

Can the Probiotic *Lactobacillus reuteri* Be Used to Treat Infant Colic?



TAKE-HOME MESSAGE

The probiotic *Lactobacillus reuteri* reduces the duration of crying and fussing in breastfed infants with colic, although its use in formula-fed infants remains unclear.

METHODS

DATA SOURCES

The authors searched PubMed, MEDLINE, EMBASE, the Cumulative Index of Nursing and Allied Health Literature, the Database of Abstracts of Reviews of Effects, and the Cochrane Central Register of Controlled Trials through December 2014. They also searched electronic abstracts from the Pediatric Academic Societies meetings, reference lists from articles, and nonpeer-reviewed articles through Internet searches.

STUDY SELECTION

Articles were selected through the use of an individual participant data meta-analysis. Studies were eligible for inclusion if they were double-blind randomized controlled trials of the probiotic *L reuteri* DSM 17938 versus a placebo, delivered orally to infants with colic. Outcomes had to include infant crying or fussing duration. Colic was defined by the modified Wessel's criteria of crying: greater than 3 hours per day for greater than or equal to 3 days per week.¹ The primary outcome was treatment success, defined as greater than or equal to 50% reduction in crying or fussing from

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Editor's Note: This is a clinical synopsis, a regular feature of the *Annals'* Systematic Review Snapshot (SRS) series. The source for this systematic review snapshot is: **Sung V, D'Amico F, Cabana MD, et al. *Lactobacillus reuteri* to treat infant colic: a meta-analysis. *Pediatrics*. 2018; <https://doi.org/10.1542/peds.2017-1811>.**

Results

Difference in change in crying or fussing duration from baseline between placebo and probiotic groups.

Patient Type	No. of Patients	No. of Studies	Day 7 (95% CI)*	Day 14 (95% CI)*	Day 21 (95% CI)*
All patients	345	4	-21 (-42.0 to -0.05)	-19.4 (-41.1 to 2.3)	-25.4 (-47.3 to -3.5)
Breastfed	246	4 [†]	-33.7 (-53.9 to -13.6)	-28.6 (-50.1 to -7.2)	-46.4 (-87.2 to -25.5)
Formula fed	99	1 [‡]	15.3 (-41.7 to 72.3)	8.4 (-50.2 to 66.9)	41.0 (-20.1 to 102.2)

*Duration of crying and fussing (minutes per day).

[†]Number of studies that included breastfed infants.

[‡]Number of studies that included formula-fed infants.

The search identified 282 abstracts, of which 4 double-blind randomized controlled trials (345 patients, 171 placebo and 174 probiotic) met the inclusion criteria.²⁻⁵ All studies used the same probiotic, manufactured by the same company and given at the same dose, and the same placebo. All trials included breastfed infants with colic, whereas only one trial included formula-fed infants with

colic. The probiotic group was approximately twice as likely as the placebo group to experience treatment success at 7, 14, and 21 days (adjusted incidence ratios were 2.08 [95% CI 1.26 to 3.42], 1.98 [95% CI 1.46 to 2.70], and 1.71 [95% CI 1.35 to 2.15], respectively) (Table). In subgroup analysis, the duration of crying or fussing was decreased in the breastfed infants at all time points but not in the

baseline at 21 days postintervention.

DATA EXTRACTION AND SYNTHESIS

All authors of eligible trials were contacted, and data were collected into a single, secure electronic database for performance of a meta-analysis of individual participant data. Two statisticians independently inspected the data and conducted analyses. The authors report mean differences with 95% confidence intervals (CIs).

formula-fed infants. There were no adverse events reported in the 4 studies.

Commentary

Infant colic, or excessive infant crying of unknown cause, affects approximately 1 in 5 infants younger than 3 months.⁶ It has been found to increase the risk of abusive shaking⁷ and maternal depression⁸ and decrease breastfeeding duration.⁹ There are limited management options. However, probiotics have been proposed as possible treatments after studies revealed gut microbiota to be different between infants with and without colic¹⁰⁻¹³ and randomized controlled trials demonstrated improvement with *L reuteri* DSM 17938. This meta-analysis found that *L reuteri* DSM 17938 reduced crying or fussing duration in breastfed infants.

This meta-analysis has limitations, most notably the inclusion of only 4 randomized clinical trials with a total of 345 patients. Across the various studies and results, the most striking differences include

feeding type (breastfed versus formula fed), definitions of infant colic, and outcome measurement. The collection of data was not standardized across the included studies, with only 2 of the studies using a validated diary, thereby potentially confounding the results in the studies that did not use a validated data collection tool. This is particularly important in a study in which the data collected are based on parental determination of infant crying or fussing duration in a stressful environment, leading to potential recall bias. In addition, only 2 of the included studies provided a clear definition for fussiness (described as sporadic vocalizations and nonrhythmic motor activity), leaving room for interpretation by parents. Finally, although the authors adjusted for some confounding factors, there are a number of other confounding factors that were not controlled across subgroups, including but not limited to proton-pump inhibitor exposure, hypoallergenic formula exposure, maternal dairy-elimination diet, infant sleep duration, and stool colonization. It is possible that these factors alter the gut microbiome of infants and thereby affect the probiotic's effectiveness.

Overall, this meta-analysis demonstrates a potentially useful treatment for infant colic, most notably in the breastfed infant. Further research is needed to gather information on the effects of the probiotic on formula-fed and breastfed infants because their gut microbiomes are known to have different compositions.¹⁰⁻¹³ In addition, a robust randomized controlled trial with an increased sample size and strict standardization across the

subgroups is necessary to better characterize the efficacy of *L reuteri* DSM 17938 in the treatment of infant colic.

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