Double-Blind Comparative Trial With 2 Antiregurgitation Formulae

*Y. Vandenplas, †B. Leluyer, ‡M. Cazaubiel, ‡B. Housez, and §A. Bocquet

ABSTRACT

Background and Aim: Many mothers consult physicians because of frequent infant regurgitation. Guidelines recommend reassurance and dietary treatment as first approaches. The aim of the present study was to test and compare the efficacy of 2 antiregurgitation formulae (ARF).

Methods: A prospective, double-blind, randomized cross-over trial was performed for a 1-month period in 115 formula-fed infants (ages 2 weeks–5 months) comparing 2 ARF (ARF-1: nonhydrolyzed protein, locust bean gum; ARF-2: specific whey hydrolysate, locust bean gum, specially treated starch). The primary endpoint was the incidence of regurgitation.

Results: At inclusion, mean age was 9.1 weeks; anthropometric parameters did not differ between the groups. According to the intention-to-treat analysis, the mean number of episodes of regurgitation decreased from 8.25 to 2.32 with ARF-1 and to 1.89 with ARF-2 (statistically significant difference between both ARF, $P = 0.0091$). The mean score of regurgitated volume decreased significantly more with ARF-2 than with ARF-1 ($P = 0.0265$). There was no significant difference in stool frequency and consistency between both groups.

Conclusions: The efficacy of both ARF was demonstrated by the decreased number and volume of regurgitations. ARF-2 was statistically more effective than ARF-1. Comparative trials enable the selection of the best therapeutic option.

Key Words: antiregurgitation formula, gastroesophageal reflux, regurgitation

(*JPGN* 2013;57: 389–393)

Infant regurgitation is considered to be physiological during early infancy; however, frequent regurgitation often causes considerable parental concern (1–4). Parents suspect an underlying organic etiology and therefore seek medical advice (5). In most cases, no organic cause is found (1,5). The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition–European Society for Pediatric Gastroenterology, Hepatology, and Nutrition guidelines discourage medical empirical antireflux treatment and recommend limiting the latter to infants at risk for acid-peptic complications of gastroesophageal reflux disease (GERD) (1). A history and physical examination, with attention to warning signs, are generally sufficient to allow the clinician to establish the diagnosis of uncomplicated GER (1). Parental education, reassurance, and anticipatory guidance are recommended as first-line approaches. In formula-fed infants, thickened formula (or antiregurgitation formula [ARF] if available) has been shown to reduce the frequency of overt regurgitation and vomiting (1). The aim of this trial was to test and compare the efficacy of 2 different ARF.

Received November 26, 2012; accepted April 26, 2013.

From the *UZ Brussel, Vrije Universiteit Brussel, Brussels, Belgium, the †Le Havre, France, the ‡Biofortis, St Herblain, and the §Pour l'Association Française des Pédiatres Ambulatoires, France.

Address correspondence and reprint requests to Yvan Vandenplas, UZ Brussel, Department of Pediatrics, Laarbeeklaan 101, 1090 Brussels, Belgium (e-mail: yvan.vandenplas@uzbrussel.be).

This study was funded by NHS Laboratories, Rungis, France.

Y.V. is a consultant for Biocodex and United Pharmaceuticals. M.C. is the head of Biofortis Clinical. B.H. is an employee of Biofortis. The other authors report no conflicts of interest.

DOI: 10.1097/MPG.0b013e318299993e

METHODS

Study Design

This prospective, comparative, randomized, controlled, multicenter, cross-over, and double-blind study comparing the efficacy of 2 ARF (formula composition: Table 1) was proposed to parents of 143 regurgitating, formula-fed infants presented in ambulatory care in France between October 2009 and June 2011. Participating physicians were 31 pediatricians practicing private primary health care, all members of the Association Française des Pédiatres Ambulatoires (French Society of Ambulatory Pediatricians). Treatment units were provided to each pediatrician, for each included infant, starting either with formula ARF-1 or ARF-2 for 2 weeks followed by formula ARF-2 or ARF-1 for another 2-week period (cross-over design, without any wash-out period) (Fig. 1: study design). Each pediatrician received treatment units for at least 4 patients. Randomization was performed and kept centrally by the independent study monitor. The protocol was approved by the ethical committee Nord Ouest 1, Rouen, France.

