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Abstract

A masked, randomized, parallel growth study was conducted in infants fed an amino acid–based formula (AF) or an extensively hydrolyzed casein-based formula (HF). Infants were enrolled between 0 and 9 days and studied to 112 days of age. Growth, formula intake, stool patterns, and serum albumin concentrations were assessed. There were no significant differences between groups in weight, length, or head circumference, gains in weight or length, or study formula intake. The number of stools parents rated as being formed, and the mean daily number of stools were greater in the HF than in the AF group at 14 and 28 days of age. Mean serum albumin concentrations were not significantly different between groups and were within the normal range. This study demonstrates that AF supports normal growth of infants comparable to that of infants fed HF during the critical first 4 months of life.

Keywords

elemental formula, free amino acid–based formula, hydrolysate formula, hypoallergenic, formula, infant feeding, infant growth, weight

Introduction

Cow milk protein allergy (CMA) is the most common food allergy in early childhood, with an estimated incidence of 2% to 3%.^{1,2} Hypoallergenic formulas based on extensively hydrolyzed casein or whey are recommended for managing formula-fed infants.^{3,4} However, allergic responses can still occur with hypoallergenic hydrolysate formulas because they may contain residual peptides that can elicit an allergic response in sensitive children.^{5–7} An alternative to hydrolysates are formulas based on free amino acids. Such formulas are indicated for infants with extreme protein hypersensitivity, for infants whose symptoms persist even with the feeding of extensively hydrolyzed formulas, and for infants with CMA who have failure-to-thrive.^{8–11}

Although studies have demonstrated that hypoallergenic amino acid–based formulas are efficacious for treating symptoms in virtually all infants with CMA, few studies have focused on the efficacy of these formulas in supporting normal growth during infancy.

Most studies of amino acid–based formulas were conducted in relatively small populations of infants with CMA or intolerance, and most studies were not designed to measure effects on growth.^{7,12–19} The present study was designed to assess the growth of healthy term infants fed an amino acid–based formula versus an extensively hydrolyzed casein–based formula in a randomized controlled trial that met robust criteria proposed²⁰ for evaluating the ability of a formula to support growth of infants.

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Table 1. Nutritional Composition of Study Formulas.

Macronutrient	AF		HF	
	Source	Content (g/L)	Source	Content (g/L)
Protein	100% free L-amino acids	20.3	100% extensively hydrolyzed casein	18.9
Carbohydrate	100% corn syrup solids	72.3	78% corn syrup solids 22% modified cornstarch	74.3
Fat	38% high-oleic safflower oil 33% medium chain triglycerides 29% soy oil	32.2	45% palm olein 20% soy oil 20% coconut oil 15% high-oleic sunflower oil	33.8

Abbreviations: AF, amino acid–based formula; HF, extensively hydrolyzed casein-based formula.

Methods

Study Design

A masked, randomized, parallel growth study (ClinicalTrials.gov Identifier NCT01699386) was conducted. Infants were randomly assigned to receive 1 of 2 formulas, a hypoallergenic amino acid–based formula (AF) or a hypoallergenic extensively hydrolyzed casein–based infant formula (HF). Formulas were fed from enrollment until 112 days of age. Parents were instructed to feed the assigned formula as the sole source of nutrition ad libitum for the duration of the study. The primary objective was to compare weight gain from 14 to 112 days of age, and weight at each study visit. Length, head circumference (HC), length gain, study formula intake, daily stool number, mean rank stool consistency (MRSC), and serum albumin were also measured.

A pseudo-random permuted-blocks computer algorithm prepared by the sponsor equally randomized treatments within gender at each site. Formula was identified by code only and study personnel, parents and caregivers were unaware of formula identity. Packaging for both formulas was similar. Blinding was not broken until after all data had been collected.

Subjects

Healthy, singleton term infants with birth weights ≥ 2500 g were enrolled between 0 and 9 days of age and studied to 112 days of age. Parents agreed to use the study formulas as the sole source of nutrition and to not administer any mineral or vitamin supplements during the study. Water was permitted ad libitum. Exclusion criteria included maternal, fetal, or perinatal medical conditions with the potential for adverse effects on growth, development, or both, such as diabetes (gestational diabetes was acceptable if the infant's birth weight was less than the 95th percentile), tuberculosis, intrauterine infections, or suspected substance abuse.

