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Lactobacillus reuteri (American Type Culture Collection Strain 55730) Versus Simethicone in the Treatment of Infantile Colic: A Prospective Randomized Study

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ABSTRACT

OBJECTIVE. The goal was to test the hypothesis that oral administration of *Lactobacillus reuteri* in a prospective randomized study would improve symptoms of infantile colic.

METHODS. Ninety breastfed colicky infants were assigned randomly to receive either the probiotic *L reuteri* (10^8 live bacteria per day) or simethicone (60 mg/day) each day for 28 days. The mothers avoided cow's milk in their diet. Parents monitored daily crying times and adverse effects by using a questionnaire.

RESULTS. Eighty-three infants completed the trial: 41 in the probiotic group and 42 in the simethicone group. The infants were similar regarding gestational age, birth weight, gender, and crying time at baseline. Daily median crying times in the probiotic and simethicone groups were 159 minutes/day and 177 minutes/day, respectively, on the seventh day and 51 minutes/day and 145 minutes/day on the 28th day. On day 28, 39 patients (95%) were responders in the probiotic group and 3 patients (7%) were responders in the simethicone group. No adverse effects were reported.

CONCLUSIONS. In our cohort, *L reuteri* improved colicky symptoms in breastfed infants within 1 week of treatment, compared with simethicone, which suggests that probiotics may have a role in the treatment of infantile colic.

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Key Words
gut microflora, Lactobacillus reuteri, simethicone, infantile colic

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INFANTILE COLIC IS one of the most common problems within the first 3 months of life, affecting as many as 3% to 28% of newborn children. It consists of a behavioral syndrome characterized by paroxysmal, excessive, inconsolable crying without identifiable cause.[1,2] According to the definition described by Wessel et al,[3] an infant with colic is described as "one who, otherwise healthy and well-fed, had paroxysms of irritability, fussing or crying lasting for a total of three hours a day and occurring on more than three days in any one week for a period of three weeks."

Although infantile colic is reported commonly and causes appreciable distress for both parents and pediatricians, its pathogenesis remains unclear, despite 40 years of research.[4] The available evidence suggests that this condition has multiple independent causes. Infantile colic has been attributed to infants' difficult temperament,[5] inadequate or inappropriate mother-infant interaction or mothers' anxiety,[6] abnormal gastrointestinal function,[7–9] transient relative lactase deficiency,[10] and allergic problems such as exposure to cow's milk proteins in formula or breast milk.[11–14] Recent studies indicated that exposure of the child to tobacco smoking by the mother during pregnancy and after delivery and smoking by the father were associated with excessive crying.[15] Moreover, it was suggested that smoking is linked to increased plasma and intestinal motilin levels,[16] and higher-than-average intestinal motilin and ghrelin levels seem to be related to elevated risk of infantile colic.[17]

The role of intestinal microflora has been growing in importance,[18] and lower counts of intestinal lactobacilli were observed in colicky infants, in comparison with healthy infants.[19,20] This is in accordance with observations by Björkstén et al[21] in atopic children, which support the hypothesis that infantile colic is often related to a food allergy and represents, particularly when severe, the first clinical manifestation of atopic disease.[22]

Lactobacillus reuteri, one of the few endogenous *Lactobacillus* species in the human gastrointestinal tract, has been used safely for many years as a probiotic dietary supplement in adults, and recent data demonstrated safety after long-term dietary supplementation for newborn infants.[23] The positive effects of this probiotic on intestinal disorders such as constipation[24] and diarrhea[25] and in protection from infection,[26] as well as its capacity to modulate immune responses,[27] have been also demonstrated.

Microbial stimulation during the first months of life modifies immune responses, affecting the development of tolerance to ubiquitous allergens. The intestinal microflora may play a particular role in this respect, because it is the major external driving force in maturation of the immune system after birth.[28] We tested the hypothesis that "modulating" the gut microflora of colicky infants through the oral administration of probiotics would decrease crying time related to infantile colic.

METHODS

Subjects and Study Design

Between April 2004 and May 2005, 90 breastfed infants with a diagnosis of infantile colic were recruited in the Department of Pediatric and Adolescence Science (Regina Margherita Children Hospital, Turin, Italy). Patients 21 to 90 days of age, appropriate for gestational age with birth weights between 2500 and 4000 g, with colic symptoms (>3 hours of crying on >3 days in the week) with debut 6 ± 1 days before enrollment, were considered for inclusion in the study. All infants enrolled were exclusively breastfed, to reduce variability in the intestinal microflora attributable to dietary variations, which might have influenced the response to probiotic. Infants were excluded if they had clinical evidence of chronic illness or gastrointestinal disorders or if they had received either antibiotics or probiotics in the week preceding recruitment.

