

Marquette University

e-Publications@Marquette

---

College of Nursing Faculty Research and  
Publications

Nursing, College of

---

3-2021

## Probiotics for the Management of Infantile Colic: A Systematic Review

Jennifer Simonson

*Medical College of Wisconsin*

Kristin Haglund

*Marquette University, kristin.haglund@marquette.edu*

Emma Weber

*Advocate Aurora Health*

Alissa Fial

*Marquette University, alissa.fial@marquette.edu*

Lisa Hanson

*Marquette University, lisa.hanson@marquette.edu*

Follow this and additional works at: [https://epublications.marquette.edu/nursing\\_fac](https://epublications.marquette.edu/nursing_fac)



Part of the [Nursing Commons](#)

---

### Recommended Citation

Simonson, Jennifer; Haglund, Kristin; Weber, Emma; Fial, Alissa; and Hanson, Lisa, "Probiotics for the Management of Infantile Colic: A Systematic Review" (2021). *College of Nursing Faculty Research and Publications*. 789.

[https://epublications.marquette.edu/nursing\\_fac/789](https://epublications.marquette.edu/nursing_fac/789)

Marquette University

e-Publications@Marquette

## ***Nursing Faculty Research and Publications/College of Nursing***

***This paper is NOT THE PUBLISHED VERSION; but the author's final, peer-reviewed manuscript.*** The published version may be accessed by following the link in the citation below.

*MCN, The American Journal of Maternal/Child Nursing*, Vol. 46, No. 2 (March/April 2021): 88-96. [DOI](#). This article is © Wolters Kluwer and permission has been granted for this version to appear in [e-Publications@Marquette](#). Wolters Kluwer does not grant permission for this article to be further copied/distributed or hosted elsewhere without the express permission from Wolters Kluwer.

# Probiotics for the Management of Infantile Colic: A Systematic Review

Jennifer Simonson

Nurse Practitioner, Medical College of Wisconsin, Milwaukee, WI.

Kristin Haglund

College of Nursing, Marquette University, Milwaukee, WI.

Emma Weber

Advocate Aurora Healthcare, Milwaukee, WI.

Alissa Fial

Research & Instruction Services Librarian, Marquette University, Milwaukee, WI.

Lisa Hanson

College of Nursing, Marquette University, Milwaukee, WI.

## Abstract

Background:

Colic is defined as periods of inconsolable crying, fussing, or irritability that have no apparent cause and present in healthy infants under 5 months of age. Although colic is a benign and self-limiting condition, it can be distressing to parents and there are few robust treatment interventions. This

systematic review explored the evidence for administration of probiotics to prevent or decrease symptoms of colic.

#### Methods:

Literature searches were conducted in PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Library, and Web of Science.

#### Sample:

Twenty articles were included: 15 randomized controlled trials and 5 meta-analyses.

#### Results:

Based on the evidence in this systematic review, the oral administration of probiotics to breastfed infants with colic resulted in at least a 50% reduction in crying time compared with placebo. Efficacy of probiotics to reduce colic symptoms in formula-fed infants needs further study. In this review, we did not find evidence to support or refute efficacy of probiotics to prevent infantile colic. Clinical Implication: Probiotics (especially the strain *Lactobacillus reuteri* DSM 17938) can safely be recommended if parents desire a treatment option for their infants with colic.



About 25% of infants experience colic or excessive crying and fussiness (Wolke et al., 2017). The phrase “infantile colic” was coined in 1954 to describe a healthy infant who had fussiness or crying lasting for at least 3 hours per day, on more than 3 days per week for a period of 3 weeks (Wessel et al., 1954). These criteria for clinical diagnosis of colic have changed and are depicted in Figure 1. Notably, there is no longer a specified duration of time for symptoms. Current criteria for diagnosis of colic are caregiver report of recurrent and prolonged periods of crying, fussing, or irritability in infants less than 5 months of age. Periods of crying occur without obvious cause and cannot be prevented or resolved by caregivers (Benninga et al., 2016). Colic typically presents at 2 weeks of life, peaks at approximately 6 to 7 weeks of life, and resolves spontaneously by 12 to 20 weeks of life (Dubois & Gregory, 2016). Colic should be diagnosed only after failure to thrive, illness, and other causes of irritability have been ruled

out (Benninga et al.). Examples of conditions that can cause excessive crying in infants include hunger, hair tourniquet, trauma, corneal abrasion, and gastrointestinal disorders such as obstruction (Loscalzo et al., 2019).



**FIGURE 1.:** INFANTILE COLIC SYMPTOMS

Etiology of colic has not been clearly established. Causative theories have included problems with attachment or infant temperament, food intolerances, hyperstimulation of the gastrointestinal nervous system, intestinal gas, and physiologic immaturity of infants' body systems (Bird et al., 2017; Gutiérrez-Castrellón et al., 2017). Current research has focused on altered gut microbiome as a cause for colic symptoms.

## Background

The communities of microbes and their genetic material that live within, and on, each human's body is called the human microbiome (the Human Microbiome Project Consortium, 2012). Each person's unique microbiome is influenced by host genetic factors and by environmental influences of early infancy including maternal-to-fetal in utero microbial transfer, mode of birth, place of birth, and exposure to antibiotics (Hanson & VandeVusse, 2013; Stiemsma & Michels, 2018). Postnatal gut colonization begins during the process of normal labor and birth, through exposure to maternal fecal and vaginal microbes (Hanson & VandeVusse). Breastfeeding and infant diet influence maturation of the human gut microbiome (Stiemsma & Michels).

