

Efficacy of a Pre-thickened Infant Formula: A Multicenter, Double-Blind, Randomized, Placebo-Controlled Parallel Group Trial in 104 Infants with Symptomatic Gastroesophageal Reflux

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Summary: To evaluate a pre-thickened formula (Enfamil AR[®]) for regurgitant gastroesophageal reflux, 104 infants were enrolled in a 5-week, multicenter, double-blind, randomized, placebo-controlled parallel group trial. The Enfamil AR group showed greater symptom reduction by the end of the first week: percent feedings with any regurgitation ($p=0.045$), total regurgitation volume score ($p=0.035$), and percent feedings with choke-gag-cough ($p=0.004$). The most symptomatic infants at baseline had a reduction in trouble sleeping significantly with Enfamil AR by the end of the study ($p=0.030$). This formula flows through a standard nipple, reduces regurgitation and choking-gagging-coughing within a week, and improves sleep in the most symptomatic babies by 5 weeks, without causing constipation. *Clin Pediatr.* 2003;42:483-495

Introduction

Symptomatic gastroesophageal reflux (GER) affects nearly half of all infants to the extent that their parents regard it as "a problem."^{1,2} Regurgitation comprises the primary

symptom; associated symptoms may include those suggesting pain (irritability, crying, fussiness), trouble sleeping, and coughing or gagging during feeding. Although such GER typically does not produce pathologic sequelae (esophagitis, failure to

thrive, or respiratory complications) and resolves spontaneously in most of these affected infants, parents often seek remedies for the symptoms.

Because volume, osmolality, caloric density, viscosity, pH, nutrient composition, and digestibility may all influence reflux,³⁻⁵ dietary modifications comprise the most common non-pharmacologic "conservative" remedies for infant GER.⁶⁻⁸ There is evidence that a protocol of such nonpharmacologic interventions is efficacious, even among infants referred to pediatric gastroenterologists for treatment,⁹ although a recent

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systematic review found limited data from randomized, controlled trials to support many of these treatments.¹⁰ In North America, increasing the viscosity—"thickening"—of infant milk formulas is usually achieved by adding dry rice cereal in a 1:2 volume ratio with the formula (~10 g starch/100 mL).¹¹ Internationally, carob bean gum preparations, carob seed flour, sodium carboxymethylcellulose, and a compound containing pectin and cellulose have been used as thickeners,¹²⁻¹⁵ although there is concern that thickening with indigestible carbohydrates interferes with availability of micronutrients¹⁶ and that the carob preparations may cause allergic responses or diarrhea.^{12,17}

The mechanisms by which changing the viscosity of feeds might reduce reflux have not been completely established. However, thickening of feedings has been widely advocated for half a century,¹⁸⁻²⁰ and, more recently, controlled trials have provided support for the practice. These trials have shown that thickened formula reduces regurgitation frequency and total volume, decreases crying, and in-

creases sleep time postprandially in infants,^{11,13-15} without a consistent effect on pH-probe-measured acid reflux.^{15,21,22}

Drawbacks of thickening routine infant formula by adding dry rice cereal include inconvenience and disturbance of the nutrient profiles of marketed infant formulas, which have been carefully designed to mimic breast milk. These considerations prompted the design of a pre-thickened infant formula that would not require addition of cereal and that would more closely mimic a routine formula nutrient distribution. The resulting formula (Enfamil AR) substitutes 30% of the lactose of routine infant formula with an unmodified, pre-gelatinized, high amylopectin (waxy) rice starch (2.3 g starch/100 mL), thus maintaining the appearance, osmolality, caloric density, and nutrient profile of routine formula (Table 1), while providing greater viscosity, which increases further in the presence of acid (Figure 1). Before acidification by gastric acid, the formula flows freely through a standard nipple. This formula, commercially available in Europe since 1995,^{15,22,23} has been shown to support

growth as effectively as a routine milk-based formula in a double-blind, randomized, parallel group study in 272 babies observed between 14 and 120 days of age.²⁴ It has also been shown, in a study of 44 infants, not to affect gastric emptying.²⁵

The objective of the current study was to evaluate rigorously the efficacy of Enfamil AR in young infants with regurgitant GER.

Methods

Subjects

Between December 1996 and July 1998, infants were recruited at six North American pediatric centers to participate in the 5-week study, which had been approved by the appropriate institutional review board or human rights committee for each center.

Inclusion criteria were ≥ 5 regurgitations per day for 2 baseline days, age 14–120 days, gestational age at birth >37 weeks, birth weight $\geq 2,500$ g, and maternal age ≥ 18 years.

Exclusion criteria were disease or congenital anomalies interfering with normal feeding or caus-

Table 1

INFANT MILKS: COMPARISON OF NUTRIENT COMPOSITIONS				
Nutrient	Breastmilk	Standard Cow Milk-based Formula + Rice Cereal (1 Tbsp/oz)	Enfamil AR	Control Formula
Energy (kcal/30 mL)	20	35	20	20
Carbohydrate (g/100 kcal)	10.6	15.0	11.0	10.5
Fat (g/100 kcal)	5.7	3.4	5.1	5.3
Protein (g/100 kcal)	1.5	1.6	2.5	2.5