In this prospective controlled study, colicky infants were assigned randomly to receive the probiotic *L reuteri* (American Type Culture Collection strain 55730) or simethicone. *L reuteri* was administered at a dose of 10^8 colony-forming units in 5 drops of a commercially available oil suspension, 30 minutes after feeding, once per day for 28 days. This oil suspension is stable for 21 months at 2°C to 8°C (as documented by the manufacturer, BioGaia AB, Stockholm, Sweden). During the study, parents were instructed to keep the product in the refrigerator when it was not in use. Simethicone was given at a dose of 60 mg/day in 15 drops twice per day of a commercially available solution, after feeding, for 28 days. At enrollment, all mothers were asked to follow a cow's milk-free diet, with avoidance of milk, yogurt, fresh cheese, cream, butter, and biscuits. Adherence to the diet was monitored with diet diaries maintained throughout the treatment period. On days 7, 14, 21, and 28, compliance with the diet was monitored. The institutional ethics committee approved the study protocol, and infants were enrolled in the study only after written informed consent was obtained from the parents.

Follow-up Visits

The day on which the pediatrician saw the infant for the first time was defined as day −1. On that occasion, each infant underwent a medical examination and the parents were interviewed to obtain background data concerning type of delivery, birth weight, gestational age, and family history of gastrointestinal disease and atopy. Atopy was considered positive if the infant had ≥1 family member (mother, father, and/or older sibling) with atopic eczema, allergic rhinitis, or asthma. Moreover, any symptoms of atopic disease during the study period

were recorded. Parents were asked to record the daily average crying time and the number of colic episodes starting the first day after recruitment, which was defined as day 0. The doctor assigned the child randomly to the study group (*L reuteri*) or to the control group (simethicone) through a computer-generated randomization list prepared by an independent person from the department. The randomization numbers were assigned sequentially to participants as they were enrolled, and each patient received *L reuteri* or simethicone directly from the department. Administration of study products began on day 1.

Parents were given written information about the study and were asked to record the daily number of inconsolable crying episodes and their duration, stool consistency and frequency, and any observed adverse effects (eg, constipation or vomiting) from day 1 to day 28, with a structured diary. To aid the uniform documentation of crying times and to confirm that the infants were given the study products correctly, one of the researchers was always available by telephone to help parents. Each patient was reexamined by the same pediatrician on days 1, 7, 14, 21, and 28.

Statistical Analyses

For evaluation of the efficacy in infantile colic, the primary outcome of this study was a reduction of the daily average crying time, from baseline to the end of the treatment period, to <3 hours/day, the cutoff value proposed by Wessel et al.[3] The secondary outcome consisted of the number of responders versus nonresponders in each group at the end of the treatment. Patients were classified as responders if they experienced a decrease in the daily average crying time of 50% during the study.

Sample size was calculated on the basis of finding a difference between groups of a 50-minute reduction in the daily average crying time, which was considered a clinically relevant difference. With $\alpha = .05$, $\beta = .20$, and an estimated SD within groups of 50 minutes, 22 patients were needed in each group.

The data refer to the 83 infants who completed the trial. The Mann-Whitney test and χ^2 test were used to compare continuous and categorical data, respectively. Two-sample Student's *t* test was used to compare the birth weights of the study groups. The proportions of responders versus nonresponders in each group were compared by using the χ^2 test. For all comparisons, *P* values of <.05 were considered statistically significant. Data are presented as median and range. Confidence intervals for differences between medians were calculated with a bootstrap procedure with 10 000 replications. All statistical calculations were performed with commercially available software (SPSS 12 [SPSS Inc, Chicago, IL] and Resampling Procedures 1.3 [Department of Psychology, University of Vermont, Burlington, VT]).