Patients

Patient characteristics are listed in Table 2. Participation in the study was proposed to parents of infants ages between 2 weeks and 5 months, term born, exclusively formula-fed, and regurgitating at least 5 times per day lasting >1 week according to the reported history (inclusion criterion), for which no treatment had been started. Exclusion criteria were breast-feeding, preterm, small-for-gestational-age at birth, GERD with complications such as hematemesis, dysphagia, apnea, failure to thrive, back arching, an intake <50% of the recommended volume of formula during 2 consecutive days in the preceding week, known cow's-milk protein allergy, or infant at high risk for atopic disease (positive parental history of atopic disease).

Once the inclusion criteria were met, the patient was randomly allocated to 1 of the 2 study arms. After randomization, baseline data with the initial formula on the daily frequency and volume of regurgitation were recorded prospectively in a diary during 3 consecutive days by the parents.

TABLE 1. Composition of the tested formulas (/100 g)

	ARF-1	ARF-2
Kcal	490	488
Protein, g	9.5	11.9
Casein, g	5.7	—
Whey, g	3.8	11.9
Carbohydrates, g	62.2	52.0
Thickening agent, g		
Fibers (bean gum)	3.0	3.3
Starch	0	1.9
Osmolarity, mOsm/L	238	203

ARF-1 = antiregurgitation formula 1 (locust bean–thickened formula); ARF-2 = antiregurgitation formula 2 (Novalac AR Digest).

TABLE 2. Characteristics of the study population (intention to treat) (mean [SD])

	Group 1 (ARF-1)	Group 2 (ARF-2)	*P*
Age at inclusion, wk	9.1 (5.1)	9.4 (4.7)	NS
Sex (boys/girls)	34/22	36/23	NS
Length, cm	57.2 (3.8)	57.5 (4.1)	NS
Weight, kg	5.20 (1.08)	5.18 (0.98)	NS
No. regurgitations/day	7.8 (4.7)	8.7 (3.4)	NS
Regurgitation score (°)	2.7 (0.8)	3.0 (0.7)	NS

(°) Score: 1: no regurgitation; 2: volume equals 1 coffee spoon; 3: >1 coffee spoon and <1 tablespoon; 4: >1 tablespoon and <half of ingested volume; 5: >half of ingested volume; no statistically significant difference between both groups. Group 1 starts with ARF-1 for 2 weeks and then receives ARF-2 for 2 weeks. Group 2 starts with ARF-2 and then receives ARF-1. ARF = antiregurgitation formula; SD = standard deviation.

Endpoints

The primary endpoint was the mean number of daily episodes of regurgitation, calculated as a mean per day during the 2 weeks that each infant received the same therapeutic formula. Secondary endpoints were the evolution of the mean score of the volume regurgitated (referred to as the ''regurgitation score''), mean formula intake, global appreciation of the efficacy and acceptability of both ARF, duration of crying per day, duration of sleeping per day, number of defecations, aspect of the stools, and diaper dermatitis. Adverse events were also monitored.

Statistical Analysis

To detect a difference of 1 regurgitation per day between both ARF and assuming a standard deviation of 2.6 (6,7), with a 2-sided 5% significance level and a power of 85%, a sample size of 140 infants was necessary given an anticipated dropout rate of 11%. Statistical analyses were performed using SAS software version 9.1.3 Service Pack 4 (SAS Institute Inc, Cary, NC). For all statistical tests, a level of significance of 0.05 was used to justify the claim of a statistically significant effect. Normality assumption was checked by visual inspection of data distribution.

The quantitative endpoints were analyzed using the Student *t* test or Wilcoxon rank sum test adapted to cross-over studies according to data distribution (8–10). The Mainland-Gart test was used for the analysis of the proportion of subjects who used an antiregurgitation treatment during the study period. In addition, daily regurgitations (number and volume) and duration of crying per day were analyzed on the subpopulation of subjects having at least 5 regurgitations per day as confirmed by the baseline diary.

