** This new free amino acid-based formula can safely be used for the dietary treatment for children with cow's milk allergy. The subjects studied showed adequate children's nutritional status evolution.

**Keywords:** Amino acids; Child nutritional status; Infant formula; Hypersensitivity; Milk protein; Cow's milk allergy

### Introduction

The prevalence of allergic diseases has increased worldwide and it can be highlighted the prevalence of food allergies that consists of any adverse reaction, immune mediated, reproducible, that is triggered by a contact with a specific food [1,2].

Among food allergies, cow's milk protein allergy (CMPA) is the first allergic disease in childhood, which is why it is the most prevalent in that age range. However, its real rate it is not well known, predominantly due to methodological differences described in the scientific literature report, as well as the diagnostic criteria vary from each other. In Brazil, the prevalence in early childhood is 5.4% [2-4].

CMPA can present a wide spectrum of clinical reactions such as cutaneous, gastrointestinal, respiratory, or systemic symptoms that might be caused by immunoglobulin (Ig)E-mediated, non-IgE-mediated, or mixed.

Diagnosis is based on the child's clinical history associated with physical examination, clinical symptoms, quantification of specific IgE to food and the oral challenge, the last one is considered the gold standard [2].

The basic treatment of CMPA consists of the complete avoidance of milk and dairy products. Milk substitutes are needed and, in general, specific infant formula or hypoallergenic diets are recommended. The purpose is to avoid triggering of symptoms and the disease progression, besides providing child a suitable growth and development pattern. The recommended formulas are: extensively or partially hydrolyzed cow's milk protein formulas (casein or whey protein), soy formula (isolated or hydrolyzed) or other vegetable milk. However only free amino acid-based formula are considered to be non-allergenic [1,2].

In Brazil, the predominant suppliers of these formulas are multinational companies. The Brazilian government is the main purchaser and the deal is made through public biddings. The important demand for national formulas rather than the foreign ones due, among other issues, the reduction of public expenditures, led a

Brazilian food industry to develop and produce an amino acid-based formula, called Amix<sup>®</sup>, to treat children with CMPA.

The current study aimed to evaluate the tolerance to this new formula and its ability to provide the nutritional needs for children with CMPA, without risks to the patient's health.

## Methods

According to research design, it was conducted, from August 2013 to June 2015, a self-controlled clinical study in a pediatric clinic, at Faculdade de Ciências Médicas de Minas Gerais (FCMMG). The research protocol and informed consent form were approved by the Ethics Committee of the FCMMG in accordance with Brazilian regulations [5]. After informing the children's parents or guardians about the research goals and all the procedures which would be conducted throughout the study, an informed consent was obtained from them.

Children from Belo Horizonte and metropolitan region, who were admitted to the pediatric clinic at FCMMG, presenting signs and symptoms of CMPA that had not improved with the consumption of extensively hydrolyzed cow's milk protein formulas were eligible for the study. The study enrolled 15 children, from birth to 5 years old.

The study consisted of two stages: a screening and a follow-up one. In the first stage, CMPA's diagnosis was confirmed based on a detailed clinical history and physical examination. Clinical evidence presented by the children while they were consuming cow's milk or cow's milk protein formulas, followed by remission of signs and symptoms after the introduction of exclusion diet, according to children guardians' reports and/or proven through medical reports were considered. In addition to the diagnosis, measurement of serum total and milk-protein IgE were assessed.

Through a questionnaire of sociodemographic, clinical and anthropometric data (such as date of birth, gender, type of delivery), information about breastfeeding, presented symptoms, type of allergic (IgE-mediated and not mediated), weight and length at birth, and also the current weight, length and head circumference, were also obtained at the first stage. From mothers were collected date of birth, educational background, and pregnancy complications. Before leaving the clinic, patients received the nutritionally complete and non-allergenic free amino acid-based formula, Amix<sup>®</sup>.

Each child attended 5 medical appointments. The follow-up stage, consisted of the assessment, at each visit, of clinical response of patients through presence or remission of gastrointestinal, respiratory and cutaneous symptoms initially presented, as well as formula acceptability, through the volume ingested. The evolution of nutritional status was also assessed by measurements of weight, length and head circumference. The variables weight and height were used to evaluate the body mass index for age (BMI/A). The WHO child growth standard charts were used to classify the nutritional status [6].

