Gastrointestinal Tolerance of a New Infant Milk Formula in Healthy Babies: An International Study Conducted in 17 Countries

Pedro A. Alarcon, MD, PhD, Randall L. Tressler, MD, Anthony Mulvaney, BS, Wayne Lam, PhD, and Gail M. Comer, MD

From Abbott Laboratories, Abbott Park, Illinois, USA

OBJECTIVE: We tested the hypothesis that the gastrointestinal tolerance of a new infant formula equals or exceeds the tolerance of other milk-based infant formulas and compared the tolerance of this new formula with that of human milk.

METHODS: This prospective, phase IV, open-label study was conducted in 17 countries. Healthy, full-term infants, 28 to 98 d old, were enrolled on their current feeding (no treatment assigned). Feeding regimens included human milk (HM), a new infant formula (NF; Similac Advance), other infant formula (OF), HM + NF, and HM + OF. Data for stool frequency, stool consistency, and gastrointestinal symptoms were collected in study diaries for 2 wk.

RESULTS: Gastrointestinal tolerance was evaluated in 6999 infants: 979 (14.0%) received HM, 1695 (24.2%) received HM + NF, 635 (9.1%) received HM + OF, 2677 (38.2%) received NF, and 1013 (14.5%) received OF. Infants fed HM had softer and more frequent stools than did those who received NF, HM + NF, or OF ($P < 0.001$). Infants fed NF had softer and more frequent stools than did those fed OF ($P < 0.001$), including those fed Enfalac or S-26 ($P < 0.001$). Regurgitation ($P < 0.001$) and colic ($P = 0.006$) were more frequent with OF than with NF. All feeding regimens were well tolerated and only 3.5% of subjects experienced adverse events.

CONCLUSIONS: This global study demonstrated that stools of infants fed NF are softer and more frequent than stools from infants fed OF and are closer to those of breast-fed infants. Infants consuming NF also experienced less regurgitation and colic than did infants in other feeding groups. *Nutrition* 2002;18: 484–489. ©Elsevier Science Inc. 2002

KEY WORDS: stool consistency, stool frequency, human milk, regurgitation, colic

INTRODUCTION

Many infants experience undesirable gastrointestinal (GI) effects such as colic, constipation, flatulence, and regurgitation. These symptoms are often thought to depend on the infant's diet, particularly in formula-fed infants, but they can be seen in infants receiving breast milk. Because infants are fed frequently, it is understandable that the formula given will be perceived as the cause of these symptoms. Most of these symptoms appear to resolve spontaneously and may be part of the infant's normal development. Perceived intolerance to infant formula is a frequently reported reason for changing formula.[1] Some infants may be switched from one formula to another because of colic, excessive spit-up, or changes in the frequency or consistency of the infants' stools. Infants with cow's milk allergy also may present with GI symptoms,[2] with or without respiratory or cutaneous symptoms. There also may be geographic differences in the reasons for switching formulas based on disease prevalence, such as diarrhea and cow's milk allergy, and maternal beliefs that may include cultural or economic factors.

Market research conducted by the Cambridge Group in 1999[3]

indicated that 61% of infants changed formula due to baby-related issues. Forty-two percent of the total were related to gastrointestinal intolerance. This is only slightly higher than the 35% reported in the United Kingdom.[4]

Stool characteristics depend on the type of diet the infant receives. Infants fed with human milk (HM) usually have an average of four or more watery and/or semiliquid bowel movements per day, which are yellowish in color in 90% of cases. Formula-fed infants normally have fewer bowel movements (one to two per day), which are usually brown or green in color, and generally soft but with a definite shape.

Stool characteristics also may depend on the type of infant formula used. Commercially available formulas differ from each other in the types and concentrations of proteins and lipids used, the concentrations of micronutrients, and processing method. These differences may affect stool consistency and frequency and overall GI tolerance. Formulas that contain palm olein oil have been associated with decreased calcium absorption and harder stools.[1,5] In addition, some formulas contain animal fats, which are less well absorbed than vegetable fats.[6] Proteins and nucleotides have been reported to influence the population of intestinal microflora.[7,8] The type of milk that infants receive during the first months of life may have an important role in the development of intestinal flora. The intestinal flora of breast-fed infants differs from that of formula-fed infants. Geographic differences in the composition of the intestinal microflora in infants have been reported; i.e., enterobacteria, enterococci, bifidobacteria, lactobacilli, and bacteroides show different occurrences in developed and developing countries.[9] In general, in breast-fed infants, *Escherichia*

TABLE I.