The communities of microbes vary in different parts of the human body and exist in various symbiotic relationships with their human hosts. Symbiosis is a relationship between organisms of two different species in an ecosystem. In commensal symbiotic relationships, one organism benefits and one is unaffected. Mutualism is a symbiotic relationship in which both species benefit from the relationship. Parasitism is a pathogenic symbiotic relationship in which one species benefits at the expense of the second species (Nelson, 2018). The gastrointestinal tract provides nutrients and suitable habitat for trillions of microbes that perform essential functions for human health. Microbes in the gastrointestinal tract create a barrier to colonization by pathogens, aid in digestion, synthesize vitamins and other beneficial compounds, and aid in development of the intestinal epithelium and immune system (Tyler et al., 2014).

Microorganisms, both beneficial and pathogenic, compete for limited nutrients aiming to colonize the human gut. Table 1 shows common gastrointestinal bacteria organized by Phylum, Genera, characteristic, and role in human health. Some bacteria, such as Proteobacteria, are pathogenic organisms that can cause disease, and inflammation and gastrointestinal symptoms such as increased gas and bloating (Savino et al., 2018). Others, such as *Bifidobacteria* and *Lactobacilli*, are natural

colonizers of the human gut and promote a healthy gut environment. Infants with colic have less microbial diversity in their gut, and more pathogenic and less beneficial organisms than infants without colic (de Weerth et al., 2013; Pärtty et al., 2015).

TABLE 1. - BACTERIAL COMPONENTS OF THE INFANT GASTROINTESTINAL MICROBIOME

Phylum	Genus	Characteristics	Role in Human Health
Actinobacteria	<i>Bifidobacterium</i>	Obligate anaerobe	<ol style="list-style-type: none"> <li>1. Commensual</li> <li>2. Nonpathogenic</li> <li>3. Produces lactic acid on mucosa</li> </ol>
Bacteroidetes	<i>Bacteroides</i>	Obligate anaerobe	Assist in digestion of nutrients
Firmicutes	<i>Lactobacillus</i>	Facultative anaerobe	<ol style="list-style-type: none"> <li>1. Commensual</li> <li>2. Nonpathogenic</li> <li>3. Produces lactic acid on mucosa</li> </ol>
Proteobacteria	<ol style="list-style-type: none"> <li>1. <i>Campylobacter</i></li> <li>2. <i>Escherichia</i></li> <li>3. <i>Klebsiella</i></li> <li>4. <i>Pseudomonas</i></li> </ol>	Facultative anaerobe	Opportunistic pathogen

In a diverse microbial environment, microbes such as *Bifidobacterium* and *Lactobacilli* use most of the available nutrients that keeps the growth of Proteobacteria under control, commonly referred to as eubiosis (Iebba et al., 2016). However, if there are fewer bacteria present to begin with, Proteobacteria may take over the intestinal environment, preventing the growth of other beneficial bacteria and stimulating intestinal inflammation, often referred to as dysbiosis (Dubois & Gregory, 2016; Iebba et al.). Elevated colonies of pathogenic bacteria induce gastrointestinal inflammation. Intestinal epithelial cells release cytokines and chemokines locally and systemically that perpetuates the inflammatory response and sensitizes local nerve tissue that increases sensations of pain. It is hypothesized that inflammation causes gastrointestinal pain and discomfort, which manifests as symptoms of colic in infants including crying, fussiness, and inconsolability (Dubois & Gregory).

There is a growing body of research on use of probiotics to reduce symptoms of infantile colic. Probiotics are supplements or food that contain viable microorganisms to alter the microflora of the host and may potentially confer health benefits (Thomas et al., 2010). Probiotics have been studied in children as a treatment to correct pathophysiological alterations in gut flora, decrease inflammation, relieve pain, and alleviate the symptoms of infant colic. Currently, *Lactobacillus reuteri* is the most commonly studied probiotic to treat colic symptoms. *L. reuteri* is of human origin and is a natural colonizer of the human gut. *L. reuteri* was first tested as a treatment for acute diarrhea in infants and young children (Shornikova et al., 1997). Safety of the daily administration of *L. reuteri* to infants over a period of 12 months was shown in a classic work by Connolly et al. in 2005. There is a physiological mechanism for *L. reuteri* to reduce symptoms of colic. *L. reuteri* is a predominant indigenous *Lactobacillus* species in the gut microbiome of infants, children, and adults. In the intestinal epithelium, effects of *L. reuteri* include suppression of growth of intestinal pathogenic bacteria, modulation of the host immune system, inducement of anti-inflammatory actions, and direct action on

enteric nerves to decrease visceral pain all of which may play a role in reducing symptoms of colic in infants (Mi et al., 2015; Savino et al., 2018). The purpose of this systematic review was to explore the evidence for probiotics to prevent or decrease the symptoms of colic in infants.

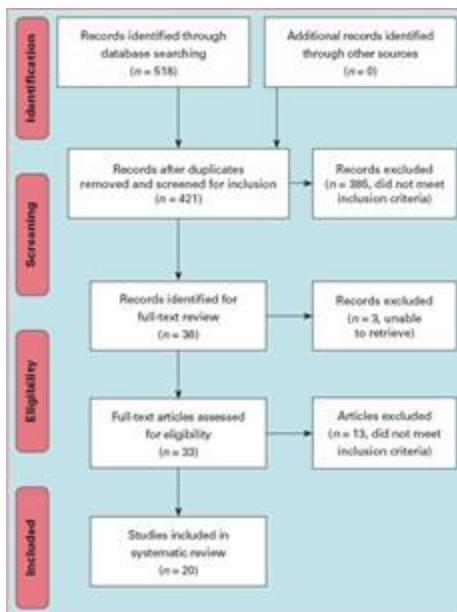
## Methods

### Search Methods

Literature searches were conducted in the following electronic databases: PubMed, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Cochrane Library, and Web of Science. The parameters included an initial focus on colic, including stomach and crying, probiotics and infants. There was no limit on the type of publication. The search strategy was first established in MEDLINE via PubMed using a combination of MeSH (medical subject headings; database-controlled vocabulary) and key words. From there, the other database search strategies were developed, and searches were conducted with database-controlled vocabulary in combination with key words. Specific MeSH terminology included infants, newborns and neonates, abdominal cramps, probiotics, and gastrointestinal agents. The complete search strategy for each database is available in Supplemental Digital Content Table 1 at <http://links.lww.com/MCN/A61>.