RESULTS

The number of patients included per pediatrician was 4 ± 0.6 (range 1–17 patients). One hundred forty-three infants were included in the trial, but 28 infants were excluded from the analyzed population because of major deviations (eg, age, product intake inversion, nonavailability of the data). The intention-to-treat (ITT) population consisted of 115 infants complying with inclusion criteria and for whom the data were available. Baseline data regarding regurgitation characteristics were collected during 3 days (expressed as mean ± 1 standard deviation [SD]) before randomization and showed no difference between the 2 groups (Table 2). According to the baseline evaluation, 89 infants were presenting ≥5 regurgitations per day. Parents evaluated the acceptability of both ARF and reports showed that 16.9% of the parents for ARF-1 and 9% for ARF-2 said that the previous formula was better ($P < 0.01$) Acceptability of the study formula was said to be better than the previous formula in 50.6% versus 58.4%, for ARF-1 and ARF-2, respectively ($P < 0.01$). Weight and length evolution increased, without significant difference between the 2 groups (Table 3; data for length not shown). Mean daily formula intake during the total intervention period (1 month) did not differ between the groups. The daily volume consumption of ARF-1 was smaller during period 1 (mean 802 mL) than during period 2 (mean 888 mL). Mean daily intake for ARF-2 was 815 mL during period 1 and 840 mL during period 2. The number of adverse events related to the dietary intervention was low in both groups.

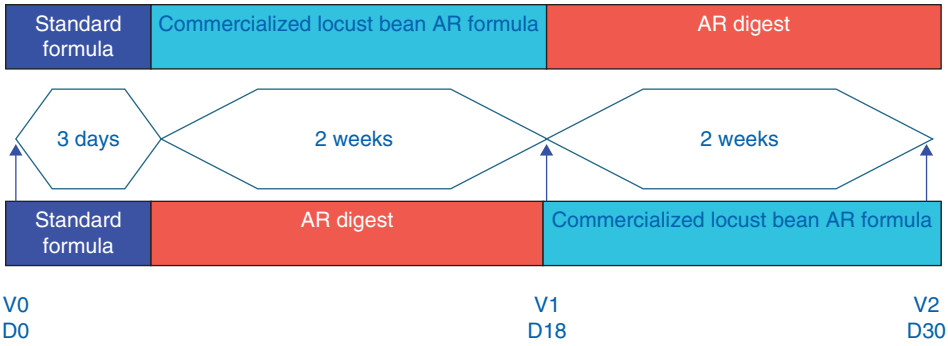

FIGURE 1. Study design.

TABLE 3. Evolution of weight and volume intake during the study period with both formulae (intention-to-treat analysis)

		ARF-1		ARF-2	
		Weight, kg	Volume, mL	Weight, kg	Volume, mL
Baseline	N	56	56	59	59
	Mean (SD)	5.20 (1.07)		5.18 (0.97)	
	(min–max)	(3.19–7.40)		(2.93–7.40)	
	Median (Q1–Q3)	5.20 (4.23–6.16)		5.27 (4.47–5.84)	
Period 1	N	56	56	59	59
	Mean (SD)	5.72 (1.02)	802 (112)	5.52 (0.93)	820 (90)
	(min–max)	(3.68–7.80)		(3.42–7.60)	
	Median (Q1–Q3)	5.67 (4.91–6.59)	802	5.56 (4.82–6.17)	812
Period 2	N	59	59	56	56
	Mean (SD)	5.97 (0.86)	883 (94)	5.98 (1.01)	837 (108)
	(min–max)	(4.40–8.00)		(3.86–8.00)	
	Median (Q1–Q3)	5.97 (5.22–6.56)	883	5.89 (5.21–6.83)	840

None of the differences at baseline, period 1, and period 2 is statistically significant. ARF = antiregurgitation formula; SD = standard deviation.