Parents or guardians provided written informed consent prior to enrollment. Subjects were recruited at 2 sites: Iowa City/Cedar Rapids, Iowa and Little Rock, Arkansas. The protocol was reviewed and approved by the University of Iowa Institutional Review Board, Iowa City; and Baptist Medical Center Institutional Review Board, Little Rock, Arkansas. Infants were enrolled from April 1999 to September 2000. The study was conducted in accordance with all applicable regulations, including Good Clinical Practices and the ethical principles originating from the Declaration of Helsinki.

Study Formulas

Both formulas provided levels of nutrients recommended by the American Academy of Pediatrics Committee on Nutrition, and were in compliance with the Infant Formula Act.^{21,22}

The AF formula was EleCare Amino Acid–Based Medical Food (Abbott Nutrition, Abbott Laboratories, Columbus, OH); the HF formula was Nutramigen Protein Hydrolysate Infant Formula (Mead Johnson Nutritionals, Evansville, IN). Both formulas were in powdered form and provided 20 kcal/fl oz when fed at standard dilution.

The macronutrient contents of both formulas were similar but the sources of macronutrients were different (Table 1).

Study Assessments

Study visits occurred when infants were 14, 28, 56, 84, and 112 ± 4 days of age. The primary outcome variables were weight gain (g/d) from 14 to 112 days of age, and weight at 14, 28, 56, 84, and 112 days of age. Secondary variables included length, HC, and length gain (mm/d) from 14 to 112 days of age, study formula intake, daily number of stools, MRSC, and serum albumin concentration. Anthropometric measurements

were made at enrollment and at each study visit, and were plotted against the World Health Organization (WHO) growth standards.²³ Parents completed 3-day intake records before each study visit, and 3-day stool records before the 14- and 28-day visits. These records included the characteristics (consistency and frequency) of the infant's stools and volume of formula consumed at each feeding. For calculation of MRSC, each stool was ranked by the parents on a scale of 1 to 5 (1 = watery to 5 = hard). The mean stool rank was calculated for each day, and the mean of these daily means was calculated over the study period and is reported as the average MRSC. Blood samples (approximately 0.75 mL) were collected by heel stick or venipuncture at the 112-day visit for measurement of serum albumin. Samples were centrifuged and serum was frozen and stored at -20°C until shipment to a central laboratory (Quest Diagnostics, Inc, San Juan Capistrano, CA), where albumin concentration was measured by the bromocresol green method.

Statistical Analysis

A sample size of 64 infants in each group would have 80% power to detect a difference in weight gain of 3 g/d from day 14 to 112, assuming that the common standard deviation is 6 g/d using a 2-group *t* test with a .05 two-sided significance level. Weight gain and length gain per day were calculated as the difference between the initial and the final measurement divided by the number of elapsed days. Weight gain (g/d) and length gain (mm/d) from 14 to 112 days were compared using analysis of variance (ANOVA). The factors in the model were feeding group and sex. Weight, length, and HC were compared using repeated measures ANOVA with the SAS procedure PROC MIXED. The factors in the model were feeding group, sex, and their interactions. The MRSC was analyzed using ANOVA with a random blocking factor for site, and the average daily number of stools and serum albumin concentrations were analyzed by ANOVA. All tests were 2-sided, and results were considered statistically significant if the *P* value was less than .05. The study results are shown as mean $\pm$ the standard error of the mean and are for the intent-to-treat group unless otherwise indicated.

Results

Disposition of Study Subjects

A total of 213 infants were enrolled into the study and randomized (Figure 1). Of these, 134 infants completed the study whereas 79 infants left the study early.

The demographic characteristics including gender, gestational age, ethnicity, age at study entry, birth weight, length, HC, and weight at study entry were similar between groups (Table 2).

Growth

There were no statistically significant differences between feeding groups in mean weight (Table 3) or in mean weight gain, which was 28.2 ± 0.7 (n = 73) and 28.2 ± 0.6 g/d (n = 81) for the AF and HF groups, respectively (*P* = .8670, 95% confidence interval = -2.2 to 1.9). The results of the per protocol analysis were similar to those of the intent-to-treat analysis. Mean weight for males and females are shown in comparison with the WHO growth standards in Figure 2. There were no statistically significant differences between the groups for length or HC (Table 3) or for length gain (data not shown) during the study.

Formula Intake

Mean study formula intakes for the groups were similar at 14, 28, 56, 84, and 112 days of age (Table 4).

Stool Patterns

There were statistically significant differences in stool patterns between groups. The average MRSC and mean daily number of stools were significantly greater in the HF group at 14 and 28 days of age (Table 4).