RESULTS

Of the 90 breastfed colicky infants enrolled, 45 were assigned randomly to treatment with *L reuteri* (probiotic) and 45 to simethicone. Seven patients were excluded from the analysis, for the following reasons: interrupted breastfeeding (2 patients), presentation of clinical symptoms of gastroesophageal reflux treated with antacid drugs (2 patients), failure to complete the diary (1 patient), and several missing data (2 patients). Eighty-three infants completed the study, 41 treated with *L reuteri* and 42 treated with simethicone (Fig 1). No infants withdrew because of any adverse effect related to the trial. The groups were similar with respect to age, birth weight, gender, type of delivery, family history of atopy or gastrointestinal diseases, and exposure to smoking ($P > .05$) (Table 1).

The median crying times per day were similar for the 2 treatment groups on day 0 (probiotic group: 197 minutes/day; range: 180–276 minutes/day; simethicone group: 197 minutes/day; range: 180–278 minutes/day; $P = .987$) and on day 1 (probiotic group: 192 minutes/day; range: 107–273 minutes/day; simethicone group: 192 minutes/day; range: 107–278 minutes/day; $P = .753$). Infants receiving *L reuteri* showed a significant reduction in daily crying time by day 7 (159 minutes/day; range: 54–211 minutes/day), compared with infants treated with simethicone (177 minutes/day; range: 38–241 minutes/day; $P = .005$). On days 14, 21, and 28, crying times were significantly different between the 2 treatment groups ($P < .001$). At the end of the study (day 28), the median crying time in the probiotic group was 51 minutes/day (range: 26–105 minutes/day), com-

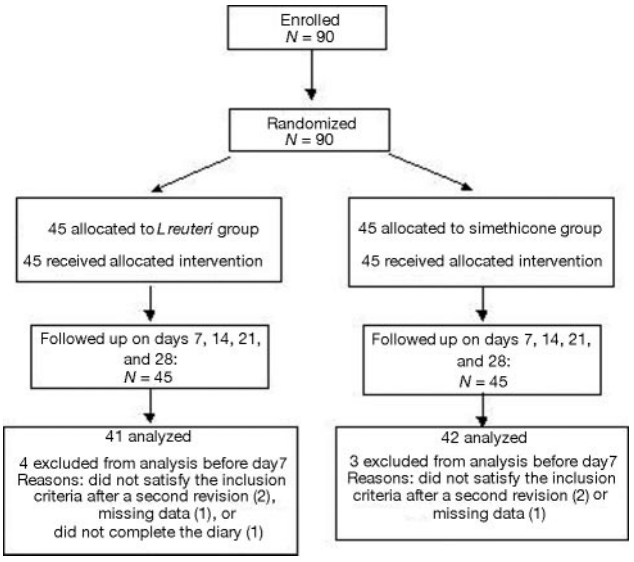

FIGURE 1
Diagram of patient enrollment and study progress.

TABLE 1 **Baseline Characteristics of the Study Population**

Variable	*L reuteri* ($n = 41$)	Simethicone ($n = 42$)	*P*
Gender, male/female, *n*	23/18	21/21	.743[a]
Birth weight, mean ± SD, g	3267 ± 383	3288 ± 377	.802[b]
Age at enrollment, median (range), d	31.0 (11–80)	31.5 (14–74)	.955[c]
Delivery, spontaneous/caesarean, *n*	27/14	27/15	.893[a]
Family history of gastrointestinal diseases, yes/no, *n*	16/25	19/23	.740[a]
Family history of atopy, yes/no, *n*	17/24	22/20	.433[a]
Exposure to smoking, yes/no, *n*	6/35	7/35	.958[a]

[a] χ^2 test.
[b] *t* test.
[c] Mann-Whitney test.

pared with 145 minutes/day (range: 70–191 minutes/day) in the simethicone group, with a difference of 94 minutes/day (Table 2). On day 28, 39 patients (95%) were responders in the probiotic group and 3 patients (7%) were responders in the simethicone group (Fig 2).

Our data were also analyzed with respect to family history of atopy. Among patients with an high risk of atopy ($n = 39$), infants receiving *L reuteri* ($n = 17$) showed significantly reduced daily crying times, compared with infants receiving simethicone ($n = 22$), on days 14, 21, and 28 (Table 3). Similarly, colicky infants without a family history of atopy ($n = 44$) demonstrated significant improvement of colic symptoms when treated with *L reuteri* ($n = 24$), compared with simethicone ($n = 20$), from day 14 to day 28 ($P < .001$) (Table 4).