Data collection was carried out by two researchers and medicine students from FCMMG previously trained and qualified in accordance with the SISVAN's anthropometric rules [7]. Children under two years were weighed and measured completely naked. For those measurements, the digital pediatric scale Urano<sup>®</sup> and the infantometer Indaiá<sup>®</sup> were used. To measure the weight and height of children older than 2 years, Filizola<sup>®</sup> scale with stadiometer was used. Head circumference was measured using an inelastic and tape measure body.

Data obtained were deposited in a database and then processed and analyzed using WHO Anthro software, version 3.2.2 [8], WHO Anthro Plus, version 1.0.4 [9] and free software R version 3.1.3 [10]. The considered confidence interval was 95% with a 5% significance level ( $p \leq 0.05$ ).

In the statistical analysis, the descriptive statistics were used to present variables collected at the first medical appointment (gender age in months, types of allergies, type of delivery, gestational complications, weight and length, gestational age and maternal age). For categorical variables were presented absolute and relative frequencies and for continuous variables, average, standard deviation and amplitude. The formula tolerability was evaluated by comparing the results of weight, height, length, head circumference and the symptoms observed at the first and last follow-up medical appointment. The McNemar Chi-square ( $\chi^2$ ) test was applied to compare paired categorical data. The Wilcoxon test compared paired continuous data.

## Results

Table 1 presents the descriptive statistics of data collected in the first medical appointment. The sample was predominantly made up of boys (53.3%) with a mean age of 28.1 months ( $\pm 18.1$ ) and non-IgE-mediated allergy (66.7%). The average birth weight was 2.89 kg ( $\pm 0.89$  kg) and the most frequent type of delivery was the cesarean section (73.3%). With relation to pregnancy, the mean gestational age was 37 weeks ( $\pm 3.34$  weeks), and prematurity, caused by a variety of factors such as premature placental abruption, constant bleeding, and maternal hypertension, occurred in 20% of cases (n=3). Some complications associated with pregnancy and childbirth were reported by 46.66% of mothers (n=7) and include pre-eclampsia and HELLP syndrome, constant bleeding, maternal hypertensive crisis and gestational diabetes.

Variables	n	%
<b>Gender</b>		
Male	8	53.3
Female	7	46.7
<b>Age (months)</b>		
Mean $\pm$ SD <sup>*</sup>	28.1 $\pm$ 18.1	
Minimum; Maximum	9.9; 78.2	
<b>Birth weight (kg)</b>		
Mean $\pm$ SD	2.89 $\pm$ 0.89	
Minimum; Maximum	1.10; 4.28	
<b>Length weight (cm)</b>		
Mean $\pm$ SD	47.50 $\pm$ 4.67	
Minimum; Maximum	36; 53	
<b>Delivery mode</b>		
Vaginal delivery	4	26.7
Cesarean section	11	73.3
<b>Gestacional age (weeks)</b>		

Mean ± SD	36.70 ± 3.34	
Minimum; Maximum	28; 41	
<b>Pregnancy Complications</b>		
No	8	53.3
Yes	7	46.7
<b>Maternal age (age)</b>		
Mean ± SD	31.21 ± 5.24	
Minimum; Maximum	21; 40	
<b>Allergy</b>		
Non-IgE-mediated	10	66.7
IgE mediated	5	33.3
*SD: Standard Deviation		

**Table 1:** Descriptive variables of the study population, Belo Horizonte, Brazil, 2015.

In the study population, 93.33% (n=14) of the children were breastfed, and 53.33% (n=7) remained on exclusive breastfeeding for the average period of 42 ± 66.64 days (1.4 ± 2.22 months). The average duration of full breastfeeding was 174.14 ± 172.0 days (5.80 ± 5.74 months).

The average age of introduction of whole cow's milk or infant formula was 69.27 ± 71.66 days (2.31 ± 2.39 months). In 60% (n=9) children milk-based formula was introduced, in 20% (n=3) whole cow's milk, in 13.33% (n=2) a free amino acid-based formula and in 6.66% (n=1) a formula with extensively hydrolyzed protein. In some cases, mothers were asked to do the elimination diet to continue breastfeeding.

Table 2 depicts the comparison of the occurrence of symptoms according to the duration of full and exclusive breastfeeding. There was no significant difference in the occurrence of symptoms in the first and fifth medical appointment to any of full breastfeeding groups. However, comparing the occurrence of symptoms according to exclusive breastfeeding, there was a significant reduction in the occurrence of gastrointestinal symptoms in children who had not been on exclusive breastfeeding (p=0.010).