Inclusion criteria included published in English, between 2015 and 2020, full text available, tested probiotic administration to infants to treat or prevent symptoms of colic versus usual care, and included patient-oriented outcomes. Articles were excluded if they were published prior to 2015, probiotics were administered to pregnant or breastfeeding mothers to test the effects in their infants, probiotics were added to formulas, prebiotics only or synbiotics were tested, or if only disease-oriented outcomes were included.

The initial search yielded 518 citation results. Removing duplicates reduced number of citations to 421. A review of titles and abstracts led to the exclusion 385 articles leaving 36 for full-text review. We were unable to retrieve three articles. We reviewed 33 full-text articles. Thirteen did not meet inclusion/exclusion criteria and were excluded. The remaining 20 articles were included in this systematic review. The PRISMA flowchart is presented in Figure 2.



Note. Adapted from Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & The PRISMA Group. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, 6(7), e1000097. <https://doi.org/10.1371/journal.pmed.1000097>

**FIGURE 2.:** PRISMA 2009 FLOW DIAGRAM

## Evaluation of Evidence

Level of evidence of each study was appraised using the Strength of Recommendation Taxonomy (SORT) criteria (Ebell et al., 2004). The SORT criteria are used to evaluate individual studies and groups of studies based on quality, quantity, and consistency of patient-oriented evidence. Patient-oriented evidence measures outcomes that matter to patients such as morbidity; mortality; or changes in symptoms, cost, or quality of life (Ebell et al.). Level of evidence of individual studies is rated on a scale of 1 to 3 with 1 being the highest. Groups of studies are referred to as bodies of evidence. Strength of recommendation for a body evidence is rated A, B, or C based on quality of studies and consistency of patient-oriented evidence across the group, with level A being the highest (i.e., strong recommendation) and level C the lowest (weak; Ebell et al.). All studies in this review included patient-oriented outcomes. Disease-oriented outcomes such as changes in fecal microbes or inflammatory markers were not part of this review.

## Results

Twenty studies were included in this systematic review. Sixteen studies tested the administration of a probiotic to reduce symptoms of infantile colic including 11 randomized control trials (RCTs) and 5 meta-analyses. Four studies tested administration of a probiotic to prevent colic symptoms in infants. Table 2 includes a summary of the evidence, risks, and benefits.

**TABLE 2. - SUMMARY OF EVIDENCE FOR PROBIOTICS FOR COLIC IN INFANTS RISKS AND BENEFITS**

Risk or Benefit	Level of Evidence
<b>Colic symptoms</b>	In 10 clinical trials, breastfed infants with colic treated with daily probiotics experienced significant reductions in crying and fussing compared with control groups (Akbarian et al., 2015; Baldassarre et al., 2018; Chau et al.,

	2015; Gerasimov et al., 2018; Martinelli et al., 2017; Mi et al., 2015; Nocerino et al., 2020; Savino et al., 2018; Tatari et al., 2017; Zoham et al., 2019).
	In 2 clinical trials, formula-fed infants with colic treated with daily probiotics experienced significant reductions in crying and fussing compared with control groups (Martinelli et al., 2017; Zoham et al., 2019).
	Results of 5 meta-analyses revealed that daily administration of <i>L. reuteri</i> led to significant reductions in crying and fussing compared with control among breast- and formula-fed infants (Bird et al., 2017; Gutiérrez-Castrellón et al., 2017; Xu et al., 2015) and among breastfed infants only (Dryl & Szajewska, 2018; Sung et al., 2018).
<b>Colic prevention</b>	Mixed evidence for probiotics to prevent development of colic was reported in 4 clinical trials among neonates without colic.
	In 2 clinical trials, there were no significant differences in development of colic symptoms between neonates treated with probiotics and control (Aloisio et al., 2018; Cabana et al., 2019).
	In 1 clinical trial, only formula-fed neonates treated with probiotics had less crying time than control. No significant differences reported for breastfed infants (Gigione et al., 2016).
	In 1 clinical trial, breast- and formula-fed infants had significantly fewer colic symptoms at 3 months than control group (Savino et al., 2015).
<b>Caregiver distress</b>	Mothers of infants with colic treated with probiotics had significant reductions in depression (measured with Edinburgh postnatal depression scale) compared with control group (Mi et al., 2015).
	One RCT reported significantly improved quality of life among parents of infants with colic treated with probiotics for 2 & 3 weeks (Baldassarre et al., 2018).
<b>Growth parameters</b>	One meta-analysis concluded that <i>L. reuteri</i> had no effect on infant growth (Xu et al., 2015).
	Two RCTs reported no differences in growth between infants treated with probiotics and control group (Baldassarre et al., 2018; Chau et al., 2015).
<b>Safety &amp; adverse events</b>	In 15 clinical trials included in this systematic review, no researchers reported serious adverse events.
	One phase 1 safety and tolerability trial found no significant changes in safety and immune markers in infants with colic treated with probiotics (Fatheree et al., 2017).
	In 1 meta-analysis, researchers reported no serious adverse events were observed in the included studies (Xu et al., 2015).

