

New treatments for infant colic

Francesco Savino and Valentina Tarasco

Department of Pediatrics, Regina Margherita Children Hospital, University of Turin, Turin, Italy

Correspondence to Francesco Savino, MD, PhD, Department of Pediatrics, 'Regina Margherita' Children Hospital, P.zza Polonia, 94 10126 Turin, Italy
Tel: +39 0113135257; fax: +39 011677082;
e-mail: francesco.savino@unito.it

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Purpose of review

Infantile colic is a common problem within the first 3 months of life and causes considerable distress for parents and paediatricians. Despite 40 years of research, its pathogenesis is incompletely understood and treatment remains an open issue. This review will describe recent studies that have examined different kinds of interventions.

Recent findings

Important advances in understanding the aetiopathogenesis of infantile colic have been recently proposed and opened new perspectives in its management.

The composition of intestinal microbiota, specially an inadequate amount of lactobacilli and an increased concentration of coliforms, might influence the pathogenesis of infantile colic. The benefit of supplementation with *Lactobacillus reuteri* has been recently reported and experimental data showed the effect of probiotics may be related to the influence on gut motility and pain perception.

Summary

Infantile colic is a clinical entity with a wide range of clinical presentations and outcome. Firstly, paediatricians have to exclude other underlying diseases with a medical examination and prevent feeding disorders. Then, considering the favourable clinical course of the disturbance, well tolerated strategies should be adopted. The findings highlighted in this review may promote the implementation of new researches and treatments to reduce abdominal pain related to infantile colic.

Keywords

dietary intervention, gut microbiota, infantile colic, lactobacilli, management

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Introduction

Infantile colic is a common but poorly understood and often frustrating problem for parents and caregivers and it is frequently a reason for consultations with paediatricians and community nurses [1[•]]. This review discusses different possible interventions for infantile colic under the following subheadings: probiotics, dietary interventions, complementary and alternative medical therapies, behavioural interventions, naturopathic interventions and pharmacological treatments.

Infantile colic

Infantile colic refers to a widespread clinical condition consisting of inconsolable crying, fussing and irritability in an otherwise healthy newborn child during the first 3 months of life. Colicky infants typically present excessive and persistent crying that tends to occur in the evening and usually increases at 6 weeks of age, with drawing up of the legs, tension of the body, flushing of the face and meteorism. The diagnosis is clinical and the classical definition is based on the rule of three, that is un-

explained episodes of paroxysmal crying for more than 3 h/day for 3 days/week for at least 3 weeks [2]. The condition shows a wide range of clinical manifestations and can be graded as mild, moderate or severe, but there is no consensus for this classification. Infants' expression of discomfort by crying can be due to a variety of reasons ranging from benign to life-threatening [1[•]]. Thus, all colicky infants should have a complete medical assessment in order to exclude underlying specific medical conditions that require investigation and treatment. The natural history of infantile colic is believed to be favourable and symptoms generally improve by the age of 3 months. Considering these aspects, hospital admission for these patients is unnecessary and detrimental and should not be encouraged [3]. Prevalence ranges widely from 3 to 40% [4], whilst fewer than 5% of distressed infants have identifiable medical explanations for their crying [5].

Over the years, many studies have been conducted to determine the cause of this condition, even though its self-limiting nature has precluded the use of invasive investigations. In fact, although the term 'colic' implies a

gastrointestinal disease, the aetiopathogenesis remains elusive and it is most likely multifactorial [6]. Gupta [7] suggested roles for both behavioural factors (psychological and social) and biological components (food hypersensitivity/allergy and gut dysmotility), assuming that certain infants are predisposed to visceral hypersensitivity and hyperalgesia in the first weeks of life. In particular, it has been observed that a subset of infants with severe colicky symptoms suffer from cow's milk allergy and in these patients dietetic treatment should be the first therapeutic approach [8].

Recently, data supporting the concept of an aberrant gut microbiota in infants suffering from colic have been presented, suggesting its influence on gut motor function and gas production [9[•]] and emphasizing the possible inflammatory origin of the condition [10[•]]. Other recent hypotheses, such as hormone alterations [11] and maternal smoking [12], still need confirmation. Considering the lack of a unifying theory in the pathogenesis of infantile colic, a graded therapeutic approach is appropriate.