Effect of pH on Viscosity

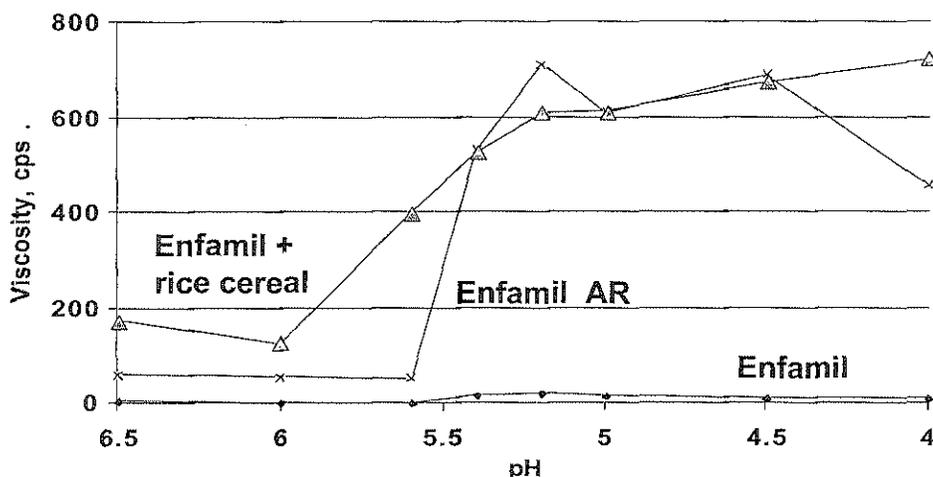


Figure 1. Viscosity of the Test formula (Enfamil AR) compared with a routine milk-based commercially-available infant formula (Enfamil) and with Enfamil plus dry rice cereal (1 Tbsp/oz) under pH conditions comparable to those before and after ingestion into the gastric milieu, measured at 97°F, 30 rpm. (Data on file; Mead Johnson Research Center, Evansville, Indiana.) Viscosity is a quantitative rheologic measure of frictional resistance in a fluid to shear, illustrated by the force required to pull one large plate across another, separated by a gap containing the fluid. Density, distinct from viscosity, quantifies the weight per volume of the fluid.³⁵ Both of these physical properties influence the flow of fluids.

ing repeated regurgitation; fever or infectious illness at enrollment; clinical diagnosis of milk or soy protein allergy; complicated gastroesophageal reflux disease (esophagitis, hematemesis, recurrent respiratory symptoms, failure to thrive, etc.); previous treatment with thickened formula; or treatment with prokinetic medication within 5 days before the start of the study.

During the study, a subject's participation could be discontinued early for a number of predetermined reasons, including any illness that necessitated hospitalization or resulted in a decrease in formula intake to below 50% of the usual intake for at least 2 consecutive days.

Design

The study design is summarized graphically in Figure 2. Informed consent was solicited from parent(s) or guardian(s)—henceforth designated “parents”—of eligible infants at Day -3 or -4. For the next 2 days, after instruction related to the diary sheets, they kept a baseline daily diary, and then returned for determination of eligibility and for randomization on Day 0. On Day 0, baseline demographics, vital signs, and anthropometric data were recorded, and infants were randomized to Test or Control formulas. The Test formula was Enfamil AR (AR); the Control formula (C) was designed to be similar to Enfamil AR except for the

replacement of the rice starch with lactose, making the Control formula comparable to standard commercially-available cow-milk-based infant formulas (Table 1). The randomization was performed separately for each site to reduce site-specific bias, and the blind was maintained for all study site personnel, parents, and industry study personnel. Parents were instructed on preparation of the study formula from the powder provided, and on the use of the formula, which was to serve as the sole source of nutrition for the duration of the study. Volume and frequency of feeding was left to parental discretion. Formula was provided in amounts adequate for the ensuing week,