The mean number of regurgitations and the regurgitation score decrease significantly with ARF-1 and even more with ARF-2 (ARF-1 vs ARF-2, Table 4, $P = 0.009$ and Table 5, $P = 0.026$, respectively; Wilcoxon test). In the subpopulation of infants having at least 5 regurgitations per day at baseline (as confirmed by the diaries), the decrease in frequency of regurgitation is highly significant in both groups (Table 6), and ARF-2 is significantly more effective than ARF-1 ($P = 0.013$). This was a blind evaluation of both formulae by the pediatricians: although both ARF were assessed as efficient by >90% of all participants (93.3% vs 97.8%, respectively), the number of unsatisfied pediatricians (considering the formula as not efficient at all) was higher for ARF-1 (6.7% vs 2.2%, $P < 0.01$) in this subpopulation (Table 7 shows data on the global ITT population). Mean duration of crying per day decreases significantly during the intervention ($P < 0.0001$) but not differently between both groups (Table 8). Also, for the other secondary outcomes (duration of sleep per day, number of defecations, aspect of the stools, diaper dermatitis), there were no difference during the intervention because there were no differences between the 2 groups after the intervention (data not shown). Only 1 child needed rescue antacid treatment (proton pump inhibitor).

DISCUSSION

Regurgitation is defined as the passage of refluxed contents into the pharynx, mouth, or from the mouth, and commonly interrupts feeding and sleep in up to 30% of infants (1). Regurgitation is a characteristic symptom of reflux in infants, but is neither necessary nor sufficient for a diagnosis of GERD because regurgitation is not sensitive or specific (1). Infants spilling >90 days are at increased risk to have reflux symptoms at the age of 9 years (2). The similarity between data from the United States and Indonesia that approximately 20% of all 3- to 4-month-old infants regurgitate >4 times per day and that 20% of the mothers are concerned about infant regurgitation (3,4), suggest that ''4 episodes of regurgitation a day'' is a cutoff value above which medical intervention is welcomed. Therefore, the inclusion criterion for this intervention study was set at ''a frequency of at least 5 episodes of regurgitation per day for at least 1 week'' based on the retrospective information provided by the parents during the first consultation. The study design included a 3-day baseline period during which the recalled information provided by the parents was then collected prospectively. The information obtained from the diary showed that, prospectively, not fewer than 32 of 115 (28%) infants actually regurgitated <5 times per day. Although important discrepancies between retrospective recall and prospective acquisition of data are well known (11,12), this is the first time that these discrepancies have been shown for infant regurgitation. The magnitude of discrepancy is similar to that regarding ''fall reports in people with stroke'' (11). Additionally, infantile colic has been reported to be overestimated by retrospective recall compared with prospective data obtained from a diary (13). Colic defined as ''crying seen as a problem by parent'' was present in 12.1% of the ''interview group,'' but in only 3.3% of the ''diary group'' (13). Therefore, prospective acquisition of data from the use of a diary documenting infant regurgitation should be included in its approach. This strategy could reassure parents without having to change formula (5).

TABLE 4. Evolution of number of regurgitations (intention-to-treat analysis; n = 115)

	N	Mean (SD)	Range	Q25–75	median
Baseline	115	8.25 (4.11)	0.0–20.3	5.00–11.30	8.30
With ARF					
ARF-1	115	2.32 (2.91)	0.0–18.5	0.60–2.70	1.30
ARF-2	115	1.89 (2.33)	0.0–13.9	0.40–2.50	1.10

P (baseline—ARF-1 or ARF-2) < 0.0001; P (ARF-1, ARF-2) = 0.0091 (Wilcoxon test); Q = quartile. ARF = antiregurgitation formula; SD = standard deviation.

TABLE 5. Evolution of mean score of regurgitated volume (intention-to-treat analysis; n = 115)

	N	Mean (SD)	Range	Q25–75	Median
Baseline	115	2.85 (0.76)	1.0–4.1	2.20–3.50	2.90
With ARF					
ARF-1	115	1.59 (0.61)	1.0–3.5	1.10–1.80	1.40
ARF-2	115	1.51 (0.56)	1.0–3.9	1.10–1.70	1.30

P (baseline—ARF-1 or ARF-2) < 0.0001; P (ARF-1, ARF2) = 0.026 (Wilcoxon test). ARF = antiregurgitation formula; Q = quartile; SD = standard deviation.

TABLE 6. Evolution of the number of daily episodes of regurgitation in the subgroup of infants that regurgitated at least 5 times/day at baseline (intention-to-treat analysis)

	N	Mean (SD)	Range	Median
Baseline	89	9.8 (3.3)	5.0–20.3	9.0
With ARF				
ARF-1	89	2.7 (3.1)	0.0–18.5	1.7
ARF-2	89	2.1 (2.5)	0.0–13.9	1.4

P (baseline—ARF-1 or ARF-2) < 0.0001; *P* (ARF-1, ARF-2) = 0.013 (Wilcoxon test). ARF = antiregurgitation formula; SD = standard deviation.