Variable	Breast feeding duration	1 <sup>st</sup> appointment		5 <sup>th</sup> appointment		P-value
		n	%	n	%	
<b>Full breast feeding duration</b>						
Gastrointestinal symptoms	<6 months (n=7)	4	57.1	0	0	0.076*
	≥ 6 months (n=8)	4	50	0	50	0.056*
Respiratory symptoms	<6 months (n=7)	3	42.9	2	28.6	1.000*
	≥ 6 months (n=8)	2	25	0	0	0.450*
Cutaneous symptoms	<6 months (n=7)	2	28.6	0	0	0.445*
	≥ 6 months (n=8)	4	50	1	12.5	0.281*
<b>Exclusive breast feeding duration</b>						
Gastrointestinal symptoms	No (n=8)	6	75	0	0	0.010*
	Yes (n=8)	3	37.5	0	0	0.200*
Respiratory symptoms	No (n=8)	4	50	2	25	0.606*
	Yes (n=8)	1	12.5	1	12.5	1.000*
Cutaneous symptoms	No (n=8)	3	37.5	0	0	0.200*
	Yes (n=8)	4	50	1	12.5	0.281*

\*P-value McNemar chi-square test to paired categorical data

**Table 2:** Comparison of CMPA symptoms occurrence according to the duration of breastfeeding in the 1<sup>st</sup> and 5<sup>th</sup> medical appointment, Belo Horizonte, Brazil, 2015.

The average age at onset of CMPA symptoms was 2.15 ± 2.33 months (64.47 ± 69.75 days). Symptoms reported were grouped into three major groups: Cutaneous (atopic dermatitis, hives, rashes, itching and perianal rash), respiratory (wheezing and bronchospasm) and gastrointestinal (cramps, gas and bloating, vomiting, nausea, diarrhea

containing mucus and blood, hematochezia, constipation, gastroesophageal reflux and severe constipation).

The average age of the children at the beginning and end of treatment with infant formula Amix<sup>®</sup> was 13 ± 13.58 months and 18 ± 14 months, respectively. All children presented good tolerance of the study formula. Average weight gain was 361.95 g/month and height

gains 2.49 cm/month. In 60% of cases (n=9) both gains were higher than theoretically expected; in 26.67% (n=4) children only the length reached the expectation, and in 13.33% (n=2), only the weight gain was higher than expected for the age group.

Table 3 presents the comparison between the measurements of weight, height, head circumference and symptoms of children in the first and fifth medical appointment. There was a significant reduction in gastrointestinal symptoms, presented by nine of 15 children in the first medical appointment (60%), and in the fifth medical appointment, these symptoms were not observed in any children (p-value=0.000). Cutaneous symptoms were presented by 7 of 15 children in the first medical appointment (46.7%), only 1 child (6.7%) presented them in the fifth one (p-value=0.016). There was a significant increase in weight, height and head circumference of children.

Variables	1 <sup>st</sup> appointment		5 <sup>th</sup> appointment		P-value
	n	%	n	%	
Gastrointestinal symptoms	9	60	0	0.0	0.000**
Respiratory symptoms	5	33.3	3	20.0	0.433**
Cutaneous symptoms	7	46.7	1	6.7	0.016**
<b>Weight (kg)</b>					
Mean ± SD <sup>†</sup>	8.80 ± 3.37		10.40 ± 2.87		0.001***
<b>Length (cm)</b>					
Mean ± SD <sup>†</sup>	70.71 ± 12.72		78.81 ± 10.90		0.001***
<b>Head Circumference (cm)</b>					
Mean ± SD <sup>†</sup>	44.48 ± 3.99		46.19 ± 2.79		0.006***

<sup>†</sup>SD=standard deviation; \*\* P-value McNemar chi-square test to paired tegorical data; \*\*\*P-value Wilcoxon test to compare paired continuous data

**Table 3:** Comparison of weight, height, head circumference and symptoms presented by the children sampled in the 1<sup>st</sup> and 5<sup>th</sup> medical appointment, Belo Horizonte, Brazil, 2015.