COMPOSITION OF MAJOR STUDY FEEDINGS*

Formula/milk	Protein (g/100 kcal)	Whey:casein ratio	Carbohydrate (g/100 kcal)	Fat (g/100 kcal)	Fat components	Nucleotides	Calcium (mg/100 kcal)	Phosphorus (mg/100 kcal)
Human milk (mature)	1.5	50:50	10.6	5.7	Saturated (44.2%), monounsaturated (41.6%), polyunsaturated (14.2%)	68–72†	41	21
NF	2.1	52:48	10.6	5.5	High-oleic safflower oil (42%), coconut oil (30%), soy oil (28%)	68†	77	43
SF	2.3	60:40	10.8	5.4	Varies by country§	29.5‡	69	50
EF	2.2	60:40	10.4	5.5	Palm olein oil (45%), coconut oil (20%), soy oil (20%), sunflower oil (15%)	26‡	67	45

* Formula content per label claims of products (1998) and Lloyd et al.[1] Composition of mature human milk from *Pediatric Nutrition Hand book*, 4th ed. Elk Grove Village, IL: American, Academy of Pediatrics, 1998.
† T Levels of total potentially available nucleotides.
‡ Free nucleotides and may vary by country
§ May vary by country (i.e. Taiwan: includes, oleo, coconut oil, soy oil, safflower oil; Mexico: includes, soy and coconut oils)
EF, Enfalac; NF, new formula (Similac Advance): SF, S-26

coli and *Streptococci* are the first bacteria to appear in the gut. They are usually, but not always, followed by a population of *Bifidobacterium*, which quickly becomes predominant. In bottle-fed infants, the intestinal flora is more variable and often includes, in addition to the organisms mentioned above, other enterobacteria and a wider range of obligate anaerobes. Dietary impact on intestinal microflora is reflected also in the profile of fecal short-chain fatty acids. Unabsorbed macronutrients, mainly carbohydrates and fats, that reach the colon can produce fermentation. However, this is not necessarily the case in standard starting formulas, where lactose and fats are normally absorbed in the small intestine. Calcium soaps might account for differences in stool consistency and frequency within formula-fed term infants and between this group and breast-fed infants. Soaps containing calcium and fatty acids may make up most of the fecal lipids in infants. Calcium soaps are preferentially formed with saturated long-chain (≥C16:0) fatty acids and from unabsorbed palmitic acid from infant formulas.[10]

The two main protein sources in HM and cow's milk are casein and whey. The ratio between these proteins in breast milk changes over time, passing from a ratio of 90:10 (whey:casein) when feeding starts[11] to 60:40 or 50:50 in mature milk.[12,13]

New formula (NF; Similac Advance) was formulated to provide an appropriate blend of lipids, simulate the whey:casein ratio and nucleotide concentrations of mature HM, and thus produce clinical outcomes similar to those associated with HM. The aim of this study was to evaluate and compare the GI tolerance of NF, other commercially available infant formulas, and HM in healthy infants.

SUBJECTS AND METHODS

This multicenter, international, observational study was conducted by Abbott Laboratories in 17 countries. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices. Each investigator was responsible for instructing parents and guardians of the subjects about completion of the diary for recording the description of parameters related to bowel function, regurgitation, and the incidence of GI intolerance variables. At investigators' meetings, the investigators were given training related to explaining the responsibilities to parents or guardians; the

same instructions and explanations were provided for all feeding groups.

Infants considered for enrollment were 28 to 98 d of age, with a gestational age of 38 to 42 wk, birth weight greater than or equal to 2500 g, in apparent good health, and free of major congenital anomalies or systemic disease. Mothers of infants to be enrolled had no evidence of significant disease such as diabetes (including gestational diabetes), tuberculosis, or perinatal infections with proven adverse effects on the fetus. Subjects were considered for enrollment from those attending routine visits to the pediatrician and no inducements were offered for enrollment. All infant formulas and HM were provided by the subject's parent or guardian.