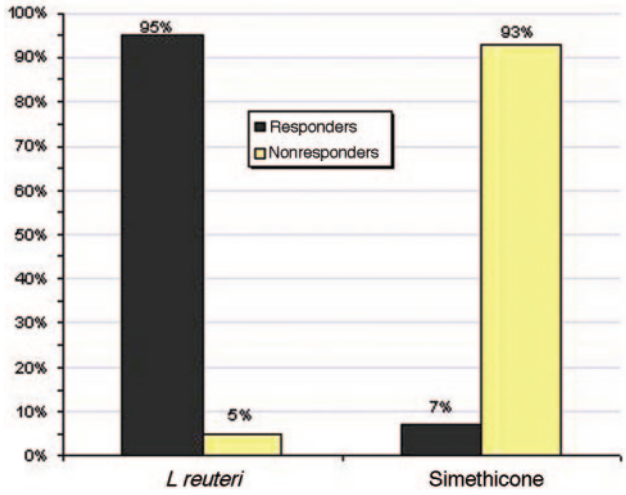

FIGURE 2
Effectiveness of *L reuteri* versus simethicone ($P < .001$, χ^2 test).

DISCUSSION

The present study demonstrated that supplementation with *L reuteri* improved colicky symptoms significantly in breastfed infants, compared with the standard therapy with simethicone, within 7 days of treatment. The response rate for the treatment with *L reuteri* was 95%, whereas only 7% of infants responded to simethicone.

The beneficial effects of probiotic supplementation in this study may be related to action on the altered balance of intestinal lactobacilli in infants with colic.[19,20] Recent studies showed that modulation of microflora with probiotics, including *L reuteri*, might shift the intestinal ecological balance from potentially harmful flora to flora that would be predominantly beneficial to the host, reducing the risk of gastrointestinal infections and allergic diseases.[26,29–31] In particular, probiotic supplementation at an early age aims to provide safe yet sufficient microbial stimulus for the immature immune system,[32,33] and *L reuteri* has been administered to newborn infants in attempts to strengthen positive effects associated with colonization by lactobacilli.[22]

There is a complex relationship between the intestinal immune system and the commensal flora. Recently, it was demonstrated that the luminal endogenous flora can initiate the key processes of bacteria-induced innate and adaptive host responses through the activation of

TABLE 2 **Crying Times for *L reuteri*–Treated and Simethicone-Treated Groups of Colicky Infants ($n = 83$)**

	Crying Time, min			*P*[a]
	L reuteri ($n = 41$)	Simethicone ($n = 42$)	Difference (95% CI)	
Day 0	197 (180–276)	197 (180–278)	0 (−10 to 10)	.987
Day 1	192 (107–273)	192 (107–278)	0 (−18 to 16)	.753
Day 7	159 (54–211)	177 (38–241)	−18 (−40 to −1)	.005
Day 14	95 (41–170)	153 (51–231)	−58 (−78 to −32)	<.001
Day 21	74 (35–139)	154 (54–229)	−80 (−95 to −60)	<.001
Day 28	51 (26–105)	145 (70–191)	−94 (−102 to −76)	<.001

Values are shown as median (range). CI indicates confidence interval.
[a] *P* values from χ^2 test for proportions.

TABLE 3 **Crying Times for Infants With a Family History of Atopy in the *L reuteri*--Treated and Simethicone-Treated Groups ($n = 39$)**

	Crying Time, min			*P*
	L reuteri ($n = 17$)	Simethicone ($n = 22$)	Difference (95% CI)	
Day 0	206 (183–276)	203 (183–278)	3 (−14 to 33)	.731
Day 1	201 (146–273)	200 (131–275)	1 (−21 to 27)	.850
Day 7	175 (95–211)	188 (66–241)	−13 (−46 to 3)	.037
Day 14	100 (63–139)	167 (57–231)	−67 (−101 to −24)	.001
Day 21	76 (44–108)	161 (54–229)	−85 (−107 to −54)	.001
Day 28	55 (28–105)	146 (70–191)	−91 (−107 to −66)	.001

Values are shown as median (range). CI indicates confidence interval.