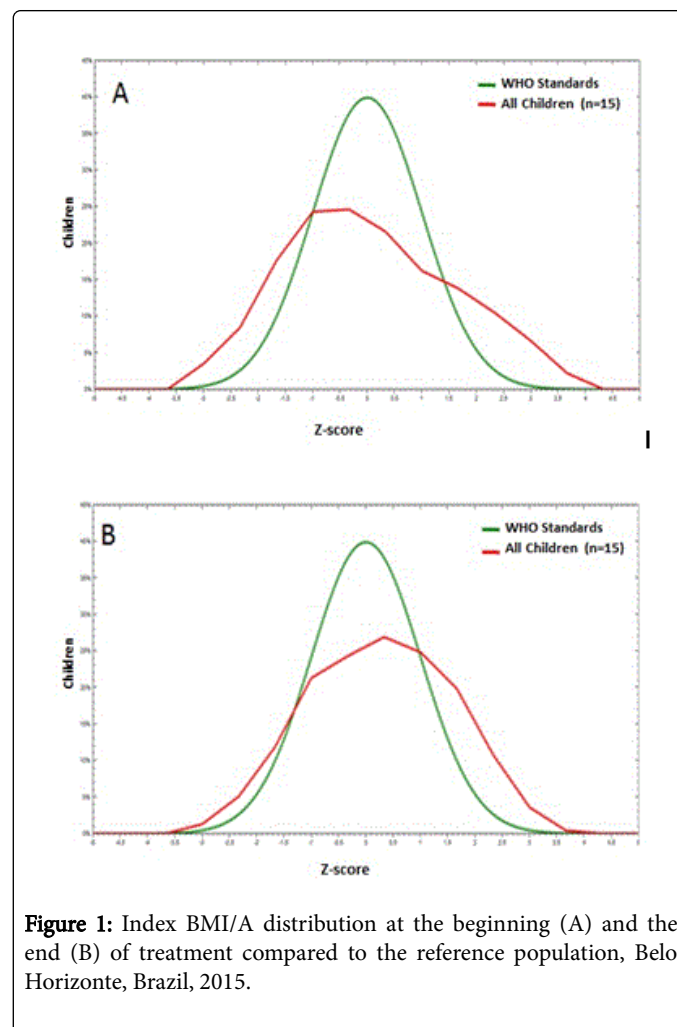
BMI index for age (BMI/A) at the beginning and at the end of treatment with infant formula Amix<sup>®</sup> compared to the WHO standard distribution (2006) presented a good improvement in nutritional status (Figure 1). The mean BMI Z-score at the first visit (Figure 1A) and five months later (Figure 1B) were 0.015 ± 1.34 and 0.067 ± 1.33, respectively (p-value=0.89) corroborating the efficacy of Amix<sup>®</sup> formula.

## Discussion

The available treatment for children diagnosed with CMPA currently described is the strict avoidance of milk and dairy products [11]. Therefore, there is great concern among health professionals and guardians in relation to the dietary intake and nutritional status of these children. If an adequate hypoallergenic diet is not implemented, the treatment may promote energy, protein and micronutrients deficits [12].

In situations which the maintenance of breastfeeding is not possible, the use of hydrolyzed cow's milk protein formulas or soy protein formulas is considered a recommended alternative to the treatment [2]. In the case of soybeans, unfortunately, about 30-50% of children

who are intolerant to milk protein are also allergic to soy protein. Furthermore, the use of soy milk is not recommended for children under 6 months of age [2,13].



**Figure 1:** Index BMI/A distribution at the beginning (A) and the end (B) of treatment compared to the reference population, Belo Horizonte, Brazil, 2015.

The formulas containing milk proteins partially hydrolyzed or extensively are alternative options for the treatment of CMPA because they are less susceptible to induce an immune reaction. However, it should be considered that formulas containing partially hydrolyzed protein may cause allergy in one-third to half of allergic individuals and therefore cannot be considered hypoallergenic. Many researchers have already reported hypersensitivity reactions to these formulas, and also corroborated that this is a relatively common problem among children [14,15]. On the other hand, formulas containing extensively hydrolyzed proteins are well tolerated by approximately 95% of allergic individuals [16].

When patients do not respond to treatment with these products, free amino acid-based formulas, the only one considered non-allergenic, are indicated [2,17]. In general, the use of these formulas consists of an effective and safe method, able to promote adequate children's weight gain, growth and the remission of allergy symptoms initially presented [17,18].

Therefore, the development of a nutritionally complete free amino acid-based formula is an advance in the treatment of CMPA when hypersensitivity to intact or hydrolyzed proteins occurs. However,



studies are needed to confirm the tolerability and nutritional adequacy of these formulas in children [19].