GI tolerance was evaluated in healthy infants who received one of the following five feeding regimens: 1) HM only; 2) NF only; 3) other commercial formula (OF) only; 4) HM supplemented with NF (HM + NF); or 5) HM supplemented with OF (HM + OF). The macronutrient composition and calcium and phosphorus levels of the study feedings are presented in Table I. The choice of feeding regimen was determined by the infant's parents or guardian and pediatrician. Infants must have received their designated feeding for at least 1 wk before enrollment and were to continue to receive that feeding, with no other milk-based feeding, for the duration of the study. To minimize selection bias, each investigator enrolled up to 10 infants, with a resulting range of demographics. A 2-wk study period was chosen to minimize the dropout rate and poor compliance that would probably confound a longer study.

GI tolerance was evaluated in terms of stool consistency and frequency, the frequency of regurgitation, and the incidence GI intolerance indicators, which were recorded in a diary by the subject's parents or guardian. Diaries were provided in the local language and cross-translation was used to ensure all countries were reporting the same variables. Subjects were evaluated by the investigator at the beginning (day 0) and the end (day 14) of the study. At the end of the study, the investigator reviewed the diary with the parent or guardian and asked questions to verify the completeness and accuracy of the diary entries.

Statistical Methods

All evaluable subjects (defined as those who completed 14 d of study feeding and were compliant with their feeding regimen)

TABLE II.

SUBJECT DISTRIBUTION BY COUNTRY

Country	*n* Subjects	%
Brazil	288	3.75
Chile	109	1.42
Colombia	203	2.64
Dominican Republic	55	0.71
Ecuador	621	8.09
Guatemala	574	7.47
Hong Kong	20	0.26
Indonesia	302	3.93
Mexico	1,527	19.92
Peru	234	3.04
Puerto Rico	72	0.93
Saudi Arabia	815	10.61
Singapore	309	4.02
Taiwan	1,000	13.02
Thailand	699	9.10
Turkey	518	6.70
Uruguay	327	2.95

were included in the outcome analyses. All enrolled subjects were included in the safety analysis.

Demographic and baseline characteristics were summarized by descriptive statistics and analyzed by analysis of variance by rank. Feeding regimens were broken down by sex, and chi-square analysis of feeding groups by sex was performed.

Stool consistency and the frequency of regurgitation as recorded in the study diaries were converted to numerical values as follows: stool consistency: 1 = watery (i.e., runny, mostly liquid), 2 = loose/mushy (i.e., mixed with water), 3 = soft (pasty), 4 = formed (i.e., had some shape, yet moist), 5 = hard (i.e., well-shaped dry pellets); regurgitation: 0 = no regurgitation, 1.5 = one to two episodes of regurgitation each day, 3.5 = three or more episodes of regurgitation each day.

Stool frequency, stool consistency, and regurgitation data were summarized by descriptive statistics and analyzed by analysis of variance by ranks (for non-parametric data). Pairwise comparisons between feeding groups were performed with Student's *t* test, with

adjustments for multiple testing by Bonferroni's method.[14] The incidence of GI intolerance indicators (general GI intolerance, spit-up, hard stools, diarrhea, flatulence, and colic) on day 14 was analyzed by the Cochran–Mantel–Haenszel test. Pairwise comparisons were performed for all variables between the following groups: HM versus SF, HM versus OF, NF versus OF, HM versus HM + SF, and HM + NF versus HM + OF. In addition, pairwise comparisons were performed between NF (with and without HM), Enfalac (EF), and S-26 (SF; with and without HM). EF and SF were the OFs most frequently consumed by the subjects (*n* = 190 for SF, *n* = 191 for EF).

Adverse events were rated for intensity and relationship to the feeding regimen and were summarized by frequency tables.

RESULTS

Subject Population

One thousand twenty investigators in 17 countries enrolled 7673 infants. Each investigator enrolled up to 10 subjects and between 20 and 1527 subjects were enrolled in each country (Table II). Of the enrolled subjects, 676 (8.8%) were excluded: 362 (4.7%) did not complete the study, 284 (3.7%) did not meet entry criteria, and 96 (1.3%) used multiple formulas. A total of 6999 subjects were evaluable: 979 (14.0%) received HM only, 1695 (24.2%) received HM + NF, 635 (9.1%) received HM + OF, 2677 (38.2%) received NF only, and 1013 (14.5%) received OF only. There were statistically significant differences between feeding groups for weight and age at enrollment (*P* < 0.001 for both), but not for any other demographic and baseline variables (Table III). The difference among all groups was less than 1 wk for mean age and less than 30 g for mean weight. These differences were not considered clinically significant.