Probiotics

Among the organic hypotheses, the role of a peculiar intestinal lactobacilli and coliform colonization pattern has been suggested and proposed in the aetiopathogenesis of infantile colic [9[•],10[•],13,14]. A recent randomized study examined the theory that modulating the intestinal microflora of colicky infants by administering a probiotic would provide health advantages. Ninety breastfed colicky infants were randomly assigned to receive either the probiotic *Lactobacillus reuteri* ATCC 55730 or simethicone each day for 28 days: *L. reuteri* reduced crying time related to colic behaviour within 7 days of treatment. Further, the response rate (patients were defined as responders if they experienced a decrease in the daily average crying time of 50%) for the treatment with the probiotic *L. reuteri* was 95%, compared with only 7% of infants on standard therapy with simethicone [15]. More recently, a double-blind, randomized, placebo-controlled trial confirmed the efficacy of the probiotic *L. reuteri* DSM 17938 (the daughter strain of *L. reuteri* ATCC 55730) in improving colic symptoms in early breastfed infants and showed that this effect may be related to induced changes in gut microbiota, particularly *Escherichia coli* [16[•]]. These findings provide important insights into the role of an aberrant bacterial flora in the pathogenesis of infantile colic and the potential efficacy of the probiotic supplementation and led to a discussion on therapeutic approach [17].

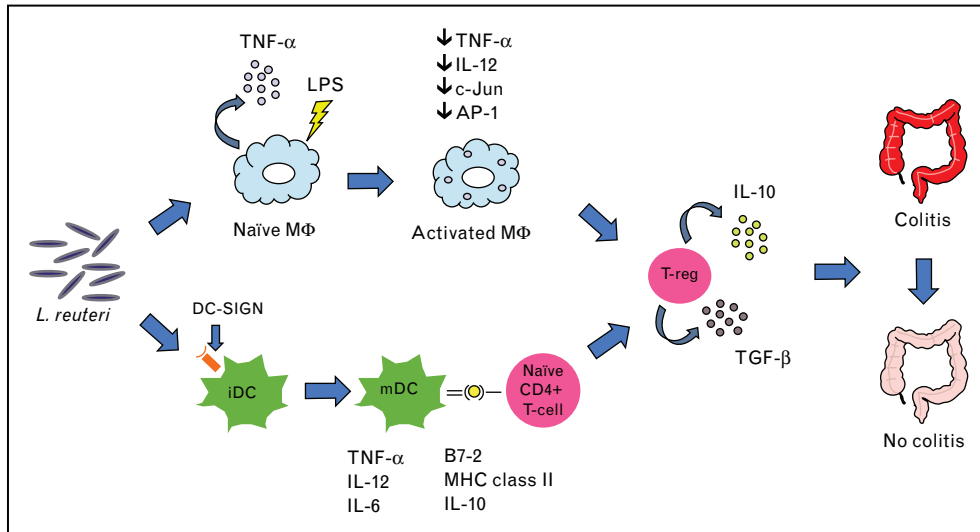
New investigational models

Experimental studies suggest a possible mechanism of action of *L. reuteri* through improvement in gut motility

and function and direct effects on visceral pain. Kunze *et al.* [18^{••}] demonstrate that *L. reuteri* acts on colon motility, targeting ion channels in enteric sensory nerves. More recently, Wang *et al.* [19[•]] suggested that *L. reuteri* ingestion enhances tonic inhibition of rat colon contractile activity by acting via the IKCa channel current in myenteric AH cells. Modulation of motility via AH cell excitability could be a pathway through which probiotics influence extrinsic sensory neurons and thus central nervous system activity [19[•]]. Ma *et al.* [20^{••}] evaluated effects on pain and observed that *L. reuteri* ingestion prevents hyperexcitability of colonic dorsal root ganglion (DRG) somas induced by noxious stimuli. Finally, effects of *L. reuteri* on immune system have been documented, showing a suppression of pro-inflammatory cytokines in macrophages, monocytes, and dendritic cells and a promotion of regulatory T cells producing interleukin (IL)-10 and tumour growth factor (TGF)- β (Fig. 1). The modulation of immune responses is likely to underlie the ability of *L. reuteri* to reduce intestinal inflammation in several murine colitis models [21^{••}].