This work presents the first study to assess the tolerability to a new free amino acid-based formula for children with CMPA, called Amix<sup>®</sup>, available in the Brazilian market. The tolerability to amino acid-based formula, in some cases can be vital since, although most children respond to the avoidance of milk protein and to the introduction of extensively hydrolyzed formulas and diets, there are some situations or more severe cases in which only the free amino acid-based diets can solve the signs and symptoms of CMPA [2,14,20].

According to Bahna [19], to be considered hypoallergenic, the formula should be well tolerated by at least 90% (with 95% confidence) of individuals who are already allergic to milk protein. This study showed, with 95% confidence that all children with CMPA who participated in the study tolerated the free amino acid-based formula, Amix<sup>®</sup>.

At the end of treatment, it was observed that one child presented signs of atopic dermatitis. However, the manifestation of this symptom does not mean lack of tolerance to the infant formula Amix<sup>®</sup>, since this patient has not had other symptoms of CMPA, presented at the beginning of the treatment. These symptoms may be associated with increased synthesis of IgE, which is common in atopic children. The natural history of atopic manifestations is characterized by a typical sequence of IgE antibody responses and clinical symptoms which may appear early in life, persist over years and often remit spontaneously with age, called atopic march. So even with the exclusion of cow's milk and dairy products, the child may present other manifestations such as asthma, rhinitis, and dermatitis [21].

During the last physical examination, it was observed sibilant rhonchus, in three children with viral infection when undergoing chest auscultation. Despite this respiratory symptom also be suggestive of CMPA, its clinical manifestation in these cases is not associated with lack of tolerability to the infant formula Amix<sup>®</sup>. It is known that during the winter, due to climatic conditions, either the low temperature or the dry season, there is an increase in hospital admissions for complications related to the respiratory system [22].

As observed in other studies, digestive symptoms showed the highest prevalence among studied children [23,24]. Most children (66.7%) were diagnosed with non-IgE mediated reactions, which are characterized by symptoms of delayed onset, involving preferably the gastrointestinal tract, reinforcing the results observed at the first medical appointment when 60% of children had gastrointestinal symptoms.

The most common type of delivery was cesarean section and prematurity occurred in 20% of cases. These two variables are considered, among other maternal and perinatal characteristics, potential risk factors for the CMPA. Therefore, these findings contributed to reinforcing results already reported by other researchers, which the mode of delivery and prematurity contribute to the increased prevalence of CMPA [25,26]. The introduction of milk based infant formula (60%) reflects the early occurrence, not only the weaning but also the allergen presence on children feeding. The average time of exclusive breastfeeding (42 days) and full breastfeeding (approximately 180 days) observed in this study, is fall far shorter than the current WHO recommendations, which states that infant should be exclusively breastfed up to six months of age with continued breastfeeding along with appropriate complementary food up to two

years of age or beyond [27]. This condition is also associated with an increased risk of developing CMPA [26].

The significant reduction in the occurrence of gastrointestinal symptoms in children, who were exclusively breastfed, does not mean that exclusive breastfeeding should not be encouraged in cases of CMPA. On the opposite, breastfeeding should be recommended due to many beneficial effects in the short and long terms for both mother and child, including as a protective agent for food allergies. Regarding this, mothers should be oriented to do the elimination diet [2].

What may explain this finding is that often the compliance to exclusion diet is not simple. Most of the time the mother consciously do not consume milk, dairy or traces, but an accidental ingestion can happen or also the lack of knowledge, especially when reading the labels of processed foods. It is for this reason that mothers and families need to receive nutritional counseling, which should address the possible cross-contamination and read not only food but also cosmetics and medicaments labels [28].

The WHO child growth standard charts were used for nutritional assessment, because they represent a prescriptive approach to how children around the world should grow and they are considered an adequate and robust instrument for assessing the nutritional status of children under five years, regardless of their ethnic and cultural characteristics, by the fact that, under optimal conditions, all children show similar growth pattern [29].

We conclude that there was an adequate improvement in children's nutritional status as well as weight gain ( $p < 0.001$ ), and improvement in other parameters, which prove the effectiveness of the formula Amix<sup>®</sup>. Therefore this formula can be used for the dietary management of children with CMPA, without prejudice to their nutritional status and without triggering immediate or late allergic symptoms.

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## Authors Note

This clinical trial was registered in "ClinicalTrials.gov Protocol Registration System", under the identification number: NCT02536482.

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