

Infantile colic: looking to old data through new eyes

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From the womb to the adult

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Abstract

This paper performs an overview about researches and clinical trials on gut microflora and the use of probiotics, and seeks to define a new picture of current literature in order to propose an evidence-based practice approach for the treatment of infantile colic. Colics are a self-limiting, benign and widespread disturbance in the first three months of life, but provide a great disturbance on family life, also because this condition is frequently undervalued by physicians and available literature doesn't provide univocal indication about management and treatment. Literature reports growing evidences about the effectiveness of dietary approach or supplementation with probiotics. This article tries to evaluate available evidences through GRADE system, in order to underline limitations, inconsistency and publication bias of old clinical trials.

However, this choice could provide multiple and discordant results. According to the growing of new systematic reviews, evaluations about evidences and recommendations in health care are complex, and might show up different results.

Moreover, up to date many different definitions and outcome measures for infantile colic have been proposed in clinical trials: many take in account crying time, but a minor part also consider parental perception.

The effectiveness of complementary and alternative treatments and behavioural interventions needs to be further investigated.

Recently, the possible action of microbiota as a cause of colics and the use of some probiotic strains for the treatment have raised great interest.

It has been also postulated that parent-infant interaction may influence infantile colic, but further researches on educational and psychological intervention are required in order to better clarify this issue, as well as further investigations are needed in order to provide more reliable evidence-based guidelines.

Keywords

Infantile colic, gut microflora, treatment, probiotics, evidence-based medicine, GRADE analysis.

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Introduction

Infantile colic is a typical paediatric disorder worldwide: about one in five infants develop colic in the first three months of life. Although it is considered to be a self-limiting and benign affection, it is a stressful condition for parents, also because it is frequently undervalued by physicians [1, 2].

Wessel was the first to propose a definition of infantile colic as inconsolable crying in a healthy infant younger than three months of age that last at least three hours a day and occur at least three days per week over the course of at least three weeks in a month [3].

A more recent definition has been given by Hyman [4], who defines them as a constant crying during the evening at about the same time each day on at least one week in healthy subjects. Therefore, we can understand that there are no single definition and outcome measures for infantile colic and this could represent a confounding factor when we compare data from different studies [5].

Other associated signs are fussing, flushing, abdominal distension and leg contracture, but these are difficultly measured. In addition, a higher crying pitch, burping, needing to eat, difficulty with passing stools, tight fists, kicking, arching the back

are reported in medical literature. Also a possible association between parent-infant interaction and the appearance of infantile colic has been suggested, but only some recent studies have considered this aspect.

This paper performs an overview about researches and clinical trials on gut microflora and the use of probiotics, and seeks to define a new picture of current literature in order to propose an evidence-based practice approach for the treatment of infantile colic.

Etiopathogenesis

In spite of the high prevalence of the disorder and many recent studies, the cause of the onset of infantile colic remains partly unknown and it is likely to be considered multifactorial. Also the risk factors remain partially indefinite, however, increased maternal age, maternal smoking and firstborn status could be related to the development of infantile colic [6]. A theory hypothesizes that an important factor is the immaturity of infant's nervous or digestive system. Other considered aspects are behavioural issues such as family tension or inadequate interaction between parents and infant, but there is no consensus about these issues. Moreover infantile colic could be related to cow's milk proteins allergy and atopy [6].

Another observed element is the correlation between colic and sleep disorders, but recent findings show that the two conditions frequently occur in different infants [7].

Recently, the role of the gut microbiota has raised an increasing interest and there are some evidences that the intestinal microbiota in colicky infants differs from that of healthy controls. Some studies have suggested that a low amount of *Lactobacilli spp.* and an increased amount of Coliform bacteria, *C. difficile* or *Klebsiella spp.*, in the intestinal microbiota could be a possible cause of gut dysmotility and increasing of gas production [8-10] and a study based on microarray revealed that infants with colic showed a higher microbiota homogeneity and instability compared to control infants in the first weeks of life [11]. Some Authors have also suggested that *Bifidobacterium spp.* and *Lactobacillus spp.* could be useful in protecting against infantile colic [12] (**Tab. 1**).