Nevertheless, both ARF significantly decreased the frequency (and volume) of regurgitation.

To the best of our knowledge, this is the largest trial with ARF ever performed. Moreover, it is the first trial comparing the efficacy of 2 ARF. Mean daily intake during 1 month and weight gain were similar for both groups. The comparator formula (ARF-1) is casein predominant and thickened with bean gum. The other ARF tested (ARF-2) is the partially hydrolyzed whey thickened with a similar amount of bean gum but also with a specific starch. A major difference between both formulas regards the protein content: casein predominance versus a whey hydrolysate. Difference in the gastric emptying rate of casein versus a hydrolysate may contribute to the difference in outcome. In control infants, gastric residual content (after 120 minutes) of human milk (18% ± 11%) or a whey hydrolysate (16 ± 21%) is similar but much smaller than that of casein (39% ± 17%) (14). Although the osmolarity of a feeding is a factor influencing transient relaxations of the lower esophageal sphincter (15), this is unlikely to play a role because osmolarity of both feedings is similar. A partial hydrolysate is known to have better tolerance and digestibility than native protein (5,16).

The results of this prospective trial confirm that reassurance and dietary intervention reduce the frequency and volume of infant regurgitation. The dropout rate was comparable in both groups: 9 while fed ARF-1 (7%) and 10 while fed ARF-2 (7.8%, not significant). The reasons for dropping out (eg, diarrhea, colic, fuzziness) were comparable in both groups.

The decrease from a mean of 8.25 episodes of regurgitation per day at baseline to 2.32 and 1.89 (mean for ARF-1 and ARF-2, respectively) in 4 weeks' time cannot be explained by the natural evolution alone. In the subpopulation of infants having at least 5 regurgitations per day at baseline confirmed by the diary data, the regurgitation score decreased from 3.1 ± 0.6 to 1.7 ± 0.7 for ARF-1 and to 1.6 ± 0.6 for ARF-2 ($P = 0.024$). Efficacy of a formula similar to ARF-1 was shown almost 20 years ago, in the very first trial with commercialized ARF (17). In that trial, half of the patients were treated with regular formula, which was shown to reduce the frequency of regurgitation by approximately 25%, confirming the efficacy of reassurance (17); however, the ARF decreased regurgitation by approximately 50% (17). A Cochrane review from 2004 concluded that thickened feeds reduce the regurgitation severity score (standardized mean difference −0.94; 95% confidence interval [CI] −1.35 to −0.52) as well as the frequency of emesis (standardized mean difference −0.91; 95% CI −1.22 to −0.61) (18). Horvath et al (19) stated that thickened feeding was only moderately effective in GER in healthy infants, although they also concluded that thickened formula significantly increased the number of infants without regurgitation, slightly reduced the number of episodes of regurgitation and vomiting, and increased weight gain. Hegar compared the evolution of the frequency of regurgitation with standard formula (evaluating natural evolution as a control group) and with standard formula thickened with rice cereals versus a bean gum–thickened formula, similar to the ARF-1 used in this study (4). The mean number of daily regurgitation episodes at baseline in the 3 groups was approximately 6, and decreased to 3 in the standard formula group, to 2 in the rice cereal-thickened group, and to 1 in the bean gum–thickened group. The latter group shows a decrease that is 3 times better than the decrease observed by natural evolution. (4). Moreover, weight gain was more increased in the bean gum–thickened formula group than in the 2 other groups (4). Chao and Vandenplas showed that cereal-thickened formula was more effective than the upright position (20).

TABLE 7. Blind evaluation of efficacy of both antiregurgitation formulas by the pediatrician (% of patients) (intention-to-treat analysis)

Efficacy	N	Not effective or moderately effective	Effective or highly effective
ARF-1	114	28.1	71.9
ARF-2	115	16.5	83.5

$P < 0.0001$ (McNemar test). ARF = antiregurgitation formula.