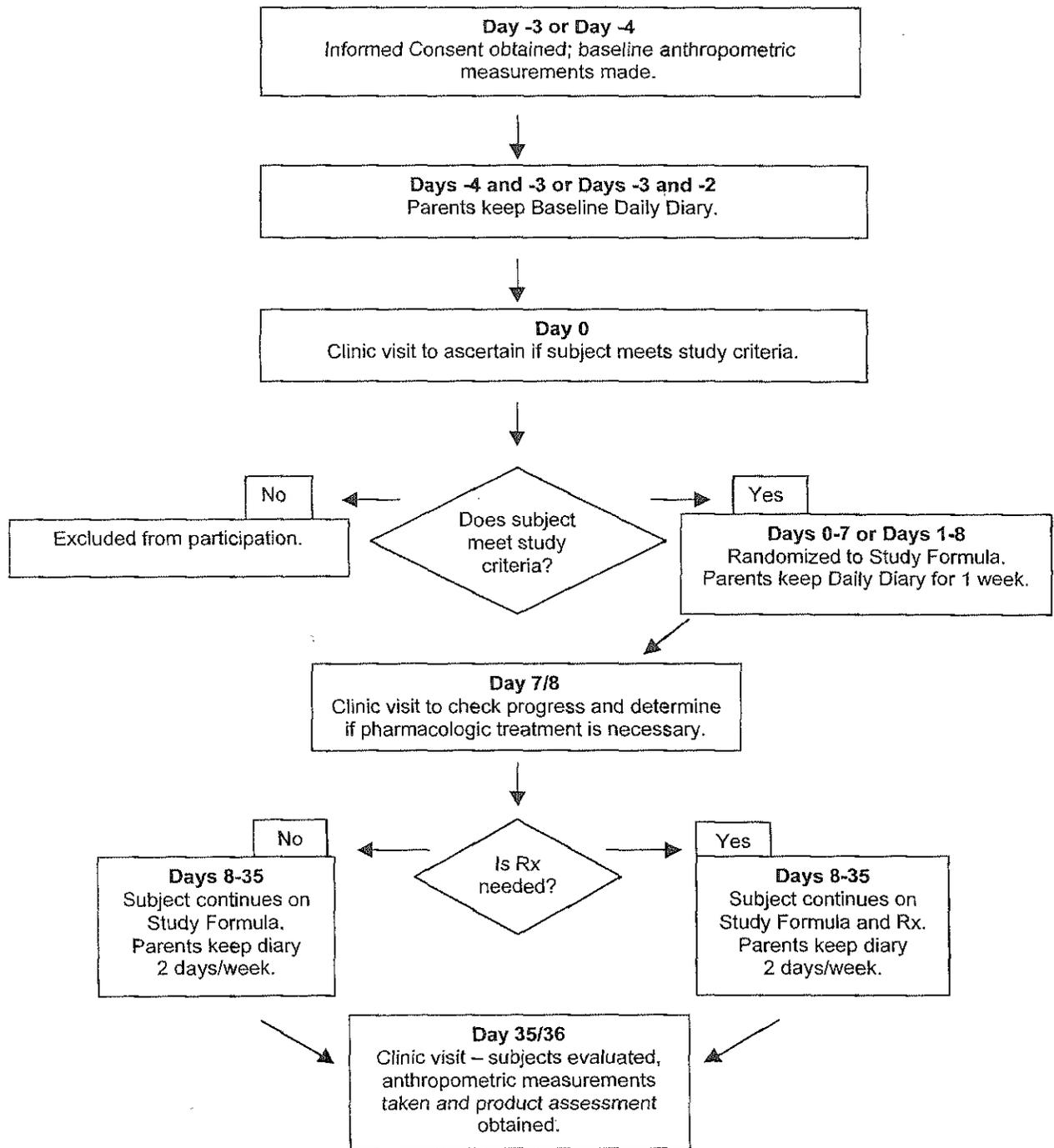


Figure 2. Study flow chart. The chart shows the sequence of study visits and telephone contacts.

based on 32 oz fed per day. Parents were also instructed to complete diary sheets daily for the next week, and for 2 days out of each week thereafter.

Follow-up evaluations were scheduled for the end of the first and fifth weeks (Day 7/8—End 1 Week, and Day 35/36—End Study). At the first of those visits,

and as needed thereafter, babies were assessed to determine the need for standardized pharmacologic intervention (ranitidine any time after day 7/8 and cisapride

any time after day 14/15); such pharmacotherapy was recorded when it occurred. At that first follow-up visit (End 1 Week), parents were also provided enough formula for the rest of the study. At the last visit (End Study), anthropometrics were measured again. Serious adverse events (SAEs) and early discontinuations from the study were monitored throughout.

Outcome Variables

Efficacy

The primary objective was to evaluate the efficacy of Enfamil AR in reducing regurgitation, as monitored by the daily diary forms. These forms, completed after each feeding except those occurring after bedtime, identified time and amount of feeding, number of regurgitations after each feeding (0,1,2,3,4,5,>5), and a score for the amount of the largest regurgitation after each bottle (1=teaspoon to tablespoon, 2=tablespoon to ounce, 3=ounce to entire feeding, 4=entire feeding). These raw data allowed calculation of 4 measures of regurgitation used as primary outcome variables to compare the Enfamil AR and Control groups: 2 that characterized frequency (percentage of feedings associated with any regurgitation; and total number of regurgitation episodes per day) and 2 that characterized volume (percentage of feedings associated with regurgitation > 1 oz; and a Total Regurgitation Volume Score). The Total Regurgitation Volume Score summed the largest regurgitation scores from each of the day's feedings (scored 1 to 4, as above), such that a score of 8, for example, could be obtained by a baby who regurgitated the whole feeding twice in a day

with no other feeding followed by regurgitation >1 tsp (4+4+0+0), or by a baby regurgitating 1 Tbsp-1oz after four separate feedings (2+2+2+2).

Secondary outcome variables recorded after each feeding were choking, gagging, or coughing; pain; and trouble sleeping. Any need for study-permitted pharmacotherapy was also evaluated as a secondary outcome variable.

Tolerability

Acceptability, tolerability, and safety of the formulas were also evaluated. A summary overview of acceptability was obtained by the number of subjects completing the study in each group. Tolerability was assessed on a daily basis by way of variables recorded on the diary sheets at the end of each scored day, so that daily symptoms of fussiness, constipation, diarrhea, and gas could be compared between the Enfamil AR and Control groups. Safety was monitored by identifying any illnesses as they occurred throughout the study; any serious adverse event (SAE) was reported immediately.

Statistical Analysis

Three study periods were analyzed: Baseline, End 1 Week, and End Participation, using the last 2 daily diaries completed for each of the 3 periods. (End Participation usually occurred at the end of the study, but for subjects discontinuing early or being started on pharmacotherapy per protocol, End Participation was defined as the last diaries available before these events.)

Gender distributions and study discontinuation data were compared by the Cochran-Mantel-Haenszel test stratified by study site. Age, anthropometric measurements, baseline regurgitation and symptom scores, and

formula consumption data were compared by analysis of variance. Need for pharmacologic intervention was compared by Fisher's Exact test.