Finally, in infants affected by colic were found higher levels of ghrelin and motilin, but this observation needs to be further clarified [11]. As a consequence of a not complete comprehension of the causes of colics, a wide spectrum of treatments has been proposed [1, 14, 15].

Table 1. Researches on colicky infants' gut microbiota.

Authors, year	Journal	Type of research	Subjects	Microbiological data
Lehtonen L. et al., 1994	<i>Journal of Pediatric Gastroenterology Nutrition</i>	Culture Chromatography	Colicky: 55 Controls: 49	<i>C. difficile</i>
Savino F. et al., 2004	<i>Acta Paediatrica</i>	Culture	Colicky: 42 Controls: 29	<i>Lactobacillus spp.</i> Anaerobic gram-bacteria
Savino F. et al., 2005	<i>Paediatric Allergy & Immunology</i>	Culture	Colicky: 30 Controls: 26	<i>L. brevis</i> <i>L. lactis</i>
Savino F. et al., 2009	<i>Acta Paediatrica</i>	Culture PCR	Colicky: 41 Controls: 39	<i>E. coli</i>
Savino F. et al., 2010	<i>Pediatrics</i>	FISH	Colicky: 50	<i>E. coli</i> <i>Clostridium B.</i> <i>Lactobacilli spp.</i> <i>Bifidobacteria spp.</i>
Savino F. et al., 2011	<i>BMC Microbiology</i>	PCR with species-specific primers	Colicky: 45 Controls: 42	Coliform bacteria <i>Enterobacteriaceae</i> <i>E. coli</i>
Rhoads JM. et al., 2009	<i>Journal of Pediatrics</i>	DGGE	Colicky: 19 Controls: 17	<i>Klebsiella spp.</i>
Pärty A. et al., 2012	<i>PLoS One</i>	DGGE qPCR FISH PCR-DGGE	Colicky: 89	<i>B. breve</i> <i>Lactobacillus spp.</i>
Roos S. et al., 2013	<i>PLoS One</i>	454-pyrosequencing	Colicky: 29	<i>Proteobacteria</i> <i>Firmicutes</i> <i>Bacteroidetes</i> <i>Actinobacteria</i>
De Weeth C. et al., 2013	<i>Pediatrics</i>	HITChip microarray hybridization	Colicky: 12 Controls: 12	<i>Proteobacteria:</i> <i>Anaerobiospirillum</i> <i>E. aerogenes</i> <i>E. coli</i> <i>Haemophilus</i> <i>K. pneumoniae</i> <i>Pseudomonas spp.</i> <i>Serratia spp.</i> <i>Vibrio spp.</i> <i>Yersinia spp.</i>
Pärty A. et al., 2015	<i>Pediatric Research</i>	Quantitative PCR	Colicky: 30	<i>Bifidobacteria</i> genus <i>B. breve</i>

Diagnosis

The diagnosis is mainly clinical and it is based on anamnesis and physical examination in order to identify signs and symptoms [16]. The main target is to firstly exclude other underlying serious diseases and feeding disorders. The personal and family anamnesis is very important and it must include the evaluation of a possible correlation between infant's behaviour and the episodes of crying, their duration and when they appear during the day. A complete physical examination is essential to evaluate the correct feeding of the infant, the increase in weight, the presence unusual stool or fever. It is necessary to look for eczema or diarrhoea because they may suggest a common condition such as cow's milk proteins allergy. Also a very common disease such as gastro-oesophageal reflux needs to

be excluded. In a exhaustive differential diagnosis we must always to consider an uncommon but life-threatening condition such as bowel intussusception. Biochemical and radiological exams are not indicated if there is a negative physical examination.

Treatments

Even though investigations on treatments for infantile colic are proceeding (e.g. reassurance, education, dietary, pharmacological, etc.), the effectiveness of many of these need to be further confirmed.

Recently, the research for a new therapeutic approach to infantile colic has been challenged by many Authors and new treatments have been investigated. Up to now, this type of clinical trial also evaluates efficacy, cost and parental life quality.