TABLE 8. Evolution of mean crying and sleeping time in minutes (intention-to-treat analysis; n = 115)

	N	Mean (SD)	Range	P25–75	Median
Crying time					
Baseline	111	153.9 (113.3)	0–810	70–200	135
With ARF					
ARF-1	111	110.1 (83.9)	0–535	50–165	90
ARF-2	111	109.0 (82.4)	0–355	45–160	85
Sleeping time					
Baseline	111	867.3 (122.8)	550–1210	800–950	860
With ARF					
ARF-1	111	887.7 (110.9)	582–1140	820–965	895
ARF-2	111	879.1 (108.5)	588–1160	800–960	878

P (ARF-1, ARF-2) = NS for both parameters. No difference was observed between both groups. ARF = antiregurgitation formula; SD = standard deviation.

The efficacy of ARF-2 was first shown by Vandenplas et al in a pilot trial in 12 infants (21). This study was also a cross-over prospective, randomized double-blind trial. The comparator formula in this pilot trial was a casein-predominant formula, thickened with locust bean gum. Gastric emptying was faster with ARF-2 (79.2 ± 14 minutes) compared with a bean gum– and starch-thickened formula (104.5 ± 15.5 minutes) or starch-thickened formula (117.1 ± 18.3 minutes) (21). Later, Leluyer et al (22) performed a large, open-label study including 692 infants (mean age 9.5 ± 5.1 weeks; >4 regurgitations/day) for 1 month with the same formula (ARF-2). The authors showed a similar decrease in the number of regurgitations (from 8.2 [6.0], mean [SD], at baseline to 2.2 [2.7]; $P < 0.0001$; 95% CI −6.72 to −5.63) after 1-month intervention (22). After 1 month, 40% of the infants were without any episode of regurgitation per day (22). The authors also showed a significant decrease in the duration of crying, from

78.3 (67) minutes (mean [SD]) at baseline to 32.4 (40) minutes after 1 month ($P < 0.001$) (22). Two different quality of life scales showed that the formula resulted in a significant improvement in quality of life of the parents. The Qualin scale evolved from 0.83 (0.46) (mean [SD]) at baseline to 1.19 (0.37) after 1 month ($P < 0.001$) and an analogical scale showed 6.2 (2.0) at baseline and 8.4 (1.3) after 1 month ($P < 0.01$) (22).

Based on a gastrointestinal artificial in vitro model, it has been suggested that locust bean potentially decreases mineral absorption (23). A nutritional study confirmed that malabsorption of micronutrients does not happen with bean gum–thickened formula because all minerals remained within normal ranges (24). As a consequence, guidelines for the treatment of regurgitation do not consider this theoretical concern as clinically relevant (1).

A history and physical examination, with attention to warning signs, are generally sufficient to allow the clinician to establish the diagnosis of uncomplicated GER. Parental education, reassurance, and anticipatory guidance are the recommended first steps in the therapeutic approach (1,5). In this study, we showed that a prospective 3-day diary confirms that parents tend to retrospectively overestimate the frequency of regurgitation. In formula-fed infants, antiregurgitation formula reduces the frequency of overt regurgitation and vomiting, and therefore contributes to the reassurance of parents (1,5). Comparative studies between different therapeutic interventions demonstrate differences in outcome. This is the first comparative trial between 2 ARF. Although both formulae have been shown to reduce regurgitations compared with baseline, ARF-2 was significantly more effective than ARF-1 and the rate of ''not or moderately effective'' was decreased by 41%, with ARF-2 compared with ARF-1. It is recommended that more comparative trials be performed in the future.

Acknowledgments: The authors acknowledge all of the paediatricians who actively recruited patients: J. Orbegozzo, M. Bricout, R. Hatahet, E. Mothe, J. Amrein, F. Lainé, V. Dagrenat, S. Boulanger El Abaddi, G. Guihard, F. Vulser, C. Leissler, F. Paratte, M. Wagner Vaucard, J. Debrand, B. Nold, B. Baszanger, R. Bressolette, I. Donikian Pujol, F. Hassid, M. Zouari, A. Bocquet, F. Ceccato, J.F. Delobbe, and M. Navel.