### Administration of Probiotics to Reduce Symptoms of Colic

Eleven studies were RCTs with six categorized as evidence level 1 (Baldassarree et al., 2018; Chau et al., 2015; Gerasimov et al., 2018; Nocerino et al., 2020; Savino et al., 2018; Zoham et al., 2019) and five categorized as evidence level 2 due to lack of control group (Akbarian et al., 2015), inadequate sample size (Fatheree et al., 2017), single-blinded design (Mi et al., 2015; Tatari et al., 2017), and open-label design (Martinelli et al., 2017). Supplemental Digital Content Table 2 at <http://links.lww.com/MCN/A61> includes characteristics of 11 RCTs that tested probiotics to reduce colic symptoms, 6 tested *L. reuteri* alone and 5 tested probiotics other than *L. reuteri* alone. Five meta-



analyses categorized as evidence level 1 were included. Study characteristics are included in Supplemental Digital Content Table 3 at <http://links.lww.com/MCN/A61>. Across the included RCTs and meta-analyses, common inclusion criteria were term infants with adequate birthweight, age birth to 6 months, no recent or concurrent antibiotic or probiotic, and no major congenital or acquired conditions, no evidence of failure to thrive, fever or illness. Infants were diagnosed with colic by physicians according to criteria for inclusion in research studies. For research, the criteria for diagnosis of colic were recurrent and prolonged periods of crying, fussing, or irritability in infants less than 5 months of age that occurred 3 or more hours per day during 3 or more days in the previous 7 days prior to a screening interview by a researcher or clinician (Benninga et al., 2016).

*Randomized controlled trials testing L. reuteri alone.*

In six RCTs, *L. reuteri* was tested in breastfed infants. In five of these six studies, breastfed infants treated for colic with *L. reuteri* experienced significantly less minutes crying and fussing per day (Akbarian et al., 2015; Chau et al., 2015; Mi et al., 2015; Savino et al., 2018; Tatari et al., 2017). Number of treatment days until appearance of significant reduction in daily minutes of crying and fussing varied. Significant reduction in colic symptoms occurred after 5 to 7 days of treatment with *L. reuteri* in two studies (Akbarian et al.; Mi et al.), after 14 days of treatment in one study (Savino et al., 2018), and after 21 to 28 days of treatment in two studies (Chau et al.; Tatari et al.). In three studies, significantly more infants in the treatment groups achieved greater than, or equal to, a 50% reduction in crying at the end of the intervention period (range 7-28 days) compared with the control group (Chau et al.; Mi et al.; Savino et al., 2018).

One of the six studies that tested only *L. reuteri* to treat colic (Fatheree et al., 2017) found no significant difference in symptom reduction compared with the control group. However, the purpose of this study was to demonstrate safety of a liquid probiotic *L. reuteri* strain and to investigate changes in biomarkers to explain mechanism of action of *L. reuteri*. Fatheree et al. (2017) had the smallest number of participants ( $N = 20$ ) and 25% ( $N = 5$ ) were taking acid-blocking medications. Acid-blocking medications should only be prescribed to infants who have gastrointestinal conditions such as severe reflux (Lightdale et al., 2013) thus, the infants taking acid-blocking medications may not have had uncomplicated colic. Alternatively, acid-blocking medications may have rendered *L. reuteri* less effective at reducing colic symptoms.

*Randomized controlled trials testing probiotics other than L. reuteri alone.*

Five studies tested probiotics other than *L. reuteri* alone or in combined probiotic mixtures. Baldassarre et al. (2018) tested a probiotic mixture containing *Lactobacilli*, *Bifidobacteria*, and *Streptococcus thermophilus* compared with placebo. The probiotic group had significantly reduced crying time per episode and per day at the end of treatment on day 21 (Baldassarre et al., 2018). Gerasimov et al. (2018) tested a mixture of *L. rhamnosus*, *L. reuteri*, and vitamin D3 compared with vitamin D3 in breastfed infants. The authors reported significant reductions in duration in crying and fussing time on days 14, 21, and 28 (Gerasimov et al., 2018). Martinelli et al. (2017) tested a probiotic-herbal mixture, *L. reuteri*, and control. The control group received simethicone. Breast- and formula-fed infants in both probiotic groups had significantly higher rates of response to treatment, defined as a 50% reduction in daily average crying time, compared with control. No significant differences were observed between the two probiotic groups (Martinelli et al., 2017). Nocerino et al.

(2020) tested *Bifidobacterium animalis* in breastfed infants. After 28 days, treated infants had significantly higher reductions in number and duration of crying episodes compared with the placebo group. Zoham et al. (2019) tested a probiotic mixture containing *Bifidobacterium infantis*, *L. reuteri*, and *Rhamnosus lactobacillus*. Breast- and formula-fed infants in the treatment group had significantly reduced number of days of crying after 7 days of treatment. After 21 days, treated infants had significantly fewer episodes of crying and fussing and these episodes were significantly shorter in duration compared with control group (Nocerino et al., 2020).

#### *Meta-analyses of studies testing probiotics to reduce colic symptoms.*

Results of the five meta-analyses included in this review demonstrated that oral administration of *L. reuteri* to breastfed infants with colic resulted in at least a 50% reduction in crying time compared with placebo. The efficacy of that *L. reuteri* to reduce colic symptoms in formula-fed infants needs further study.

Supplemental Digital Content Table 4 at <http://links.lww.com/MCN/A61> contains a table indicating which RCTs were included in each meta-analysis. Bird et al. (2017) included five RCTs and concluded that infants treated with *L. reuteri* had a 2.3-fold reduction of crying and fussing time compared with control (Bird et al., 2017). Dryl and Szajewska in 2018 analyzed seven RCT studies that tested probiotic administration to reduce symptoms of infant colic. Analysis of pooled data from these trials revealed that daily *L. reuteri* increased the treatment success > 50% reduction in crying time in breastfed infants (4 RCTs, RR = 2.11, 95% CI: 1.22-3.66, NNT = 2, 95% CI: 2 to 25), but not in formula-fed infants (1 RCT, RR = 0.9, 95% CI: 0.59-1.38). Administration of probiotics was found to reduce overall cry time by 50 minutes compared with the placebo groups (Dryl & Szajewska, 2018). Gutiérrez-Castrellón et al. (2017) conducted a network meta-analysis of 32 RCTs conducted between 1960 and 2015. Included studies tested *L. reuteri* administration versus control, diet versus control, or acupuncture versus control. Daily administration of *L. reuteri* for 21 to 28 days significantly reduced crying time and was the most effective intervention to reduce crying time in colic.