Analysis of covariance was required for comparisons of symptom changes from baseline between the Enfamil AR and Control groups, due to the differences between the groups with regard to some baseline variables. The covariance statistical model incorporated terms for baseline score, study site, baseline score by treatment group interaction, and treatment group by study site interaction, as well as the feeding regimen itself. Analyses removing both interaction terms from the statistical model were also conducted. The detection of interactions between baseline scores and treatment group at $p < .10$ led to the performance of exploratory analyses that were not pre-specified—separately examining the subgroups with the worst baseline scores, using analysis of variance.

Analyses that excluded the three individuals (1 AR, 2 C) who suffered intercurrent illnesses produced similar results to analyses that did not exclude them, so those babies were not excluded in the data presented here. There were no interim analyses performed.

Results

Subject Characteristics and Accounting

Of the 110 babies whose parent signed informed consent and who were randomized, 6 never consumed study formula. Thus 104 babies comprise the study subjects (Table 2). Minor protocol violations of the inclusion criteria occurred for several subjects: 2 regurgitated ≥ 5 times on only 1 baseline day, 2 were 123 and 127

Table 2

SUBJECTS: DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Enfamil AR (n=55)	Control (n=49* 48)
Gender (M:F)	27:28	26:23
Age (d)	61 ± 4	58 ± 4
Anthropometrics:		
Weight (g)	5207 ± 154	5023 ± 164
Length (cm)	56.6 ± 0.8	56.3 ± 0.8
Head circum. (cm)	39.0 ± 0.3	38.8 ± 0.3
Baseline formula type:		
Standard cow milk (%)	85	86
Soy (%)	13	12
Partial hydrolysate (%)	2	2
Baseline feedings:		
Number (feedings/day)	5.8 ± 0.2	5.6 ± 0.2
Volume (oz/day)	26.3 ± 0.9	25.1 ± 0.9
Calories (cal/kg/day)	103 ± 3	100 ± 3
Baseline regurgitation frequency:		
% feeds with any regurgitation	87 ± 2	85 ± 2
Total # regurgitations/d	13 ± 1	11 ± 1
Baseline regurgitation volume:		
% feeds with regurgitation > 1oz	17 ± 3	10 ± 3
Total regurgitation volume score**	8.9 ± 0.5	7.6 ± 0.5
Other baseline symptoms:		
Pain (% of feedings)	17 ± 4	13 ± 4
Trouble sleeping (% of feedings)	20 ± 4	17 ± 4
Choking/gagging/coughing (% of feedings)	40 ± 5	37 ± 5

NS for all items except Total Volume Score, $p = .042$.

*One baby, randomized to the Control group, was excluded from all efficacy analyses because of an extreme protocol violation, consisting of maternally administered pharmacotherapy (cisapride and omeprazole) throughout the baseline and treatment periods; thus 48 babies comprise the Control group for all efficacy analyses, and thus for all symptom categories in the above Table.

**Total volume score was the only category in which Enfamil AR and Control groups differed significantly at Baseline, and for this category the Enfamil AR babies had greater daily regurgitation volume scores than the Control babies at Baseline ($p = .042$).

days of age, 2 were 36 weeks' gestational age, and 1 mother was <18 years. Data from these subjects were not excluded from analysis.

At baseline, there were no differences in gender, age, anthropometrics, feedings (type of formula or the feeding number, volumes, or calories per day), or

symptoms, between the 55 randomized to Enfamil AR and the 49 randomized to the Control formula (Table 2), except that the babies assigned to AR had a worse

Efficacy of a Prethickened Infant Formula

average Total Regurgitation Volume Score than those assigned to C ($p=.042$).

The majority of the babies in both the AR and C groups completed to the first week visit (89%, 90%) and to the end of the study (84%, 73%)—Table 3. The 22 babies who discontinued during the study included 17 (13% of AR, 20% of C) who discontinued due to the formula—intolerance, fail-

ure to thrive, or parent election—with similar numbers of AR and C subjects in each category. The non-formula reasons for discontinuation of the other 5 subjects were loss to follow-up, illness-induced failure to consume adequate formula (<50% of usual intake for ≥ 2 days), and an SAE in 1 baby (the first SAE described below).

Three SAEs occurred: hospitalization for pH probe, renal dys-

plasia, and failure to thrive. The first of the 3 SAEs occurred in a subject randomized to C, who was treated by his mother, contrary to instructions, with omeprazole and cisapride throughout the Baseline and Study periods, until he was hospitalized for a pH probe study because of persisting symptoms after nearly 2 weeks in the study. This protocol violation prompted his data being ex-