REFERENCES

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, et al., North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). *J Pediatr Gastroenterol Nutr* 2009;49:498–547.
2. Martin AJ. Natural history and familial relationships of infant spilling to 9 years of age. *Pediatrics* 2002;109:1061–7.
3. Nelson SP, Chen EH, Syniar GM, et al. Prevalence of symptoms of gastroesophageal reflux during infancy. A pediatric practice-based survey. Pediatric Practice Research Group. *Arch Pediatr Adolesc Med* 1997;151:569–72.
4. Hegar B. Natural evolution of infantile regurgitation versus the efficacy of thickened formula. *J Pediatr Gastroenterol Nutr* 2008; 47:26–30.
5. Vandenplas Y, Gutierrez P, Velasco C, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. *Nutrition* 2013;29:184–94.
6. Moukarzel AA, Abdelnour H, Akatcherian C. Effects of a prethickened formula on esophageal pH and gastric emptying of infants with GER. *J Clin Gastroenterol* 2007;41:823–9.
7. Xinias I, Mouane N, Le Luyer B, et al. Cornstarch thickened formula reduces oesophageal acid exposure time in infants. *Dig Liver Dis* 2005;37:23–7.
8. Grizzle JE. The two-period change-over design and its use in clinical trials. *Biometrics* 1965;21:467–80.
9. Feng WW, Ding D. PharmaSUG. *http://www.lexjansen.com/pharmasug 2004/statisticspharmacokinetics/sp02.pdf.* Accessed August 5, 2013.
10. Jones B, Kenward MG. *Design and Analysis of Cross-over Trials*. 2nd ed. London: Chapman and Hall; 2003.
11. Kunkel D, Pickering RM, Ashburn AM. Comparison of retrospective interviews and prospective diaries to facilitate fall reports among people with stroke. *Age Ageing* 2011;40:277–80.
12. Corti B, Binns CW, Howat PA, et al. Comparison of 7-day retrospective and prospective alcohol consumption diaries in a female population in Perth, Western Australia—methodological issues. *Br J Addict* 1990; 85:379–88.
13. Canivet C, Hagander B, Jakobsson I, et al. Infantile colic—less common than previously estimated? *Acta Paediatr* 1996;85:454–8.
14. Billeaud C, Guillet J, Sandler B. Gastric emptying in infants with or without gastro-oesophageal reflux according to the type of milk. *Eur J Clin Nutr* 1990;44:577–83.
15. Salvia G, De Vizia B, Manguso F, et al. Effect of intragastric volume and osmolality on mechanisms of gastroesophageal reflux in children with gastroesophageal reflux disease. *Am J Gastroenterol* 2001; 96:1725–32.
16. Shergill-Bonner R. Infantile colic: practicalities of management, including dietary aspects. *J Fam Health Care* 2010;20:206–9.
17. Vandenplas Y, Hachimi-Idrissi S, Casteels A, et al. A clinical trial with an ''anti-regurgitation'' formula. *Eur J Pediatr* 1994;153: 419–23.
18. Craig WR, Hanlon-Dearman A, Sinclair C, et al. Metoclopramide, thickened feedings, and positioning for GOR in children under two years. *Cochrane Database Syst Rev* 2004:CD003502.
19. Horvath H, Dziechciarz P, Szajewska H. Infants systematic review and meta-analysis of randomized, controlled trials. *Pediatrics* 2008;122: e1268–77.
20. Chao HC, Vandenplas Y. Effect of cereal-thickened formula and upright positioning on regurgitation, gastric emptying, and weight gain in infants with regurgitation. *Nutrition* 2007;23:23–8.
21. Vandenplas Y. A double-blind, prospective trial with a new formula in distresses and regurgitating infants. *Open Nutr J* 2008;2:48–50.
22. Leluyer B, Perrissin L, Seigle S. Evaluation of efficacy, tolerance and impact on regurgitating infants' quality of life of a new thickened formula: Novalac AR Digest®. *Nutr Pediatr* 2012;14:20–1.
23. Bosscher D, Van Caillie-Bertrand M, Van Cauwenbergh R, et al. Availabilities of calcium, iron, and zinc from dairy infant formulas is affected by soluble dietary fibers and modified starch fractions. *Nutrition* 2003;19:641–5.
24. Levtchenko E, Hauser B, Vandenplas Y. Nutritional value of an ''anti-regurgitation'' formula. *Acta Gastroenterol Belg* 1998;61:285–7.