Sung et al. (2018) conducted a meta-analysis that included individual participant data from four double-blind RCTs. Infants treated with *L. reuteri* had significantly less crying and fussing at all time points (95% CI: -47.3 to -3.5) and were nearly twice as likely to experience treatment success compared with placebo (95% CI: 1.4-2.2). Xu et al. (2015) included six RCTs. Treated infants had significantly reduced crying at 2 and 3 weeks of treatment. The number needed to treat (NNT) was 2.56 at 2 weeks and 2.23 at 4 weeks. An NNT of  $\leq 5$  indicates that the treatment is likely to have a large health benefit (Chong et al., 2006). Number needed to treat is a measure of the impact of a treatment by estimating the number of patients who need to be treated in order to have an impact on one person (The NNT Group, n.d.). The NNT of 2.56 and 2.23 means that two to three infants would need to be treated with probiotics for one infant to experience relief of their symptoms.

#### Administration of Probiotics to Prevent Colic Symptoms

Characteristics of four RCTs that tested probiotics to prevent symptoms of infantile colic were included in Supplemental Digital Content Table 5 at <http://links.lww.com/MCN/A61>. These studies were categorized as evidence level 1 (Aloisio et al., 2018; Cabana et al., 2019; Giglione et al., 2016; Savino et al., 2015). Across studies, daily administration of probiotics to infants began within the first 2 weeks of life and continued for 3 to 6 months. Common inclusion criteria were full-term healthy infants with

adequate birthweight who had not been treated with medications or probiotic during the study period. Infants were randomized to treatment and control groups. Outcome measures included daily minutes of crying (Giglione et al.), inconsolable crying (Aloisio et al., 2018), provider or parent diagnosis of colic (Cabana et al.), and use of colic medications and calls or visits to primary care providers for colic symptoms (Savino et al., 2015).

Two studies of colic prevention tested *Bifidobacterium breve*. Giglione et al. (2016) tested daily administration of *B. breve* versus control. Breast- and formula-fed infants were included. Among formula-fed infants only, those in the treatment group had less crying time than control infants. This difference became larger each month reaching statistical significance after 3 months of treatment. There were no significant differences in crying time between the breastfed infants in the probiotic and control groups (Giglione et al., 2016). Aloisio et al. (2018) tested *B. breve* versus placebo and found no significant differences in crying time between probiotic and control groups together or when analyzed by feeding type. Savino et al. (2015) tested drops containing *L. reuteri* plus vitamin D3 400 IU in a sample of breastfed infants. The control group was given daily drops of vitamin D3 400 IU only. Researchers reported that at 3 months, the treatment group had significantly less use of colic medications and fewer calls and visits to primary care providers for colic symptoms. Cabana et al. (2019) tested *L. rhamnosus* GG (LGG) mixed with inulin. The control took a daily dose of inulin only. Inulin is a type of soluble fiber and is a prebiotic supplement to feed the beneficial bacteria in the gut. Researchers found no significant differences in development of symptoms of colic between groups (Cabana et al., 2019).

## Strengths & Limitations

This systematic review included high-quality studies rated level 1 and level 2; review as a total body of evidence increases strength of the recommendation. Strengths included randomized control designs; studies conducted in multiple nations; comparison of multiple probiotics; and evaluation of other colic remedies in addition to probiotics. The studies have several limitations including small samples; small numbers of formula-fed infants; reliance on parent-reported data; and lack of procedure to check adherence to intervention.

## Discussion and Recommendation

In this systematic review, we found evidence of efficacy of probiotics to treat infantile colic. Oral administration of probiotics to breastfed infants with colic resulted in at least a 50% reduction in crying time compared with placebo. The quality of the body of evidence that supports administration of probiotics to breastfed infants to relieve colic symptoms was level A. The quality of the body of evidence that supports the administration of probiotics to relieve colic symptoms in formula-fed infants was level B due to small numbers of formula-fed infants in the included studies (Ebell et al., 2004). Strength of recommendation for probiotics as a treatment for infant colic was based on consistent and good quality patient-oriented evidence. Administration of probiotics significantly reduced crying in breastfed infants with colic (Akbarian et al., 2015; Bird et al., 2017; Chau et al., 2015; Dryl & Szajewska, 2018; Gerasimov et al., 2018; Gutiérrez-Castrellón, 2017; Martinelli et al., 2017; Mi et al., 2015; Savino et al., 2018; Sung et al., 2018; Tatari et al., 2017; Xu et al., 2015). Fewer studies included formula-fed infants; however, these studies did find that administration

of probiotics significantly reduced crying in formula-fed infants with colic (Martinelli et al.; Zoham et al., 2019).

We did not find evidence to support or refute the efficacy of probiotics to prevent infantile colic. Available evidence for probiotics to prevent colic symptoms is inadequate to make a recommendation. About 25% of infants will develop colic, and it is impossible to predict which infants will develop colic symptoms, thus the studies included in this review may have had sample sizes too small to detect significant differences.

None of the studies in this review reported any adverse effects of probiotic administration on the infants. Anthropometric data obtained between treatment and control groups made up of healthy, term infants showed no statistical differences, both groups grew and gained weight at the same rates (Baldassarre et al., 2018). Although probiotics are generally considered safe, the American Academy of Pediatrics practice guideline recommends that probiotics should not be used in infants who are immunocompromised, chronically debilitated, or seriously ill with indwelling medical devices (Thomas et al., 2010).