Table 3

RESULTS: SUBJECT ACCOUNTING, FORMULA CONSUMPTION, AND REGURGITATION VARIABLES				
Variable	Number n AR/ n C	Enfamil AR (AR)	Control (C)	p Value
Completed 1 wk		89%	90%	NS
Completed study		84%	73%	NS
Used pharmacotherapy		4%	2%	NS
Formula consumed (cal/kg/d):				
Baseline	55 / 49	103 ± 3	100 ± 3	NS
End 1 wk	50 / 47	101 ± 4	92 ± 4	NS
End participation	50 / 46	114 ± 5	98 ± 5	.004
Regurgitation frequency (% feeds with any):				
Baseline (%)	55 / 48	87 ± 2	85 ± 2	NS
End 1 wk (Δ %)	50 / 47	-34 ± 5	-22 ± 5	.045
End Participation (Δ %)	50 / 47	-38 ± 5	-24 ± 5	.036
Regurgitation frequency (total #/d):				
Baseline (#)	55 / 48	13 ± 1	11 ± 1	NS
End 1 wk (Δ #)	50 / 47	-6 ± 1	-6 ± 1	NS
End participation (Δ #)	50 / 47	-7 ± 1	-5 ± 1	NS
Regurgitation volume: (% feeds with >1oz):				
Baseline (%)	55 / 48	17 ± 3	10 ± 3	NS
End 1 wk (Δ %)	50 / 47	-7 ± 2	-7 ± 2	NS
End participation (Δ %)	50 / 47	-8 ± 2	-7 ± 2	NS
Regurgitation volume: (total volume score):				
Baseline (score)	55 / 48	8.9 ± 0.5	7.6 ± 0.5	.042
End 1 wk (Δ score)	50 / 47	-4.5 ± 0.4	-3.4 ± 0.4	.035
End participation (Δ score)	50 / 47	-4.6 ± 0.5	-3.4 ± 0.5	.050

cluded from all efficacy data, including data on study formula consumption and reflux pharmacotherapy use. His data are included in the safety data. The second SAE, in another infant randomized to C, was renal dysplasia associated with failure to thrive. The third SAE was failure to thrive diagnosed after 3 days of consumption of AR in a baby who responded to a switch to a soy formula. This infant's probable cow milk allergy presumably would have occurred regardless of treatment group assignment.

Three babies (2 AR, 1C) received pharmacotherapy as allowed by the protocol.

Outcome Variables: Efficacy

Enfamil AR significantly reduced the percentage of feedings associated with regurgitation at the end of both 1 week and the study as a whole, when the entire AR and C groups are compared (Table 3, Figure 3). In addition to this regurgitation frequency variable, AR also reduced the Total Regurgitation Volume Score, both at End 1 Week and End Par-

ticipation (Table 3, Figure 3). This latter effect was observed despite a significantly greater formula intake by the end of the study in the AR group.

The non-regurgitation post-feeding symptoms used as secondary outcome variables—choking, gagging, or coughing; pain; and trouble sleeping—were evaluated similarly to the regurgitation variables. Significant improvement was observed both at End 1 Week ($p=0.004$, Figure 3) and at End Participation ($p=0.049$) for choking/gagging/coughing. De-