Serum Albumin

At 112 days of age, the mean serum albumin concentration was not statistically different between groups (42.2 ± 0.3 and 43.3 ± 0.4 g/L for the AF [n = 59] and HF [n = 68] groups, respectively, *P* = .0513, 95% confidence interval = -2.0 to 0.2).

Safety

No safety concerns emerged during this study.

Discussion

We report that the growth of infants fed a hypoallergenic amino acid-based formula (AF) was similar to that of infants fed a hypoallergenic extensively hydrolyzed casein-based formula (HF). Infants started to receive study formulas at a mean age of approximately 6 days and continued until 112 days of age; 65 and 69 infants completed the study in the AF and HF groups,

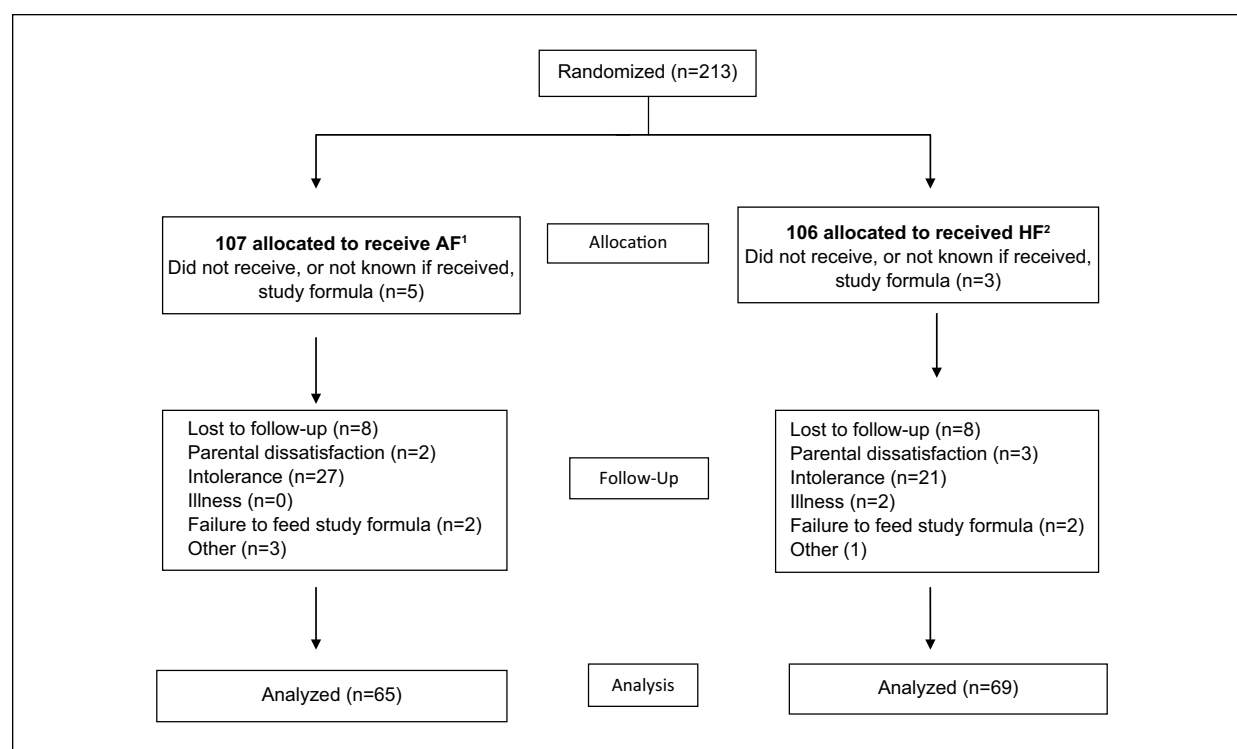


Figure 1. Flowchart of the study design.

¹Amino-acid based formula

²Extensively hydrolyzed casein-based formula

Table 2. Infant Characteristics.

Variable	AF	HF	P
Total enrolled (n)	107	106	—
Males/females (n)	57/50	55/51	.8416
Ethnicity, n (%)			
Caucasian	96 (90)	94 (89)	.4657
African American	9 (8)	7 (7)	
Other	2 (2)	5 (5)	
At birth ^a			
Gestational age (weeks)	39.4 ± 0.1	39.4 ± 0.1	.8185
Weight (g)	3505 ± 40	3488 ± 43	.7761
Length (cm)	51.2 ± 0.2	51.5 ± 0.2	.3151
Head circumference (cm)	34.8 ± 0.2	34.5 ± 0.2	.2052
At study entry ^a			
Age (days)	6.4 ± 0.2	6.2 ± 0.2	.1168
Weight (g)	3515 ± 40	3499 ± 42	.7664

Abbreviations: AF, amino acid–based formula; HF, extensively hydrolyzed casein-based formula.