Tolerance Variables

There was a statistically significant difference among all feeding groups in mean stool consistency (*P* < 0.001). Subjects who received HM had average stool consistencies of semiliquid to soft; whereas those fed OF had only average stool consistencies of soft to formed. Subjects who received NF only had softer stools than those who received OF only (*P* < 0.001) but harder stools than those who received HM only (*P* < 0.001; Table IV). Infants who

TABLE III.

SUBJECT DEMOGRAPHICS AND WEIGHT

	HM only	HM + NF	HM + OF	NF only	OF only	*P*
Birth weight (g)						
n	973	1685	627	2669	1011	
Mean	3217.4	3194.2	3219.9	3190.7	3204.0	0.453*
Present weight (g)						
n	974	1683	628	2663	1011	
Mean	4817.4	4724.1	4801.3	4756.1	4995.9	<0.001*
Age (wk)						
n	969	1682	627	2656	1001	
Mean	7.3	7.3	7.5	7.7	8.3	<0.001*
Sex						
n	959	1649	617	2626	995	0.458†
Female (%)	498 (51.9)	827 (50.2)	295 (47.8)	1286 (49.0)	501 (50.4)	
Male (%)	461 (48.1)	822 (49.8)	322 (52.2)	1340 (51.0)	494 (49.6)	

* *P* value from *F* test. † *P* value from chi-square test.
HM, human milk; NF, new formula (Similac Advance); OF, other infant formula

TABLE IV.

COMPARISON OF STOOL CONSISTENCY BETWEEN FEEDING GROUPS

Comparison	Mean stool consistency*	P†
HM versus OF	2.59 versus 3.27	<0.001
HM versus NF	2.59 versus 2.99	<0.001
NF versus OF	2.99 versus 3.27	<0.001
NF versus EF	2.99 versus 3.23	<0.001
NF versus SF	2.99 versus 3.38	<0.001

* Based on a score of 1 = watery, 2 = loose/mushy, 3 = soft, 4 = formed, 5 = hard.
† P values from Student's *t* test.
EF, Enfalac; HM, human milk; NF, new formula (Similac Advance); OF, other infant formula; SF, S-26

received NF only had significantly softer stools than did infants who received EF or SF only ($P < 0.001$ for both).

There was also a significant difference among all feeding groups in mean stool frequency ($P < 0.001$). Subjects in the HM-only group had the most frequent stools (3.15 stools/d), subjects who received NF only had an average of 2.22 stools/d, and subjects who received OF only had the least frequent stools (1.82 stools/d; Table V). Subjects who received SF only or EF only had less frequent stools than did those who received NF only ($P < 0.001$ for both).

There were also significant differences among all feeding groups in mean frequency of regurgitation ($P < 0.001$). Infants fed NF only had fewer episodes of regurgitation than did infants fed HM only or OF only ($P < 0.001$ for both), and infants fed HM + NF had less regurgitation than did those fed HM + OF ($P = 0.001$). In addition, infants fed HM + NF had fewer episodes of regurgitation than did infants fed HM + SF ($P = 0.006$; Table VI).

The overall incidence of GI intolerance indicators was generally low. At the end of the study (day 14), general intolerance was reported for 12.5% of all subjects, spit-up for 5.4% of subjects, flatulence for 8.0% of subjects, hard stools for 3.8% of subjects, diarrhea for 1.7%, and colic for 2.5% of subjects. There were statistically significant differences among feeding groups in the incidence of all GI intolerance indicators ($P < 0.001$ for all except diarrhea, $P < 0.05$). Infants fed NF only had fewer episodes of general intolerance, spit-up, and colic than did those fed OF only ($P < 0.001$ for all). Infants fed HM + NF also had fewer episodes of general intolerance, spit-up, and colic than did those fed HM +

TABLE V.

COMPARISON OF STOOL FREQUENCY BETWEEN FEEDING GROUPS

Comparison	Mean stool frequency/d	P*
HM versus OF	3.15 versus 1.82	<0.001
HM versus NF	3.15 versus 2.22	<0.001
NF versus OF	2.22 versus 1.82	<0.001
NF versus EF	2.22 versus 1.44	<0.001
NF versus SF	2.22 versus 1.54	<0.001

* P values from Student's *t* test.
EF, Enfalac; HM, human milk; NF, new formula (Similac Advance); OF, other infant formula; SF, S-26

TABLE VI.