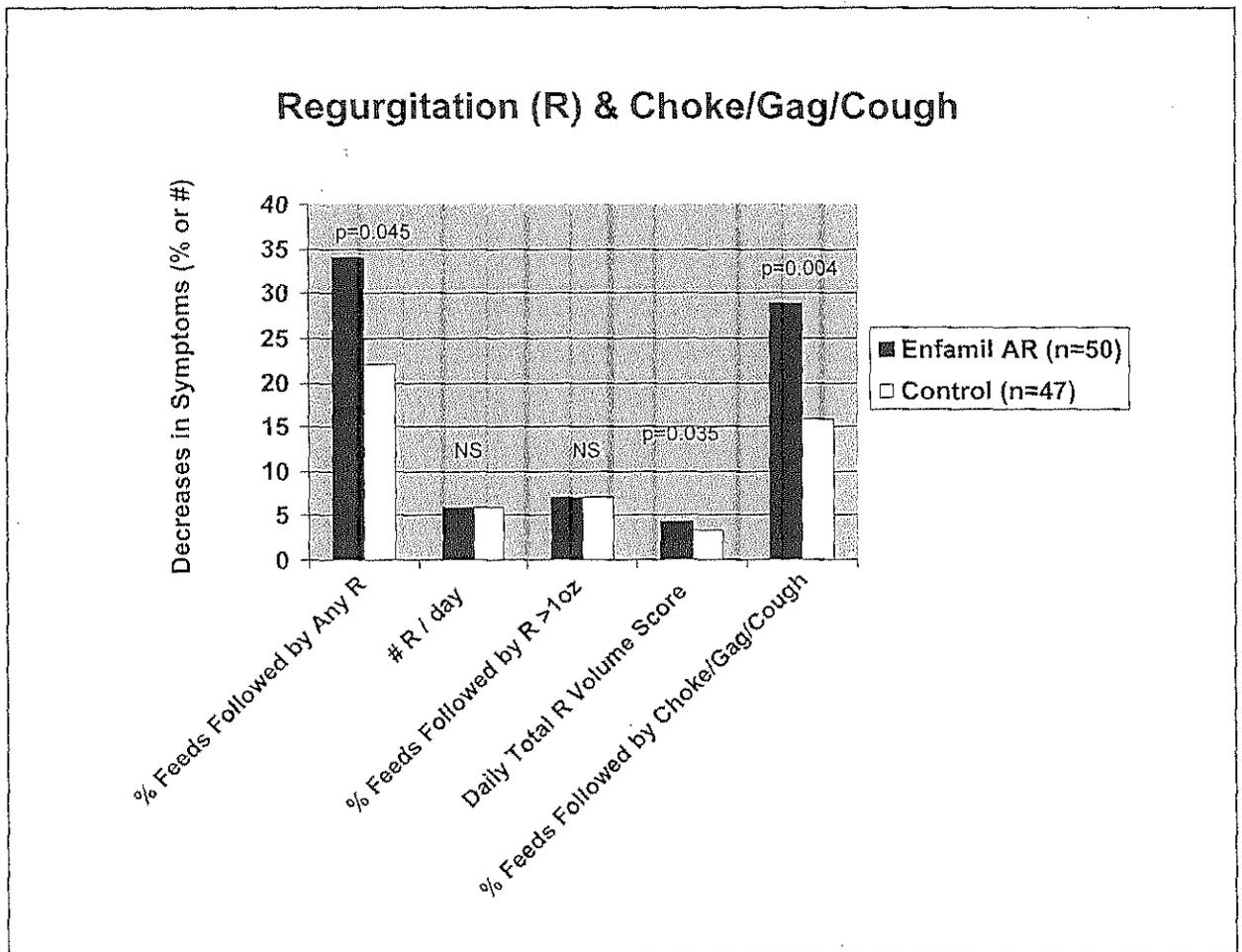


Figure 3. Results: regurgitation and choke-gag-cough variables: improvements at end 1 week. The histogram demonstrates the significantly greater improvements in two of the regurgitation variables and in the choke-gag-cough variable in the Enfamil AR group compared to the Control group, as early as 1 week after starting the formula.

tection of baseline-by-treatment interactions for pain and trouble sleeping meant that these variables improved significantly more with Enfamil AR in those babies with the worst symptoms at Baseline. These analyses for pain and for trouble sleeping in the most severely affected infants demonstrate considerably greater improvement in those treated with AR than in those treated with C, a difference that reached significance for trouble sleeping despite the small size of the subgroups (Figure 4).

The other secondary outcome variable, any need for study-permitted pharmacotherapy, did not differ between the Enfamil AR and the Control groups.

Outcome Variables: Tolerability

There were no differences in the number of subjects completing the study between the two treatment groups. There were also no differences between the Enfamil AR and Control groups at Baseline, at End 1 Week, or at End Participation in any of the four variables recorded daily—fussi-

ness, constipation, diarrhea, or gas. Finally, there were no differences between AR and C in the incidence of SAEs.

Discussion

This sizeable, multicenter, randomized, double blind, placebo-controlled trial has confirmed a beneficial effect of a commercially available pre-thickened formula on a number of symptoms prevalent in infants with symptomatic gastroesophageal

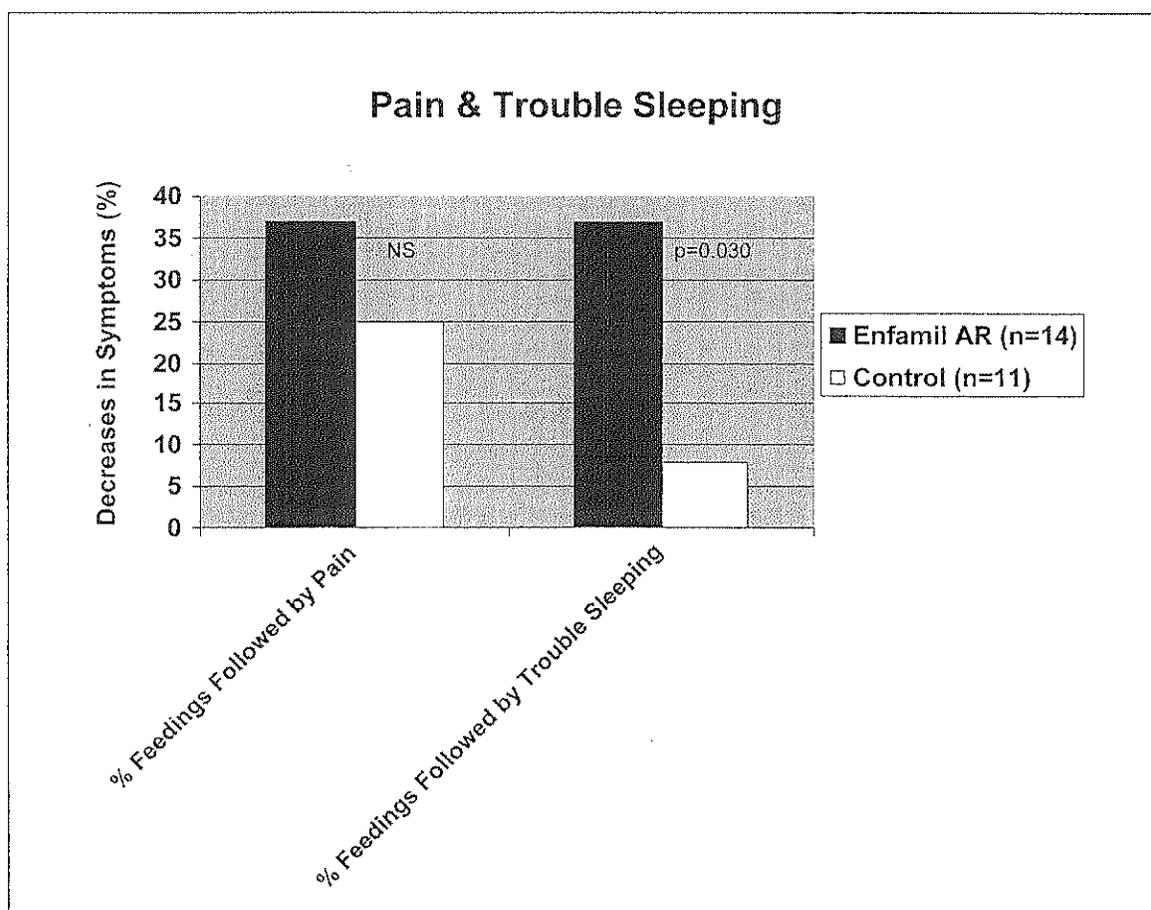


Figure 4. Results: pain and trouble sleeping: improvements at end participation in the most symptomatic quartile of the infants. The histogram shows the greater improvements in pain and in trouble sleeping in the quartile of infants with the most severe symptoms at Baseline when fed Enfamil AR, in comparison with Control formula. This improvement reached significance for babies with trouble sleeping, despite the small number of infants.