More studies on safety and efficacy of probiotics to treat colic especially among formula-fed infants are needed. There is a growing practice in the United States to pump breast milk and feed it to infants exclusively with a bottle. The effect of probiotics on the colic symptoms of infants who drink breast milk from a bottle is unknown and warrants study. Larger, prospective studies are needed to determine whether probiotic administration to newborns can prevent colic.

## Clinical Implications

Colic is a self-limiting condition, yet it can be distressing for infants, their parents, and caregivers. Evidence supports probiotics safety, low cost, and likely effectiveness to reduce symptoms of colic. Nurses may recommend probiotics for infants with colic to caregivers who desire a treatment option. *L. reuteri* is the most studied probiotic for treating infants for colic and has been shown to be effective. Probiotic supplements containing *Bifidobacteria*, *Lactobacillus GG*, and mixed probiotics containing multiple strains of various genera, also significantly decreased colic symptoms in breastfed infants (Baldassarre et al., 2018; Dryl & Szajewska, 2018; Giglione et al., 2016). Probiotic drops for infants are readily available. Probiotic drops with vitamin D3 are also readily available. Vitamin D3 400 IU is a vitamin supplement that is recommended for infants who are breastfed or consuming <1 L/day of infant formula (Perrine et al., 2010). Parents may choose to use drops containing only probiotic or drops containing probiotic and vitamin D. Administration of drops containing *L. reuteri* and vitamin D have been shown to decrease symptoms of colic (Gerasimov et al., 2018).

Parents and caregivers should be counseled that infantile colic is a benign condition that does not require treatment to resolve. Nurses should teach all parents and caregivers strategies for calming infant during fussy periods and ways caregivers can manage their own stress in response to the infant crying. Supportive strategies for calming fussy infants include swaddling, calm music, gentle rhythmic rocking or walking, using a pacifier, tummy time, and avoidance of overstimulation and overfeeding. Encourage parents and caregivers to seek support from friends and family when caring for a fussy child and provide clear messages to never strike or shake a baby (American Academy of Pediatrics, 2015).

## CLINICAL IMPLICATIONS

- Rule out alternative causes of infant crying and fussiness such as hunger, infection, trauma, constipation, or reflux.
- Reassure parents and caregivers that colic will eventually resolve on its own.
- Reassure parents and caregivers that treatment is not required for colic.
- Parents may safely choose to give their infant probiotics to treat colic.
- Teach all parents and caregivers how to sooth their infants such as swaddling, rocking, pacifiers, tummy time.
- Discuss stress management measures with caregivers as colic can provoke stress in adults.
- Reinforce that no one should ever strike or shake infants.

## INSTRUCTIONS Probiotics for the Management of Infantile Colic: A Systematic Review

### TEST INSTRUCTIONS

- Read the article. The test for this nursing continuing professional development (NCPD) activity is to be taken online at [www.nursingcenter.com/CE/MCN](http://www.nursingcenter.com/CE/MCN). Tests can no longer be mailed or faxed.
- You'll need to create an account (it's free!) and log in to access My Planner before taking online tests. Your planner will keep track of all your Lippincott Professional Development online NCPD activities for you.
- There's only one correct answer for each question. A passing score for this test is 7 correct answers. If you pass, you can print your certificate of earned contact hours and access the answer key. If you fail, you have the option of taking the test again at no additional cost.
- For questions, contact Lippincott Professional Development: 1-800-787-8985.
- Registration deadline is March 3, 2023.

### PROVIDER ACCREDITATION

Lippincott Professional Development will award 2.5 contact hours for this nursing continuing professional development activity.

Lippincott Professional Development is accredited as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

This activity is also provider approved by the California Board of Registered Nursing, Provider Number CEP 11749 for 2.5 contact hours. Lippincott Professional Development is also an approved provider of continuing nursing education by the District of Columbia, Georgia, and Florida, CE Broker #50-1223. Your certificate is valid in all states.