COMPARISON OF REGURGITATION BETWEEN FEEDING GROUPS

Comparison	Mean	P*
NF < HM	0.56 versus 0.81	<0.001
NF < OF	0.56 versus 0.69	<0.001
HM+NF < HM+OF	0.72 versus 0.84	0.001
HM+NF < HM+SF	0.72 versus 0.97	0.006

* *P* values from Student's *t* test.
HM, human milk; NF, new formula (Similac Advance); OF, other infant formula; SF, S-26

OF ($P < 0.01$ for all; Fig. 1). However, there were no statistically significant differences between infants fed NF and those fed EF or SF for the incidence of GI intolerance indicators, except that infants fed NF had a lower incidence of general intolerance than did infants fed SF ($P < 0.01$).

Safety

The overall incidence of adverse events was low and similar for all feeding groups. A total of 270 subjects (3.5%) experienced one or more adverse events. The most common events were regurgitation (77 subjects), flatulence (68 subjects), and constipation (44 subjects). Most adverse events were mild or moderate in severity and considered unrelated to the study feeding. Six subjects had serious adverse events during the study, all of which were resolved when the study product was discontinued or with other treatment.

A total of 66 subjects (0.9%) discontinued the study due to an adverse event, 24 (0.8%) in the NF-only group, 20 (1.1%) in the HM + NF group, 13 (1.2%) in the OF-only group, 9 (1.3%) in the HM + OF group, and none in the HM-only group. The most
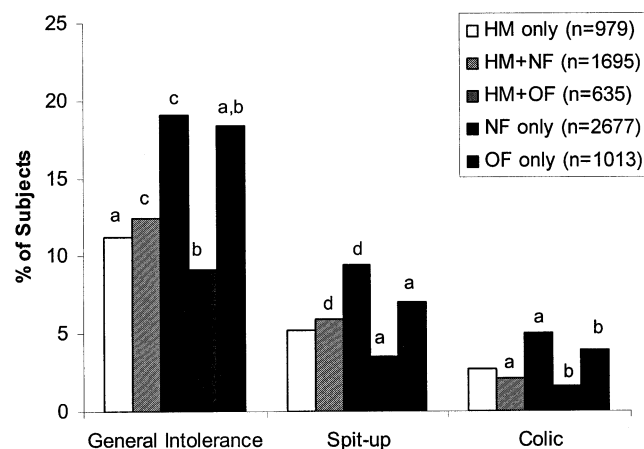

FIG. 1. Incidence of gastrointestinal intolerance indicators on day 14. Statistical differences between feeding groups are represented by letters (a, b, c, d) above the respective bars in the graphs. When two bars within the same section of the graph have the same letter, this indicates a statistical difference between these two groups. If a bar has more than one letter, this group is statistically different from more than one other group. If a bar has no letters, there are no statistical differences between this group and any other group. The groups labeled a, b, and c have a significant difference at the level of $P < 0.001$, χ^2 test; the groups labeled d differ significantly at the level of $P < 0.01$, χ^2 test. HM, human milk; NF, new formula (Similac Advance); OF, other infant formula.

common adverse events leading to discontinuation were regurgitation (16 subjects), diarrhea (15 subjects), constipation (11 subjects), and flatulence (9 subjects). Most of these events were mild or moderate in severity and were considered possibly or probably related to the study feeding.

DISCUSSION

HM is ideal nutrition and sufficient to support growth and development for most growing infants. HM is defined as living tissue because it contains not only macro- and micronutrients but also hormones, enzymes, growth factors, immunologic elements, and whole cells. Consequently, HM is impossible to imitate.[15]

Commercially available infant formulas serve as the best alternative to HM when breast-feeding is not possible. A position paper from the Committee of Nutrition includes the following recommendation: "Although the composition of human milk can be a guide to that of infant formulas and breast milk substitutes, gross compositional similarities is not, in itself, an ideal determinant or indicator of the safety and nutritional adequacy of dietary products for infants. A better approach is considered to be the comparison of outcomes in infants fed such products with those seen in healthy infants who have been breast-fed exclusively for 4–6 mo."[15]

Given that perceived abnormalities in stooling patterns and GI symptoms are very common among children on infant formulas, the primary objective of this study was to evaluate GI tolerance of young infants to different dietary regimens, considering HM-fed infants as the "gold standard."

