

Effectiveness of probiotics for the treatment of infantile colic

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Background

Infantile colic is one of the most common health issues that can occur during an infant's first months of life, affecting approximately 20% of all infants. The aetiology of infantile colic is not well understood; however, studies have suggested that changes in the intestinal microbiota can lead to symptoms of infantile colic. For this reason, different strains of probiotics have been studied to help understand their effectiveness in the treatment of infantile colic.

Objective

The aim of this evidence-based review is to summarise the evidence of the effectiveness of probiotics in the treatment of infantile colic.

Discussion

Several strains of probiotics have been studied, with some presenting positive results for reducing the symptoms of infantile colic in groups with specific characteristics. However, more studies are required to evaluate efficacy and effectiveness of probiotics in different degrees of severity and in larger and more heterogeneous samples.

INFANTILE COLIC is a benign, self-limiting condition and is a common problem during early childhood, affecting approximately 20% of all infants worldwide.¹⁻¹⁴ Symptoms peak around the sixth week of age, with symptoms ceasing naturally after 4-6 months of age.^{2,4,6-10,12,13} According to Rome IV criteria, the diagnosis of infantile colic requires all of the following: infant under five months of age when the symptoms start and stop; periods of recurrent and/or prolonged crying, agitation and irritability reported by caregivers, which occur without any obvious cause and cannot be prevented or resolved by caregivers; and absence of infantile failure to thrive, fever or illness.^{2,4-6,9,12,13} Despite infantile colic being a benign and self-limiting condition, it is important for the physician to be aware of potential warning signs that could indicate a pathological nature to the clinical presentation, such as fever, prostration, vomiting, diarrhoea and suboptimal growth velocity rate.²

Several aetiologies have been proposed: psychosocial causes (caregiver anxiety, insufficient caregiver-child relationship, or child of difficult temperament), immaturity of the nervous and digestive systems, changes in gut microbiota, and inflammation of the gastrointestinal system. The possibility that infantile

colic occurs because of changes in gut microbiota leads to curiosity about the efficacy of probiotics.^{1,2,4-6,8-12,14,15}

The inability to calm a child's cry can be stressful for a caregiver who believes they are failing to provide adequate care, resulting in frustration, depression, deterioration or postponement of the establishment of the caregiver-child relationship and, in the worst-case scenario, child abuse. Caregivers of infants with colic often turn to healthcare professionals for help. When not adequately helped or enlightened, they may actively pursue alternative methods, most of them lacking scientific evidence and potentially unsafe. As an approach to colic, it is important that the general practitioner tries to relieve symptoms to reduce the impact on the family dynamics and the future relationship of the caregiver or parents with the child.^{1,2,4,6-9,13,14}

Intestinal microbiota

It is suggested that intestinal colonisation begins in utero.¹⁶ The initial intestinal microbiota is composed of facultative anaerobes such as *Staphylococcus* spp., *Enterobacteriaceae* spp. and *Streptococcus* spp. Several individual factors are known to influence the intestinal microbiota, particularly the type of delivery and

the type of feeding (Table 1). Changes in the intestinal microbiota can lead to the appearance of intestinal symptoms (abdominal pain, bloating and flatulence).^{2-5,8,10-12,14} Studies have reported that children with colic have higher levels of proteobacteria (*Escherichia coli*) and lower levels of *Bifidobacterium* spp. and *Lactobacillus* spp. when compared with healthy infants.^{3,5,6,10,11,15,17,18}

Probiotics

Probiotics are defined as microorganisms that have scientific evidence of safety and efficacy.¹⁶ *Lactobacillus reuteri* DSM 17938 is the most studied probiotic strain for infantile colic, followed by other strains of *Lactobacillus* spp. and strains of *Bifidobacterium* spp. All the probiotics strains studied for infantile colic were safe and well tolerated in healthy infants.¹⁸

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Materials and methods

Pubmed, UpToDate and Cochrane Library were searched in August 2021 for articles published during the past decade regarding the treatment of infantile colic with probiotics applying the MESH terms ‘infantile colic’, ‘infant colic’ and ‘probiotics’. Included in this review were original studies, narrative reviews and systematic reviews written in English. Studies were excluded if they focused on infants over six months of age or infants with a diagnosis other than infantile colic (Figure 1). To better assess the evidence levels and attribution of recommendation strengths, the strength of recommendation taxonomy (SORT) scale was used.

Results

Lactobacillus spp.