reflux. It has also demonstrated, yet again, the importance of blinding and placebo controls for a disorder like infantile reflux, in which spontaneous amelioration is common.

Mechanisms

The effects of thickening of formula on reflux into the esophagus and regurgitation from the mouth have been somewhat challenging to rationalize and to understand mechanistically. Thickening of feedings has nutrient effects that modify the gastrointestinal tract's handling of them, as well as physical effects. Although rice-cereal-thickened feedings may seem more likely to "stick to the ribs,"²⁶ their potential to slow gastric emptying¹¹ because of their increased caloric density challenges the idea that they might have a beneficial effect on reflux. In contrast, the increased viscosity may accelerate gastric emptying, thus providing benefit for infants with reflux.²⁷ The actual rheologic aspects of fluids that determine their subjective "thickness" incorporate the physical characteristics of viscosity (Figure 1), density, and yield stress, physical characteristics that may not be subjectively appreciated accurately.²⁸

Regurgitation

The reduction of regurgitation is the most consistent improvement in studies of thickened feedings; this "visible" effect led to the early and sustained adoption of thickened feedings as a central component of non-pharmacologic treatment of reflux.¹⁸⁻²⁰ Thickened feedings reduced the frequency of regurgitation in several studies,^{11,13,15,22,29} without a clear decrease in the volume of the individual regurgitation episodes that

persisted.¹¹ The current study found reductions in the percentage of feedings associated with any regurgitation and by the daily Total Regurgitation Volume Score, without a reduction in the percentage of feedings associated with large volume regurgitations nor in the number of regurgitation episodes each day. The lack of reduction in the latter may be because the frequency measures in the current study are non-discriminating among post-meal regurgitation frequencies greater than 5.

pH Probe Reflux

Although most studies have shown improvement in regurgitation with thickening of feedings, their effect on pH probe-quantified acid reflux has not been so clear, consistent with the fact that the pH probe measures reflux only after the neutral pH feedings have been emptied from the stomach (in contrast to the reflux measured by scintigraphy¹¹). An uncontrolled Belgian study found addition of 1 g/115 mL of a milk-thickening agent "carob bean gum preparations derived from St. John's Bread" to be associated with ambiguous effects on pH probe reflux 1-2 weeks later: no change in the total time with pH <4, but a decrease in number of episodes and an increase in the duration of the longest episode.¹³ Another small (2 groups of 10 infants) trial of a commercial version of a similar formula compared to a control formula found significant pH probe improvement after a week of treatment in the thickened feeding group only in the total time with pH <4;²² a similar study comparing that same commercial formula and a control formula within the same 24 babies alternating feedings of the 2 formulas found less

esophageal acid exposure following the thickened feedings than following the control feedings.¹⁵ Similar ambiguous effects were demonstrated for rice-cereal thickened formula in a tiny study with paired pH probe studies in 6 infants separated by 2 to 5 days.²⁹ A controlled and even shorter term study, using 34 infants as their own controls during 2 sequential 12-hour periods, found feedings thickened with rice cereal (1 Tbsp/oz) to be associated with less pH probe reflux in all 3 positions tested (prone, seated, supine), although it is unclear that day-night effects on reflux were adequately controlled for.³⁰ In a study that thickened apple juice feedings (pH~4), instead of standard milk formula, with rice cereal, to allow the pH probe to detect postprandial reflux, no clear improvement was found with the thickened formula.²¹

A recent review addressed the apparent incongruity between positive symptomatic relief of regurgitation by thickening feedings, and ambiguity regarding improvement of pH probe results.¹⁰ As the authors suggest, "clinical scores may be a more clinically relevant outcome measure in the study of infant GERD."

Caloric Intake

While the increased caloric retention due to decreased regurgitation was anticipated, the increased caloric intake in infants consuming Enfamil AR, in comparison to the Control infants, was unexpected. Indeed, one of the potential beneficial effects of thickening standard formula with rice cereal at 1 Tbsp/oz, which Enfamil AR lacks, has been the increase in the meal's caloric density to ≥ 1 cal/cc,¹¹ although this increased caloric intake may not produce a comparable increase in

caloric absorption in the healthy infant, in whom it may contribute to nutrition of colonic bacteria.^{31,32} Nonetheless, upward crossing of weight percentiles is a common observation in infants fed formula thickened with rice cereal. To the degree that adding cereal increases the calories absorbed by the baby, it would be a boon for regurgitating babies with failure to thrive, or for those whose reflux might respond to decreasing gastric volume while maintaining caloric content of feedings,³ but it would not be beneficial for babies at the opposite end of the nutritional spectrum—age at introduction of solids is a predictor of obesity at 12 months.³³ Although Enfamil AR has the same caloric density as routine infant formula, apparently it was appealing enough to the infants in the current study that they consumed it in greater volumes than the Control formula.²⁴

Choke-Gag-Cough

The reduction in these symptoms associated with feeding was not completely anticipated. However, in patients with dysphagia from various causes, thickening liquid barium (which increases both viscosity and density) improves its handling during the oropharyngeal phase of swallowing.^{28,34,35} Similar thickening of the diet is used for treatment of oropharyngeal dysphagia, thereby reducing gagging and choking on feedings. Infants' immature swallowing may benefit from the same effects that thickening has for pathologic disorders of swallowing in older individuals.