This open-label, observational, international study was designed to evaluate and compare the GI tolerance of various feeding regimens, including NF, a novel milk-based infant formula, in almost 7000 healthy infants. Due to the large sample size and the number of countries involved in the study, blinding was not feasible. Therefore, an open-label design was chosen for this study. Open-label studies like this allow the risk of some bias from the investigators and parents who are aware of the kind of feeding the infant is receiving. However, we believe this risk was highly minimized by 1) the many dietary regimens involved in this trial, 2) infants not being required to change feeding regimen, and 3) GI symptoms being recorded by parents through a diary. Feeding groups were comparable with respect to most demographic and baseline characteristics, but there were significant differences among groups for age and weight at enrollment. Infants in the OF-only group were slightly heavier and older at enrollment than were infants in the other groups. In addition, there were differences in the number of subjects per group. Regarding the statistical methodology, the statistical analyses were performed on the rank scores of the variables rather than on the actual values, for several reasons. Rank analyses require relatively few assumptions about the underlying distributions and characteristics of the variables. These analyses do not require equal sample sizes for use as valid data.

Although infants fed HM had softer and more frequent stools than did infants fed any other regimen, infants who received NF only had softer and more frequent stools than did those who received OF only, including those who received EF only and SF only.

Numerous balance studies have demonstrated that HM is remarkably well absorbed.[16] The specific components in infant formula, particularly the lipids, can affect GI absorption and stool characteristics.[1,5] Some infant formulas include animal fat as part of the oil blend, which is not absorbed as well as vegetable fats. Indeed, full-term infants between 8 and 180 d of age demonstrated better fat absorption when fed HM or a formula containing vegetable oil, whereas formula containing animal fat was absorbed less completely.[17] These results are consistent with those of others. In infants fed HM or formulas with fat supplied as vegetable oil, fecal fat excretion was not excessive.[18] In contrast, the fat blend in NF

contains all vegetable fats: high-oleic sunflower or safflower oil (42%), coconut oil (30%), and soy oil (28%) and no palm olein.[1] The fat blend in EF contains palm olein (45%) in addition to soy (20%), coconut (20%), and high-oleic sunflower (15%) oils.[1] HM fat is very well absorbed by infants despite its high content of saturated fatty acids (44% fatty acids, including 23% palmitic acid). This good absorption is attributed to the fact that approximately 70% of the palmitic acid is in the *sn*-2 position. In contrast, in fats of vegetable origin, less than 15% of palmitic acid is located in the *sn*-2 position. In palm oil, which contains 44% to 48% palmitic acid, only approximately 9% of the palmitic acid is in the *sn*-2 position.[5] Unabsorbed palmitic acid binds to calcium and forms insoluble soaps and may be responsible for differences in GI tolerance.[19] Increased levels of insoluble soaps are associated with harder stools, so infants fed EF could be expected to have harder stools than infants fed NF. NF contains only vegetable-derived fats without palm olein. Thus, the fat blend in NF may be the reason that infants fed NF produced a pattern of stool consistency and frequency that more closely resembled that of infants fed HM only than did the stool characteristics of infants fed OF only.

Regarding the role of lipids and nucleotides on intestinal microflora, it is important to mention that, by the time fatty acids from a standard started infant formula leave the small intestine, very little fat remains to pass into the colon where microflora reside (i.e., NF has 98% absorption). Unabsorbed, unsaturated dietary fatty acids have been shown to alter water secretion by the small intestine and colon such that the amount of fecal water requiring colonic absorption increases.[20] Infants fed a nucleotide-fortified formula have a microbial pattern of the stool similar to that of breast-fed infants, with a predominance of bifidobacteria and enterobacteria.[21]

It is well known that hard stools sometimes cause infants to have difficulty with bowel movements and may be associated with pain or trauma. Thus, softer stools are generally preferable for the infant and parents. The softer stool consistency and more frequent bowel movements observed in the NF groups indicated that the outcomes for infants fed NF are similar to those associated with the consumption of HM.

Feeding intolerance can also result in regurgitation. There was less frequent regurgitation among infants who received NF only than among those who received OFs and we speculate that the reason for this observed difference was the source of lipids. The formulas tested in this trial had a similar carbohydrate source and a comparable casein:whey ratio (52:48 versus 40:60). GI tolerance is generally not affected by nucleotide level. Also, all formulas were iron fortified. Nelson et al.[19] demonstrated that NF achieves a 98% level of fat absorption. Thus, carbohydrate source, protein source, and nucleotide levels are unlikely to explain the observed differences in regurgitation. Unabsorbed fats may form insoluble soaps, produce harder stools and more gas, flatulence, and perhaps more regurgitation. Thus NF appears to be better tolerated than some other infant formulas.