The evidence found on *Lactobacillus* spp. leads to the belief that a low intestinal concentration of *Lactobacillus* spp. has an important role in the pathophysiology of infantile colic. *L. reuteri* DSM 17938 is the most studied probiotic for infantile colic and is supported by the strongest evidence in the treatment of infantile colic and reduction of its symptoms (decrease in crying time and fussing).^{1-5,11,12}

Moreover, *L. reuteri* DSM 17938 reduces pain perception through two pathways: via the transient receptor potential vanilloid 1 channel, influencing potassium-dependent calcium channel activity;^{2,5} and a reduction in capsaicin- and distension-evoked firing of spinal nerve action potentials.⁶ In addition, a reduction in anaerobic Gram-negative bacteria (*Enterobacteriaceae* spp. and

Enterococci spp.) was verified.¹⁶ One study reported the ability of *L. reuteri* to inhibit the growth of glyco-genic forms of gas in the intestine.¹⁴ Some studies observed a reduction of faecal calprotectin (an intestinal marker of inflammation) with *L. reuteri* DSM 17938.^{4,6}

There are several randomised controlled trials (RCTs) purporting to the use of *L. reuteri* DSM 17938 as a treatment for infantile colic (Appendix 1, available online only). These RCTs took place in Australia, China, Canada and Europe (Italy and Poland). On the twenty-first day of treatment, most studies found a reduction of approximately 50% in crying time and fussing in the intervention group when compared with the placebo group. However, the Australian study, which had the largest sample size, did not find a significant difference between

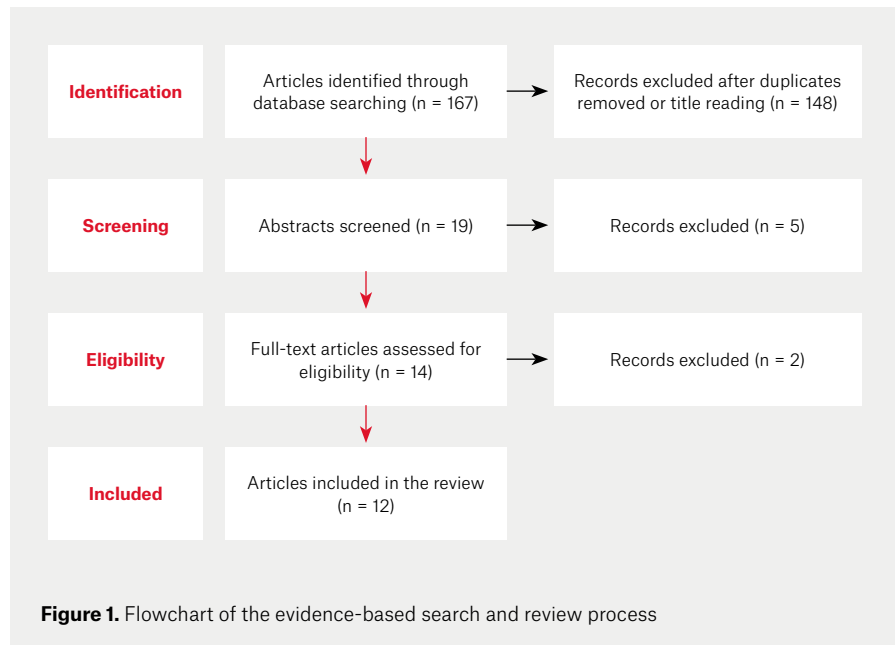


Figure 1. Flowchart of the evidence-based search and review process

Table 1. Individual factors known to influence intestinal microbiota¹⁶

Vaginal delivery	Caesarean	Formula-fed infant	Breastfed infant
Similar to the mother’s vagina (<i>Lactobacillus</i> and <i>Prevotella</i> spp.)	Similar to the mother’s skin (<i>Streptococcus</i> , <i>Corynebacterium</i> and <i>Propionibacterium</i> spp.)	Higher concentration of <i>Escherichia</i> , <i>Veillonella</i> , <i>Enterococcus</i> and <i>Enterobacter</i> spp.	Higher concentration of <i>Lactobacillus</i> and <i>Bifidobacterium</i> spp. (compared with formula-fed)

intervention and placebo. Theories emerged to justify these results, such as it being the first study to also include formula-fed infants, and that intestinal microbiota may differ across and within different countries. A meta-analysis of four high-quality double-blind trials presenting a total sample of 345 infants (174 probiotic/171 placebo) noticed a reduction in daily crying of 25 minutes from baseline by the 21st day in the probiotic group when compared with the placebo group. In addition, infants in the probiotic group were more likely to have treatment success than those in the placebo group, showing greater reduction in crying and/or fussing duration. It is also important to note that the authors of the meta-analysis considered that there was insufficient evidence to draw conclusions in formula-fed infants with colic.^{1-4,6,7,11-13,19,20}