^aData are presented as mean ± standard error of the mean.

respectively. There were no significant differences between groups in the rates of gain in weight or length, or in weight, length, or HC during the study. The mean weight of males and females was close to the

50th percentile of the WHO standards, indicating a normal growth pattern. Serum albumin levels at 112 days of age were similar between groups and were within the normal range.

Table 3. Weight, Length, and Head Circumference at 14, 28, 56, 84, and 112 Days of Age of AF- and HF-Fed Infants.^a

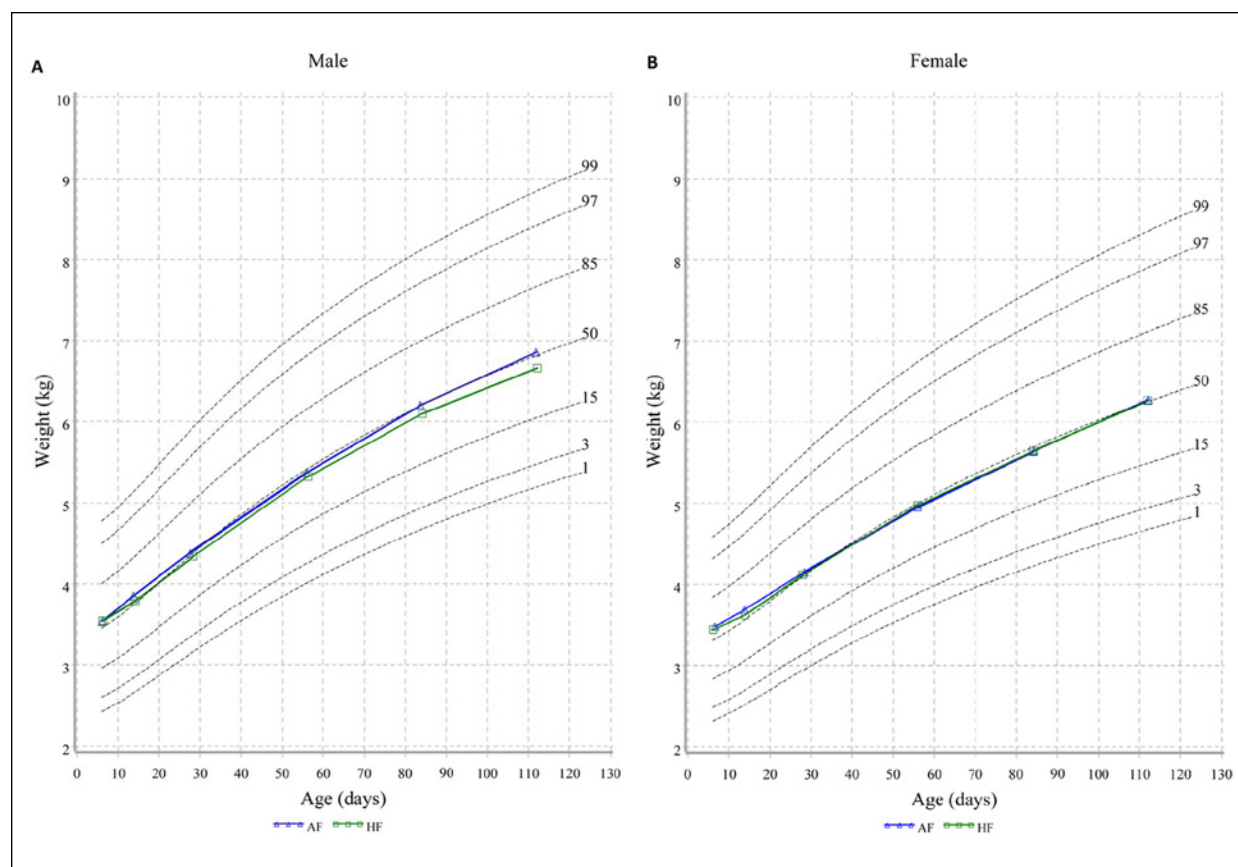
Parameter	Age (Days)					<i>P</i> ^b
	14	28	56	84	112	
Weight (g)						
AF	3777 ± 45 (93)	4273 ± 54 (76)	5178 ± 71 (71)	5944 ± 86 (67)	6601 ± 84 (75)	.5882
HF	3713 ± 43 (97)	4237 ± 50 (81)	5163 ± 63 (76)	5890 ± 77 (72)	6468 ± 77 (82)	
95% CI ^c	(-78.88, 220.06)	(-115.76, 189.56)	(-174.70, 191.38)	(-183.87, 231.43)	(-151.89, 290.09)	
Length (cm)						
AF	51.8 ± 0.2 (93)	53.7 ± 0.2 (76)	57.1 ± 0.2 (71)	60.2 ± 0.2 (67)	62.8 ± 0.2 (75)	.6040
HF	51.9 ± 0.2 (97)	53.8 ± 0.2 (81)	57.1 ± 0.2 (76)	60.3 ± 0.2 (72)	62.6 ± 0.2 (82)	
95% CI	(-0.65, 0.45)	(-0.74, 0.36)	(-0.72, 0.46)	(-0.76, 0.44)	(-0.69, 0.55)	
Head circumference (cm)						
AF	36.1 ± 0.1 (93)	37.3 ± 0.1 (76)	39.1 ± 0.1 (71)	40.4 ± 0.1 (67)	41.5 ± 0.1 (75)	.0687
HF	35.9 ± 0.1 (97)	37.1 ± 0.1 (81)	38.9 ± 0.1 (76)	40.2 ± 0.1 (72)	41.3 ± 0.1 (82)	
95% CI	(-0.14, 0.54)	(-0.01, 0.65)	(-0.07, 0.59)	(-0.10, 0.58)	(-0.06, 0.62)	