Dietary intervention

The treatment of infantile colic with dietary modifications has been proposed by many authors supporting the possible allergic origin of the condition: about 25% of infants with moderate or severe symptoms have cow's milk-dependent colic that improves after a few days of a hypoallergenic diet [22]. In bottle-fed babies, extensively hydrolysed formulas based on casein or whey have been widely demonstrated to be effective in the treatment of colic [23–26]. In these cases, family should be informed about the increased cost of these formulas, their poor palatability and the efficacy only in infants sensitive to intact protein. Formerly, the use of soy formula milk has also been suggested, but recently the ESPGHAN Committee on Nutrition assessed that there is no evidence to support its use for managing colic and soy protein-based infant formula should not be used in infants with food allergy during the first 6 months of life [27]. In our point of view, in accordance with other authors, exclusive hypoallergenic formulas should only be reserved for children with severe infantile colic or additional atopic symptoms (eczema, wheezing, allergic rhinitis, and gastroesophageal reflux) [7,28^{••}]. On the contrary, a prospective controlled trial randomized 275 infants to receive a new formula containing partially hydrolysed whey proteins, low amounts of lactose, prebiotic oligosaccharides, and a high beta-palmitic acid content. The study formula was more effective than a standard formula and simethicone, and could represent a useful baseline approach for colic treatment in otherwise healthy infants [29]. More recently, a double-blind, placebo-controlled trial showed that an alpha-lactalbumin-enriched and probiotic-supplemented formula guaranteed adequate

Figure 1 Summary of the immune effects provided by *Lactobacillus reuteri* in the gut

Effects of *L. reuteri* on immune cells that contribute to tolerance in the gut. *L. reuteri* suppresses the production of pro-inflammatory cytokines and promotes the development of regulatory T cells. TNF- α , tumour necrosis factor α ; IL-12, cytokine interleukin 12; c-Jun is the name of the protein product of the c-jun gene; AP-1, antigen-presenting cells 1; TGF- β , tumour growth factor β ; IL-6, cytokine interleukin 6; B7-2, B-lymphocyte activation antigen B7-2; MHC class II, major histocompatibility complex class II molecules; IL-10, cytokine interleukin 10; MDC, mature dendritic cell; iDC, immature dendritic cell; DC-SIGN, dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin; activated M Φ , activated macrophages; naïve M Φ , naïve macrophages; LPS, lipopolysaccharides; T-reg, regulatory T cells; *L. reuteri*, *Lactobacillus reuteri*. N.B. This figure has been previously published [21**]. We obtained the artwork from the authors.

weight and length gains to colicky infants and seemed to provide good gastrointestinal tolerance; however, no differences were found in crying duration compared with control formula [30*].

For colicky breastfed infants, a monitored (with appropriate intake of essential vitamins and minerals) low allergen maternal diet with exclusion of cow's milk, eggs, peanuts, tree nuts, wheat, soy, and fish has been associated with a reduction in distressed behaviour [31]. In our opinion a period of at least 2 weeks is necessary to check the effectiveness of maternal diet. Whereas a brief interruption of breastfeeding and a temporary substitution with an amino-acid-based formula has been proposed by Estep and Kulczycki [32], this intervention could have negative effects on maternal–infant interaction and should be considered a last resort for selected severely colicky infants who have not responded to more conventional therapies [23,24,33].

Complementary and alternative medical therapies

Since there is no widely accepted conventional treatment for colic, many families turn to complementary and alternative medical interventions, such as manipulative therapy and homeopathic preparations, to provide relief for their infants.

Manipulative therapy

Conventional therapies often failed to solve colicky symptoms. Therefore, a significant proportion of parents referred to chiropractors seeking medical help [34]. A number of systematic reviews and randomized trials published in recent years focused on this kind of intervention for infantile colic [35**,36]. It seems that chiropractic treatment may offer short-term relief, but it is unclear if any long-term benefits were obtained. A recent study showed that late effects of colic are fewer in children who had been treated with chiropractic care than controls [37*].