Coughing, in contrast, was found to be increased in 25 infants with GER following a rice-cereal-thickened formula feeding, in comparison to an isocaloric feeding of standard formula, dur-

ing a randomized, controlled, double-blind crossover study.³⁶ The coughing in this study may have played a role in the reflexive clearance of the adherent particulate cereal particles in the vicinity of the larynx. Reassuringly, a similar protocol used for 19 infants with respiratory disease and reflux symptoms did not find a similar increase in cough.³⁷ Furthermore, in 9 infants with respiratory syncytial virus-associated laryngeal penetration (with tracheal penetration or frank aspiration in some of them) by thin barium during fluoroscopy, thickening of the thin barium by rice cereal (1 "heaping" Tbsp/oz) normalized the immediately repeated fluoroscopy in all but 1 infant.³⁸ An early upper esophageal pH probe study in 34 babies with reflux and respiratory disease (pneumonia or apnea) did not quantify cough, but found less acid reflux in the upper esophagus after thickened than unthickened formula.³⁰

Pain

The nonsignificant reduction of "pain" recorded following feedings in these infants without pathologic reflux disease may be analogous to the significant reduction of crying in more severely affected infants by rice cereal-thickened formula.¹¹ The baseline-by-treatment-group interaction suggests that, indeed, this symptom is more likely to be improved by Enfamil AR in infants in whom it is a predominant symptom initially. The lack of effect of the Test formula on "fussiness" recorded at the end of the day is consistent with the lack of improvement in "pain" in the treatment groups as a whole, and also suggests that any beneficial effect on crying may be focused in the postprandial period.

Sleep

Thickening formula with rice cereal has been used for evening feedings for infants for some time, because of its anecdotal improvement of sleep and enhancement of the likelihood that an infant will sleep through the night. In one study two-thirds of mothers of 5-week-old infants held this belief.³⁹ This anecdotal benefit was provided support by a short-term study evaluating a single pair of feedings in infants with gastroesophageal reflux disease, which found significantly greater sleep time following a thickened infant formula feeding than following an isocaloric routine formula feeding;¹¹ the increase in sleep time was by way of a decrease in crying time, leaving non-crying awake time essentially unchanged. Two other, longer-term studies did not demonstrate an increase in sleep time in normal infants. One of them found no beneficial effect of adding cereal to the diet of 5-week-old infants for 2 weeks, compared to a control group without added cereal.³⁹ The other, a study in which 106 babies were randomized to receive their bedtime feeding of formula either thickened with cereal (1 Tbsp/oz) or not, found no consistent effects on nocturnal sleep duration by the early addition of bedtime cereal.⁴⁰ That thickened feedings improve the sleep of infants with reflux because their baseline sleep is disturbed is suggested by data showing that 76 babies with reflux disease manifested disruption of many parameters of sleep, compared both to a contemporaneous control group of 26 babies and to population norms based on 3,102 babies.⁴¹ Results of the current study correspond to these findings, in that Enfamil AR significantly improved trouble sleeping

in the quartile of infants with the most trouble sleeping at baseline.

Tolerability

The excellent tolerance of the Test formula was not unexpected. Clinical studies have shown that moderate amounts of rice starch are easily digested and tolerated by most infants.^{31,32} A metabolic balance study demonstrated greater than 95% digestibility of rice starch in 1- and 3-month-old infants, with the younger group tolerating up to 25 g of rice starch per day.³² Anecdotally, however, rice cereal added generously to the infant diet increases the firmness of stools, and induces constipation in many babies. This effect comprises a major drawback to rice cereal-thickening of infant formulas to treat regurgitant reflux. Indeed, many practitioners either thicken infants' formula with less rice cereal, thereby possibly compromising efficacy, or prescribe treatment for this common "side effect" at the time of the prescription of the thickening. The lack of difference between Enfamil AR and the Control formula in this regard suggests a benefit of the use of this pre-thickened formula.

A recent review of nonpharmacologic and nonsurgical therapies for infant gastroesophageal reflux noted, "many conservative measures commonly used to treat GERD in infants have no proven efficacy."¹⁰ The authors call for further randomized, controlled clinical trials of conservative therapies, using symptomatic outcomes. The present randomized, double-blind, controlled study demonstrates symptomatic benefits of feeding a pre-thickened, nutritionally complete and balanced infant formula containing pregelatinized rice starch to infants with uncomplicated gastroesophageal reflux. The study indi-

cates that significant reduction in regurgitation and in choking-gagging-coughing associated with meals, and improvement in sleep in the most symptomatic babies, are benefits that can be achieved using a commercially available formula fed through a standard nipple, and without engendering constipation. Additional controlled studies in more symptomatic infants are needed to explore further the effects of this formula on symptoms such as crying.

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