Abbreviations: AF, amino acid-based formula; HF, extensively hydrolyzed casein-based formula; CI, confidence interval.

^aData are presented as mean ± standard error of the mean (number of subjects).

^bRepeated-measures analysis of variance.

^c95% confidence interval is for the difference in least square means between AF and HF.

**Figure 2.** Mean weight shown in comparison with the World Health Organization growth standards for (A) males and (B) females.

Abbreviations: AF, amino acid-based formula; HF, extensively hydrolyzed casein-based formula.

Table 4. Study Formula Intake, Average Mean Rank Stool Consistency, and Number of Stools/Day.^a

Age	AF	HF	P	95% CI
Study formula intake (mL per day)				
14 days	591 ± 15 (78)	564 ± 14 (89)	.1495	(-16.0, 73.5)
28 days	709 ± 23 (74)	693 ± 18 (77)	.5801	(-48.3, 80.0)
56 days	797 ± 28 (69)	787 ± 20 (73)	.7329	(-64.7, 88.2)
84 days	861 ± 34 (66)	812 ± 19 (70)	.1692	(-30.9, 134.9)
112 days	894 ± 39 (65)	842 ± 21 (66)	.1926	(-37.4, 149.2)
Average mean rank stool consistency ^b				
14 days	2.5 ± 0.1 (77)	2.8 ± 0.1 (89)	.0004	(-0.55, -0.13)
28 days	2.3 ± 0.1 (73)	2.8 ± 0.1 (77)	<.0001	(-0.65, -0.23)
Daily number of stools				
14 days	2.0 ± 0.2 (78)	3.5 ± 0.2 (89)	<.0001	(-2.14, -0.86)
28 days	1.5 ± 0.2 (74)	2.9 ± 0.2 (77)	<.0001	(-1.96, -0.82)

Abbreviations: AF, amino acid-based formula; HF, extensively hydrolyzed casein-based formula; CI, confidence interval.

^aData are presented as mean ± standard error of the mean (number of subjects).

^bCalculated as 1 = watery to 5 = hard.

Our results are in agreement with those of other investigators who reported normal growth patterns in infants fed HF.²⁴⁻²⁶ However, only a few studies assessed the growth of normal infants fed amino acid-based formulas as a primary outcome, and some did not meet rigorous standards for clinical evaluation of infant growth. The US Food and Drug Administration,²⁰ with guidance from the American Academy of Pediatrics Committee on Nutrition,²⁷ proposed rules for evaluating the ability of formulas to support growth of infants, including that (a) the evaluation should be made when the formulas are used as the sole source of nutrition; (b) the rate of weight gain should be determined over an interval of 3 to 4 months; (c) that growth assessment should include the first 8 weeks of life because nutrient requirements per kilogram of body weight are greatest during this period; (d) that growth measurements should be made at the beginning of the study, 2 and 4 weeks later, and at least monthly thereafter until conclusion of the study; and (e) that studies need to have sufficient statistical power to detect a feeding-related difference in weight gain of more than 3 g/d over a 3- to 4-month period, which is considered to be nutritionally relevant. The number of subjects of a specified sex needed in each of 2 groups to detect this difference at $P < .05$ with a power of 80% in a 1-tailed test is 28.