These findings of improved tolerance in infants consuming NF are supported by the lower incidence of GI intolerance indicators among infants fed NF only. Infants fed NF only had less general intolerance, spit-up, hard stools, and colic than did those fed OFs. In addition, infants fed HM + NF had fewer episodes of general intolerance, spit-up, hard stools, and colic than did those fed HM + OF.

In conclusion, infants fed the NF (Similac Advance) had stool characteristics that more closely resembled those of infants fed HM than did the stool characteristics of infants fed other formulas. In addition, the NF appeared to be associated with a lower incidence of GI intolerance than were other infant formulas. This multinational study was designed to evaluate the comparative gastrointestinal tolerance of a novel infant formula (Similac Advance), other infant formulas, and human milk in healthy full-term infants. The novel formula was associated with relatively superior

gastrointestinal tolerability and stooling patterns similar to those produced with breast feeding.

REFERENCES

1. Lloyd B, Halter RJ, Kuchan MJ, et al. Formula tolerance in postbreastfed and exclusively formula-fed infants. Pediatrics 1999;103:E7
2. Vanderhoof JA, Murray ND, Kaufman SS, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. J Pediatr 1997;131:741
3. Ross Laboratories. Data on file, 1999
4. *Infant feeding. Survey of infant feeding practices in the United Kingdom.* London: Welsh Office and the Department of Health and Social Services in Northern Island, London Stationery Office, 1995:1997
5. Nelson SE, Rogers RR, Frantz JA, et al. Palm olein in infant formula: absorption of fat and minerals by normal infants. Am J Clin Nutr 1996;64:291
6. Lebenthal E, ed. *Textbook of gastroenterology and nutrition in infancy.* New York: Raven Press, 1981
7. Dean T. Cow's milk allergy: therapeutic options and immunological aspects. Eur J Clin Nutr 1995;49(suppl 1):S19
8. De Boissieu D, Matarazzo P, Dupont C. Allergy to extensively hydrolyzed cow milk proteins in infants: identification and treatment with an amino acid-based formula. J Pediatr 1997;131:744
9. Orrhage K, Nord CE. Factors controlling the bacterial colonization of the intestine in breastfed infants. Acta Paediatr 1999;88(suppl):47
10. Quinlan PT, Lockton S, Irwin J, et al. The relationship between stool hardness and stool composition in breast- and formula-fed infants. J Pediatr Gastroenterol Nutr 1995;20:81
11. Sánchez-Hidalgo VM, Flores-Huerta S, Matute G, et al. Whey protein/casein ratio and nonprotein nitrogen in preterm human milk during the first 10 days postpartum. J Pediat Gastroenterol Nutr 1998;26:64
12. Ronayne De Ferrer PA, Sambucetti ME. Casein to whey protein ratio in rat and human milks: effects of maternal protein intake. J Dairy Sci 1993;76:1645
13. Kunz C, Lönnerdal B. Human-milk proteins: analysis of casein and casein subunits by anion-exchange chromatography, gel electrophoresis, and specific staining methods. Am J Clin Nutr 1990;51:37
14. Milliken GA, Dallas EJ. *Analysis of messy data, Vol 1.* Reinhold, NY: Van Nostrand, 1989:33
15. Aggett PJ, Agostini C, Goulet O, et al. The nutritional and safety assessment of breast milk substitutes and other dietary products for infants: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2001;32:256
16. Fomon SJ. Fat. In: Craven L, ed. *Nutrition of normal infants.* St Louis: Mosby, 1993:162
17. Fomon, SJ, Ziegler EE, Thomas LN, et al. Excretion of fat by normal full term infants fed various milks and formulas. Am J Clin Nutr 1970;23:1299
18. Fomon SJ. Fat. In: Craven L, ed. *Nutrition of normal infants.* St Louis: Mosby, 1993:147
19. Nelson SE, Frantz JA, Ziegler EE. Absorption of fat and calcium by infants fed a milk-based formula containing palm olein. J Am Coll Nutr 1998;17:327
20. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. Gastroenterology 1986;91:100
21. Gil A, Corral E, Martinez A, et al. Effects of the addition of nucleotides to an adapted milk formula on the microbial pattern of feces in at term newborn infants. J Clin Nutr Gastroenterol 1986;1:127

(For an additional perspective, see Editorial Opinions)