TABLE 4 **Crying Times for Infants Without a Family History of Atopy in the *L reuteri*–Treated and Simethicone-Treated Groups ($n = 44$)**

	Crying Time, min			*P*
	L reuteri ($n = 24$)	Simethicone ($n = 20$)	Difference (95% CI)	
Day 0	193 (180–240)	192 (180–244)	1 (−9 to 8)	.940
Day 1	182 (107–261)	180 (107–278)	2 (−20 to 17)	.930
Day 7	144 (54–197)	161 (38–205)	−17 (−51 to 2)	.066
Day 14	93 (41–170)	150 (51–198)	−57 (−80 to −28)	<.001
Day 21	59 (35–139)	150 (56–181)	−91 (−102 to −55)	<.001
Day 28	49 (26–101)	145 (78–175)	−96 (−108 to −71)	<.001

Values are shown as median (range). CI indicates confidence interval.

toll-like receptors and nucleotide oligomerization domain receptors, located on intestinal epithelial cells.[34,35] In animal models, cytokines can initiate a hyper-reflex response of the enteric neuromusculature through neuroimmune and myoimmune interactions.[36] Furthermore, inappropriate interaction between the microflora and the toll-like receptors might affect gut motor function, leading to abdominal dysmotility and colicky behavior.[37] In particular, *L reuteri* and other commensal bacteria influence dendritic cell activity, type 1/type 2 T helper cell balance, and cytokine production in the intestinal epithelium.[38–40] An interesting recent study showed that *L reuteri* has inhibitory effects on visceral pain, modulating the inflammation-associated visceral hypersensitivity response through a more-direct action on enteric nerves.[41]

The self-limiting nature of colic has precluded the use of invasive investigations to establish a pathophysiologic model of infantile colic; therefore, the mechanisms through which probiotics act on colic symptoms among breastfed infants remain speculative. It is possible that *L reuteri* contributes to the antiinflammatory tone of the intestinal environment, modulating immune responses and thereby motility of the infant gut.

The infants in our study were exclusively breastfed, because it is thought that human milk works in synergy with probiotic bacteria in the development of immune responses.[42] The low-allergen maternal diet used in the study might have contributed to the reduction in distressed behavior observed during the trial, which suggests a role of maternal diet in the pathogenesis of infantile colic, as reported recently by Hill et al.[14] Although all of the mothers followed this kind of diet in both study groups, the high degree of maintained colic in the control infants (treated with simethicone) indicates that supplementation with *L reuteri* leads to an effect over and above that of cow's milk removal. Therefore, the use of *L reuteri* can be recommended for mothers whether or not they avoid cow's milk. The study does not, however, examine the use of probiotics for formula-fed infants with colic.

Literature data support the hypothesis that infantile colic is often related to a food allergy and represents, particularly when severe, the first clinical manifestation of atopic disease.[13,22] Previous studies demonstrated beneficial effects of probiotics, particularly for infants with an allergic background.[43] It has been reported that the combination of *Lactobacillus rhamnosus* and *L reuteri* stabilizes the impaired intestinal mucosal barrier[44] and improves dermatitis[45] in children with atopic dermatitis. In our study, a family history of atopy did not seem to be predictive of the effect of *L reuteri* on infantile colic. The independence of the effect of *L reuteri* from the risk for atopy could be related to the small size of the study population, and additional studies are needed to investigate this topic.

The study is not without limitations. First, this was an open trial, which could not be conducted in a blinded manner because there was a difference in dosage and time of administration of *L reuteri* and simethicone. Simethicone is used widely for infants with colic, but it has been shown to be no better than placebo.[11,12] There-

fore, rather than a true placebo, simethicone was chosen for comparison because it is the best available and most commonly used treatment for colicky infants. However, the lack of a true placebo group in the study is a limitation, which might have affected the outcome.

In our study, we observed a high prevalence of colicky infants with a family history of atopy, in agreement with our recent finding that infants with infantile colic have a higher frequency of a family history of atopy[20] and an increased risk of developing gastrointestinal and atopic diseases later in life.[46] However, these study results indicated that both infants with an atopic history and those with no history of allergy received significant benefits from using *L reuteri*.

CONCLUSIONS

Our results suggest a potential role of *L reuteri* as a new therapeutic approach to infantile colic. The safety profile of probiotics makes them a favorable alternative to all other therapeutic options for breastfed infants with colic. Because this is the first study performed to evaluate the efficacy of probiotic agents for colicky infants, additional research, from clinical observation to microbiologic analysis, is needed to confirm the beneficial effects of *L reuteri*. Moreover, because specific probiotic strains have specific properties and targets in the human intestinal microbiota, exerting different health effects, additional studies might be performed to examine the role of other probiotic species and to identify the ideal strain for the treatment of infantile colic.

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