Although the published studies concerning amino acid-based formulas report that they supported the growth of infants,^{7,12-17,28} growth was not the primary outcome variable for most studies. In a well-designed growth study, Burks et al²⁴ reported that healthy, term infants fed an amino acid-based formula or HF had similar rates of growth. However, most studies of amino acid-based formulas involved infants with established

allergy or intolerance to cow milk, and such infants often have multiple confounding clinical factors, including growth restriction, and the studies therefore did not meet the more stringent criteria for evaluating the ability of a formula to support the growth of normal infants.^{7,12-15,17-19} The evaluation of growth was the primary outcome variable of the present study, which met the stringent criteria for evaluation of infant growth.

In the present study, 42 infants fed AF and 37 fed HF exited from the study early, with 25% fed AF and 20% fed HF exiting because of intolerance symptoms. In our experience, these attrition rates are typical of long-term studies with extensively hydrolyzed or amino acid-based formula when fed to healthy term infants. When these formulas are fed to intended populations, attrition rates are dramatically lower. These formulas are noticeably different from standard formulas in appearance, taste, and smell and because of their elemental nature may modify typical feeding and stooling patterns of healthy infants. We speculate that parents of healthy term infants are less tolerant of these differences than are parents of sick infants where, in fact, feeding and stooling patterns of their infant may normalize on these formulas.

A strength of our study is that tolerance and formula intake were assessed systematically. Parents completed 3-day intake records before the visits at 14, 28, 56, 84, and 112 days, and they completed 3-day stool records before the visits at 14 and 28 days. The records included 24-hour intake data and detailed information about the consistency of each stool. The volume of formula consumed was similar between groups throughout the study. However, infants fed the HF had significantly more stools that parents rated as firm or hard, and a significantly greater number of stools per day than infants fed

AF. This difference in stooling pattern and consistency is likely because of the use of palm olein oil as a source of fat in the HF fed in this study. Lloyd et al²⁹ reported that formula with palm olein oil is associated with firmer stools.

Although extensively hydrolyzed formulas and amino acid–based formulas are effective in relieving symptoms in most infants with CMA, amino acid–based formulas are preferable for certain patients.^{8–11} Hill et al¹⁰ reported that specific subgroups of infants have better resolution of symptoms on amino acid–based formulas than on extensively hydrolyzed formula, and they more often have catch-up growth. The subgroups include infants with non-IgE mediated food-induced gastroenterocolitis–proctitis syndromes with failure-to-thrive, those with severe atopic eczema, and those with symptoms during exclusive breast-feeding. Isolauri et al¹⁴ reported that growth of infants with CMA was improved in infants fed an amino acid–based formula but not in infants fed an extensively hydrolyzed whey-based formula, and concluded that an amino acid–based formula is preferable for infants with multiple food allergies, especially because it maintains normal growth. Niggemann et al¹⁷ reported that atopic dermatitis improved in infants with CMA who were fed an amino acid–based formula but remained constant in those fed an extensively hydrolyzed whey-based formula. Other investigators report that infants with CMA did not react to amino acid–based formula, but some infants react to extensively hydrolyzed formula with bloody stools, vomiting, diarrhea, irritability, eczema, and failure to gain weight.^{5,19} Caution is needed, however, in comparing studies of amino acid–based formulas with studies of hydrolyzed formulas. Clinical outcomes can be affected by other differences in the composition of formulas, including hydrolysate source, the extent of hydrolysis, fat blend with possible effects on energy availability, amino acid blend, protein content, and fortification with other nutrients.

The present robust study meets rigorous criteria for the evaluation of infant formulas, and demonstrates that this amino acid–based formula supports normal growth of infants during the critical first 4 months of life. As the incidence of food allergy continues to increase,¹ the use of amino acid–based formulas will likely increase, especially for infants with severe CMA and for specific subsets of infants whose symptoms are resolved more effectively with amino acid–based formulas than with extensively hydrolyzed formulas.

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Declaration of Conflicting Interests

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