**Payment:** The registration fee for this test is \$24.95.

## References

- Akbarian Rad Z., Haghshenas Mojaveri M., Zahed Pasha Y., Ahmadpour-Kacho M., Hajian K., Taghipoor Y. (2015). The effect of probiotic lactobacillus reuteri on reducing the period of restlessness in infants with colic. *Journal of Babol University of Medical Sciences*, 17(5), 7–11.
- Aloisio I., Prodam F., Giglione E., Bozzi Cionci N., Solito A., Bellone S., Baffoni L., Mogna L., Pane M., Bona G., Di Gioia D. (2018). Three-month feeding integration with bifidobacterium strains prevents gastrointestinal symptoms in healthy newborns. *Frontiers in Nutrition*, 5, 39. <https://doi.org/10.3389/fnut.2018.00039>
- American Academy of Pediatrics. (2015, June 24). *Colic relief tips for parents*. HealthyChildren. <https://www.healthychildren.org/English/ages-stages/baby/crying-colic/Pages/Colic.aspx>
- Baldassarre M. E., Di Mauro A., Tafuri S., Rizzo V., Gallone M. S., Mastromarino P., Capobianco D., Laghi L., Zhu C., Capozza M., Laforgia N. (2018). Effectiveness and safety of a probiotic-mixture for the treatment of infantile colic: A double-blind, randomized, placebo-controlled clinical trial with fecal real-time PCR and NMR-based metabolomics analysis. *Nutrients*, 10(2), 195. <https://doi.org/10.3390/nu10020195>
- Benninga M. A., Faure C., Hyman P. E., St. James Roberts I., Schechter N. L., Nurko S. (2016). Childhood functional gastrointestinal disorders: Neonate/toddler. *Gastroenterology*, 150(6), 1443–1455. <https://doi.org/10.1053/j.gastro.2016.02.016>
- Bird A. S., Gregory P. J., Jalloh M. A., Cochrane Z. R., Hein D. J. (2017). Probiotics for the treatment of infantile colic: A systematic review. *Journal of Pharmacy Practice*, 30(3), 366–374. <https://doi.org/10.1177/0897190016634516>
- Cabana M. D., McKean M., Beck A. L., Flaherman V. (2019). Pilot analysis of early *Lactobacillus rhamnosus* GG for infant colic prevention. *Journal of Pediatric Gastroenterology and Nutrition*, 68(1), 17–19. <https://doi.org/10.1097/MPG.0000000000002113>
- Chau K., Lau E., Greenberg S., Jacobson S., Yazdani-Brojeni P., Verma N., Koren G. (2015). Probiotics for infantile colic: A randomized, double-blind, placebo-controlled trial investigating *Lactobacillus reuteri* DSM 17938. *The Journal of Pediatrics*, 166(1), 74–78. <https://doi.org/10.1016/j.jpeds.2014.09.020>
- Chong C. A. K. Y., Tomlinson G., Chodirker L., Figdor N., Uster M., Naglie G., Krahn M. D. (2006). An unadjusted NNT was a moderately good predictor of health benefit. *Journal of Clinical Epidemiology*, 59(3), 224–233. <https://doi.org/10.1016/j.jclinepi.2005.08.005>
- Connolly E., Abrahamsson T., Björkstén B. (2005). Safety of D(-)-lactic acid producing bacteria in the human infant. *Journal of Pediatric Gastroenterology and Nutrition*, 41(4), 489–492. <https://doi.org/10.1097/01.mpg.0000176179.81638.45>
- De Weerth C., Fuentes S., Puylaert P., de Vos W. M. (2013). Intestinal microbiota of infants with colic: Development and specific signatures. *Pediatrics*, 131(2), e550–e558. <https://doi.org/10.1542/peds.2012-1449>
- Dryl R., Szajewska H. (2018). Probiotics for management of infantile colic: A systematic review of randomized controlled trials. *Archives of Medical Science*, 14(5), 1137–1143. <https://doi.org/10.5114/aoms.2017.66055>
- Dubois N. E., Gregory K. E. (2016). Characterizing the intestinal microbiome in infantile colic: Findings based on an integrative review of the literature. *Biological Research for Nursing*, 18(3), 307–315. <https://doi.org/10.1177/1099800415620840>
- Ebell M. H., Siwek J., Weiss B. D., Woolf S. H., Susman J., Ewigman B., Bowman M. (2004). Strength of recommendation taxonomy (SORT): A patient-centered approach to grading evidence in the medical Cited Here
- Fatheree N. Y., Liu Y., Taylor C. M., Hoang T. K., Cai C., Rahbar M. H., Hessabi M., Ferris M., McMurtry V., Wong C., Vu T., Dancsak T., Wang T., Gleason W., Bandla V., Navarro F., Tran D. Q., Rhoads J. M. (2017). *Lactobacillus reuteri* for infants with colic: A double-blind, placebo-controlled, randomized

- clinical trial. *The Journal of Pediatrics*, 191, 170.e2–178.e2. <https://doi.org/10.1016/j.jpeds.2017.07.036>
- Gerasimov S., Gantzel J., Dementieva N., Schevchenko O., Tsitsura O., Guta N., Bobyk V., Kaprus V. (2018). Role of *Lactobacillus rhamnosus* (FloraActive™) 19070-2 and *Lactobacillus reuteri* (FloraActive™) 12246 in infant colic: A randomized dietary study. *Nutrients*, 10(12), 1975. <https://doi.org/10.3390/nu10121975>
- Giglione E., Prodam F., Bellone S., Monticone S., Beux S., Marolda A., Pagani A., Di Gioia D., Del Piano M., Mogna G., Bona G. (2016). The association of *Bifidobacterium breve* BR03 and B632 is effective to prevent colics in bottle-fed infants: A pilot, controlled, randomized, and double-blind study. *Journal of Clinical Gastroenterology*, 50(Suppl. 2), S164–S167. <https://doi.org/10.1097/mcg.0000000000000693>
- Gutiérrez-Castrellón P., Indrio F., Bolio-Galvis A., Jiménez-Gutiérrez C., Jimenez-Escobar I., López-Velázquez G. (2017). Efficacy of *Lactobacillus reuteri* DSM 17938 for infantile colic: Systematic review with network meta-analysis. *Medicine*, 96(51), e9375. <https://doi.org/10.1097/MD.00000000000009375>
- Hanson L., VandeVusse L. (2013). The microbiology and immunology of normal physiologic birth: A plea for the nature of mother. *Journal of Perinatal and Neonatal Nursing*, 27(4), 278–280. <https://doi.org/10.1097/JPN.0b013e3182a9c996>
- Human Microbiome Project Consortium. (2012). A framework for human microbiome research. *Nature*, 486(7402), 215–221. <https://doi.org/10.1038/nature11209>
- Iebba V., Totino V., Gagliardi A., Santangelo F., Cacciotti F., Trancassini M., Mancini C., Cicerone C., Corazziari E., Pantanella F., Schippa S. (2016). Eubiosis and dysbiosis: The two sides of the microbiota. *The New Microbiologica*, 39(1), 1–12.
- Lightdale J. R., Gremse D. A.; and Section on Gastroenterology, Hepatology, and Nutrition. (2013). Gastroesophageal reflux: Management guidance for the pediatrician. *Pediatrics*, 131(5), e1684–e1695. <https://doi.org/10.1542/peds.2013-0421>
- Loscalzo S., Brower K., Del Vecchio M. (2019). Case 3: Persistent fussiness in a 2-month-old girl. *Pediatrics in Review*, 40(11), 596–598. <https://doi.org/10.1542/pir.2017-0041>
- Martinelli M., Ummano D., Giugliano F. P., Sciorio E., Tortora C., Bruzzese D., De Giovanni D., Rutigliano I., Valenti S., Romano C., Campanozzi A., Miele E., Staiano A. (2017). Efficacy of a standardized extract of *Matricariae chamomilla* L., *Melissa officinalis* L. and tyndallized *Lactobacillus acidophilus* (HA122) in infantile colic: An open randomized controlled trial. *Neurogastroenterology and Motility: The Official Journal of the European Gastrointestinal Motility Society*, 29(12), 1–8. <https://doi.org/10.1111/nmo.13145>
- Mi G. L., Zhao L., Qiao D. D., Kang W. Q., Tang M. Q., Xu J. K. (2015). Effectiveness of *Lactobacillus reuteri* in infantile colic and colicky induced maternal depression: A prospective single blind randomized trial. *Antonie Van Leeuwenhoek*, 107(6), 1547–1553. <https://doi.org/10.1007/s10482-015-0448-9>
- Nelson D. (2018). *Mutualism, Commensalism, Parasitism: Types of Symbiosis With Examples*. Science Trends LLC. Retrieved August 24, 2020, from <https://sciencetrends.com/comparing-examples-mutualism-commensalism-parasitism-symbiosis/>
- Nocerino R., De Filippis F., Cecere G., Marino A., Micillo M., Di Scala C., de Caro C., Calignano A., Bruno C., Paparo L., Iannicelli A. M., Cosenza L., Maddalena Y., Della Gatta G., Coppola S., Carucci L., Ercolini D., Canani R. B. (2020). The therapeutic efficacy of *Bifidobacterium animalis* subsp. *Lactis* BB-12® in infant colic: A randomised, double blind, placebo-controlled trial. *Alimentary Pharmacology & Therapeutics*, 51(1), 110–120. <https://doi.org/10.1111/apt.15561>
- Pärty A., Lehtonen L., Kalliomaki M., Salminen S., Isolauri E. (2015). Probiotic *Lactobacillus rhamnosus* GG therapy and microbiological programming in infantile colic: A randomized, controlled trial. *Pediatric Research*, 78(4), 470–475. <https://doi.org/10.1038/pr.2015.127>
- Perrine C. G., Sharma A. J., Jefferds M. E. D., Serdula M. K., Scanlon K. S. (2010). Adherence to Vitamin D recommendations among US infants. *Pediatrics*, 125(4), 627–632. <https://doi.org/10.1542/peds.2009-2571>