The controversial nature of these interventions, their popularity among caregivers and the presence of some very weak supportive evidence means that more evidence is needed [38*]. Thus, even if remedies of proven safety and effectiveness are lacking, chiropractic ones should not be recommended and physicians should discourage families from treating infantile colic with spinal manipulation. The majority of chiropractic claims are not supported by sound evidence [39*].

Homeopathic preparations

In recent years, many families turn to homeopathic medications to relieve colic symptoms, considering them nontoxic because of the very low concentrations of active agents. In a retrospective case–control study, Aviner *et al.* [40**] described an association between a homeopathic

remedy (Gali-col Baby - Unida SA, Brussels, Belgium) administered for infantile colic and apparent life-threatening event (ALTE). The efficacy and safety of these preparations should be verified before administration in infancy to ensure low risk of adverse effects.

Behavioural interventions

Healthcare intervention represents the first approach to support parents whose infants cry excessively. The paediatrician has to provide reassurance and offer general advice about the condition, emphasizing its favourable and self-limiting nature. Parents' responsiveness should be stimulated but with recommendations not to exhaust themselves and to leave their baby with others when necessary [23].

Behavioural remedies aimed at decreasing crying in colicky infants have produced different results. Current data do not support supplemental carrying, car ride stimulators and other behavioural interventions as effective interventions [24,41^{*}]. Many studies suggest 'infant massage', although, typically, it does not significantly improve symptoms. A recent *Cochrane Database Systematic Review* acknowledges that 'there is some evidence of benefits on mother–infant interaction, sleeping and crying, and on hormones influencing stress levels. Further research is needed, however, before it will be possible to recommend universal provision' [42]. A more recent study describes an approach based on regularity and uniformity in daily infant care and reduction of external stimuli accompanied by instructions to swaddle during sleep. The goal is to help the infants to establish a stable sleep–wake rhythm that can reduce parental distress, improve family health and quality of interaction between parents and child [43].

Concerning psychological problems, dissatisfaction with the family daily functioning [44], development of high maternal depression scores [45^{*}] and persistence of behavioural problems later in childhood have been described [46]. Attention to parent–child interaction at an early age is important and family supportive interventions represent the first step in treating infantile colic, but there are many complementary strategies that may provide additional relief.

Naturopathic interventions

Naturopathic remedies, such as hypertonic glucose solution and herbal formulations, may also be considered for the treatment of infantile colic.

Hypertonic glucose solution

The analgesic effect of sucrose solution has been evaluated in colicky infants [23,47]. A recent *Cochrane Data-*

base Systematic Review investigated the effectiveness of sucrose for the treatment of pain other than colic. The reviewers suggested that sucrose is well tolerated and effective for reducing procedural pain from single painful events in preterm and term infants, even though the optimal dose of sucrose has not been established yet [48^{**}]. More recently, 30% glucose solution has been found to be an alternative therapy for infantile colic as it is effective, easily achievable and well tolerated [49]. Arikian *et al.* [25] demonstrated that varied interventions such as sucrose solution, administration of massage, herbal tea and hydrolysed formula could be used by nurses in neonatal and primary healthcare settings as an aid for treatment of infantile colic. However, further research is needed before suggesting this remedy in clinical practice.

Herbal formulations

Few studies have been conducted on this kind of intervention. Weizman *et al.* [50] showed that herbal teas containing mixtures of chamomile, vervain, licorice, fennel and lemon balm administered at least three times a day decreased crying time related to colic behaviour. More recently, a randomized, double-blind, placebo-controlled trial observed the effectiveness of a phytotherapeutic agent with standardized concentration of *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* in breastfed colicky infants administered twice a day at a standard dosage [51]. In animal models, it has been tested by oral administration of the herbal formulation showing a dose-dependently delayed upper gastrointestinal transit [52].