In essence, the treatment of infantile colic with *L. reuteri* DSM 17938 at a dose of 1×10^8 colony-forming units (CFU)/day significantly reduces crying time in infants who are predominantly breastfed and offers a superior treatment in comparison to placebo and other therapies (diet, manipulative interventions, reassurance, massage, herbal treatment, acupuncture and simethicone).^{6,13,14,19,20}

Regarding the *Lactobacillus* family, there were two trials that used the *L. rhamnosus* GG strain, but there was no symptomatic improvement when compared with the placebo group (although parental report of crying suggested that the probiotic intervention was effective).¹⁸ Therefore, it is important to emphasise that the positive results of one strain do not necessarily imply the same effects using other strains.

***Bifidobacterium* spp.**

Breastmilk contains commensal, mutualistic and/or potentially probiotic bacteria for the infant gut, including the *B. breve* strain, which becomes the dominant species in the intestinal microbiota of breastfed infants. *B. breve* colonises the newborn's intestine, protecting it against infections, and plays a major part in the maturation of the immune system.¹⁶

The effect of *B. breve* B632 as a probiotic was verified in vitro by inhibiting

the growth of *Enterobacteriaceae* spp. in a model that simulated the intestinal microbiota of an infant with colic aged two months.¹⁶ Another study observed the percentage of children who cried more than three hours per day, with this value being lower in the group treated with *B. breve* CECT7263 (12% of children) when compared with those treated with *L. fermentum* CECT5716 (21%) and the control group (29%). In this trial, *B. breve* CECT7263 showed a greater efficacy in decreasing the daily crying time in both breastmilk-fed and formula-fed infants. At the same time, the *B. breve* CECT7263 strain was associated with an intestinal anti-inflammatory effect, which could be considered relevant as it suggests that infantile colic can be associated with a systemic low-grade inflammation.¹⁸

Another *Bifidobacterium* strain (*Bifidobacterium animalis* subsp. *lactis* BB-12), when provided alone, reduced the daily crying mean value in infants with colic.^{8,18}

It should also be noted that there have not been many clinical trials performed evaluating the effectiveness of the use of *Bifidobacterium* spp. in infantile colic.

Mixture of probiotics

One study combined *L. rhamnosus* GG with another strain and found that this mixture had no effect on infantile colic symptoms. Conversely, a symbiotic product containing *L. rhamnosus*, *L. reuteri* and *B. infantis* probiotics and fructo-oligosaccharide showed efficacy on the seventh day of treatment.¹⁴

The aim of most of the studies was to understand the effect of isolated strains on the treatment of infantile colic. The effects of mixing different strains of probiotics could not be predicted from the results of using a single strain.

Guidelines

There are several guidelines on the treatment and management of infantile colic that recommend supplementation with *L. reuteri* DSM17938 in exclusively breastfed infants, such as the Northern America and Irish guidelines.¹³ In contrast, in the UK guideline and the clinical practice guideline from Royal Children's

Hospital, Melbourne, it is noted that there is limited evidence to support generalised probiotic use, with only *L. reuteri* DSM17938 having evidence of efficacy in exclusively breastfed infants.^{13,21}

Conclusion

Infantile colic is distressing to parents whose infant is inconsolable during their crying episodes. The physician's role is to exclude a pathological cause for the complaints, offer evidence-based treatment and advice, give support to the family, and assure the parents that their child is healthy. The evidence needed to support the use of probiotics for infantile colic is limited and still emerging. *L. reuteri* DSM 17938 offers positive results in exclusively breastfed infants, and *B. breve* CECT7263 has shown efficacy in both breastfed and formula-fed infants. Of note, there have been no reports of adverse effects in all the trials performed thus far. More studies with larger samples and different variables (population from different countries and different feeding types) are required to obtain a better understanding and greater evidence of when and how probiotics can be used in the treatment of infantile colic.

Key points

- There is a growing belief in the scientific community that probiotics could be a safe and effective treatment for infantile colic.
- Several studies have concluded that *L. reuteri* DSM17938 was effective in exclusively breastfed infants with colic.
- There was insufficient evidence to make conclusions of the effectiveness of probiotics in formula-fed infants with colic.
- More studies with larger samples and less bias are needed.

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