- Savino F., Ceratto S., Poggi E., Cartosio M. E., Cordero di Montezemolo L., Giannattasio A. (2015). Preventive effects of oral probiotic on infantile colic: A prospective, randomised, blinded, controlled trial using *Lactobacillus reuteri* DSM 17938. *Beneficial Microbes*, 6(3), 245–251. <https://doi.org/10.3920/BM2014.0090>
- Savino F., Garro M., Montanari P., Galliano I., Bergallo M. (2018). Crying time and RORy/FOXP3 expression in *Lactobacillus reuteri* DSM17938-treated infants with colic: A randomized trial. *The Journal of Pediatrics*, 192, 171.e1–177.e1. <https://doi.org/10.1016/j.jpeds.2017.08.062>
- Shornikova A. V., Casas I. A., Isolauri E., Mykkänen H., Vesikari T. (1997). *Lactobacillus reuteri* as a therapeutic agent in acute diarrhea in young children. *Journal of Pediatric Gastroenterology & Nutrition*, 24(4), 399–404. <https://doi.org/10.1097/00005176-199704000-00008>
- Stiemsma L. T., Michels K. B. (2018). The role of the microbiome in the developmental origins of health and disease. *Pediatrics*, 141(4), e20172437. <https://doi.org/10.1542/peds.2017-2437>
- Sung V., D'Amico F., Cabana M. D., Chau K., Koren G., Savino F., Szajewska H., Deshpande G., Dupont C., Indrio F., Mentula S., Partty A., Tancredi D. (2018). *Lactobacillus reuteri* to treat infant colic: A meta-Cited Here
- Tatari M., Charati J., Karami H., Rouhanizadeh H. (2017). Effect of probiotics on infantile colic using the quadratic inference functions. *Iranian Journal of Neonatology*, 8(3), 66–71. <https://doi.org/10.22038/ijn.2017.19901.1225>
- The NNT Group, 2010-2020. (n.d.). *The NNT, Explained*. Retrieved August 24, 2020, from <https://www.thennt.com/>
- Thomas D. W., Greer F. R.; Committee on Nutrition; Section on Gastroenterology, Hepatology, and Nutrition. (2010). Probiotics and prebiotics in pediatrics. *Pediatrics*, 126(6), 1217–1231. <https://doi.org/10.1542/peds.2010-2548>
- Tyler A. D., Smith M. I., Silverberg M. S. (2014). Analyzing the human microbiome: A “how to” guide for physicians. *The American Journal of Gastroenterology*, 109(7), 983–993. <https://doi.org/10.1038/ajg.2014.73>
- Wessel M. A., Cobb J. C., Jackson E. B., Harris G. S. Jr., Detwiler A. C. (1954). Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics*, 14(5), 421–435.
- Wolke D., Bilgin A., Samara M. (2017). Systematic review and meta-analysis: Fussing and crying durations and prevalence of colic in infants. *The Journal of Pediatrics*, 185, 55.e4–61.e4 <https://doi.org/10.1016/j.jpeds.2017.02.020>
- Xu M., Wang J., Wang N., Sun F., Wang L., Liu X. H. (2015). The efficacy and safety of the probiotic bacterium *Lactobacillus reuteri* DSM 17938 for infantile colic: A meta-analysis of randomized controlled trials. *PLOS ONE*, 10(10), e0141445. <https://doi.org/10.1371/journal.pone.0141445>
- Zoham M., Zafar F., Malekiantaghi A., Ettehadi R., Jazayeri S., Eftekhari K. (2019). Evaluation of the efficacy of probiotics in the treatment of infantile colic: A randomized, double blind; placebo controlled trial. *Acta Medica Iranica*, 57(7), 405–411.