However, the administration of herbal products in early infancy in infants with infantile colic raises some concerns about the potential nutritional effects (if prolonged treatment leads to a decreased intake of milk), the lacking standardization of dosage of formulations containing herbs and herbal oil and the possible content of sugar and alcohol; so parents have to use them with care and precise advice.

Pharmacological treatments

Dicyclomine, an anticholinergic drug, is more effective than placebo in colic, but its use is contraindicated in infants below 6 months old because of the severe adverse effects reported in literature (i.e. breathing difficulties and seizures) [24]. A randomized controlled trial re-evaluated the use of an alternative anticholinergic agent, cimetropium bromide, in reducing crying only during colic episodes in breastfed infants [53]. It has been observed that its use is well tolerated in infancy when used at the tested dosage. Existing data do not demonstrate conclusive benefit of simethicone, a defoaming agent, on infantile crying but only in reducing meteorism [24].

Antiacid therapy

There is no evidence to support the empiric use of acid suppression for the treatment of irritable infants, because reflux is not a common cause of unexplained crying, irritability, or distressed behaviour in otherwise healthy infants [54]. Infantile colic must be clearly distinguished from gastroesophageal reflux disease (GERD), because only the latter should be treated with antireflux medication. We are alarmed by the high percentage of infants who receive proton-pump inhibitors (PPIs) in infancy [55]. During the last years concerns have been raised regarding their excessive use in benign conditions, such as gastroesophageal reflux disease, and the risk of adverse events related to long-term use [56^{*}]. For these reasons PPI cannot be suggested to treat crying time related to colic.

Conclusion

Infantile colic is a common clinical entity, which causes abdominal pain for infants and parental discomfort worldwide. Current literature suggests that infantile colic has several independent causes: behavioural factors, food hypersensitivity or allergy, immaturity of gut function and dysmotility. More recently hormone alterations and gut microflora dismicrobism have been observed as triggers of infantile colic and the beneficial effects of a lactobacilli supplementation have been reported. Initial clinical examination for a fussy crying infant by the paediatrician, with the exclusion of other underlying serious diseases and feeding disorders, is key, after which follow-up with parental assurance that symptoms will fully resolve. In the mean time a well tolerated but, if necessary, multifactorial and graded strategy should be adopted (given below). Ultimately, specific guidelines for infants with colic are needed in the future.

Potential remedies for the management of infantile colic:

- (1) Behavioural interventions: The first step is to provide reassurance and offer general advice, emphasizing the self-limiting nature of the condition.
- (2) Probiotics: *Lactobacillus reuteri* (American Type Culture Collection Strain 55730 and DSM 17938) improves symptoms of infantile colic and was well tolerated in early breastfed infants.
- (3) Dietary intervention:
 - (a) Breast fed infants: A monitored (with appropriate intake of vitamins and minerals) low allergen maternal diet could be suggested. A period of at least 2 weeks is necessary to check the effectiveness of the diet. Dietary intervention in mother to be continued only if effective.
 - (b) Formula-fed infants: First-line approach is represented by formulas based on partially

hydrolysed whey proteins with prebiotic oligosaccharides and probiotics, that have to be recommended for at least 2 weeks.

- (c) Extensively hydrolysed formulas based on casein or whey could be effective in children with severe infantile colic or additional atopic symptoms.
 - (d) The ESPGHAN Committee on Nutrition has recommended that soy protein formula should not be used in infants during the first 6 months of life.
- (4) Complementary and alternative medical therapies: Parents sometimes have recourse to manipulative therapies and homeopathic preparations, but more evidence is needed for these treatments.
 - (5) Naturopathic interventions: Further research is needed before these remedies (hypertonic glucose solution and herbal formulations) can be suggested in clinical practice. Parents have to use herbal products with care and precise advice.
 - (6) Pharmacological treatments:
 - (a) Dicyclomine is contraindicated in infants below 6 months old because of the severe adverse effects.
 - (b) Cimetropium bromide could be useful to reduce crying only during colic episodes in breastfed infants.
 - (c) Available data do not demonstrate conclusive benefit of simethicone on infantile crying but only in reducing meteorism.

References and recommended reading

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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 839–840).

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