Dietary advices based on the type of nutrition:

- breast-fed infants: an adequate intake of vitamins and minerals and the avoidance of food allergens, cow's milk and dairy products is commonly recommended. A period of at least two weeks is necessary in order to verify the effectiveness of dietary intervention, that has to be continued only if effective [1, 17-19].
- bottle-fed infants: formulas based on partially hydrolysed whey proteins with prebiotic oligosaccharides are commonly used as an effective first approach [20], while the efficacy of other formulas need to be further evaluated [21]. If atopic symptoms are present, the employment of extensively hydrolysed formulas based on casein or whey could be taken in account. However, any change in diet or in therapy should be evaluated by a Paediatrician [22].

Pharmacological treatments: simethicone can be helpful for some infants and it is supposed to decrease the production of gas, but some randomized controlled trials consider it such as a placebo [1, 14]. The employment of cimetropium bromide, an anticholinergic drug, has been reported to be useful in reducing crying during colic episodes in breast-fed infants [23]. In literature there is no evidence that recommend the use of other drugs because of side effects [1]. A new pharmacological agent (Nepadutant) acting on intestinal motility and sensitivity is under investigation with multi-center, multinational, randomized, double-blind, placebo controlled study at phase IIa [24]. A Cochrane Review on pain relieving agents is in progress [25].

Probiotics: this approach is based on the hypothesis that aberrant intestinal microflora could cause gut dysfunction, contributing to the symptoms of infantile colic.

The administration of *L. reuteri* ATCC 55730 or *L. reuteri* DSM 17938 to breastfed infants is well tolerated and improves symptoms of infantile colic compared with simethicone or placebo [24, 27, 28].

Some Authors have speculated that *L. reuteri* could improve the functionality and motility of intestine and seems to have a beneficial effect on visceral pain. This strain may act by inducing changes in the fecal microbiota, for instance reducing *E. coli* colonization [26].

Currently, data on the role of probiotics in colic are growing [29]. Many medical researchers are trying to understand the mechanism by

which probiotic strains antagonize pathogenic gastrointestinal microorganisms or exert other beneficial effects *in vivo* [30]. The use of 454-pyrosequencing analysis has shown an increased value of *Bacteroidetes spp.* in infants responding to probiotics [31]. According to a meta-analysis, *L. reuteri* may be effective as treatment for infantile colic in exclusively breastfed infants, but there is still a lack of evidence to support its employment in formula-fed infants or for the prevention of colics [21]. Recently, a trial by Sung et al. involving a population of breastfed and formula-fed infants showed no efficacy of probiotics in the treatment of infantile colic compared to placebo, but this outcome could be due to the great heterogeneity of the sample [32]. Otherwise, recent studies performed in Canada and China in breastfed infants have shown a significant efficacy of *L. reuteri* compared to placebo [31, 32]. Recently, Savino et al. [35] have reported that the early supplementation of *L. reuteri* DSM 17398 could significantly reduce the administration of pain relieving agents, paediatric consultations and employment of infant formula for infantile colic. Further, early use of oral probiotic seems to preserve gut health by reducing pathogens colonization [36] (**Tab. 2**).

Complementary and alternative therapies: nowadays complementary and alternative therapies have assumed great resonance.

- Herbal supplements: fennel (*Foeniculum vulgare*), chamomile (*Matricariae recutita*) and lemon balm (*Melissa officinalis*) could be effective [37, 38]. However, the administration of these remedies during infancy has raised many concerns about the lack of standard dosages and the nutritional effects (long-term treatment can reduce the intake of milk) In conclusion, these remedies have to be administered with great attention and under medical control.
- Manipulative therapies: Cochrane Database Systematic Reviews and randomized trials published in last years focused on this type of intervention. Chiropractic treatment should give short-term relief (reduction of daily hours of crying compared with no treatment or placebo), but long-term benefits are not demonstrated. Further researches concerning these therapies are needed [39].
- Acupuncture: standardized light stimulation of the acupuncture point LI4 twice a week

Table 2. Clinical trials on probiotics for infantile colic.

Authors, year	Study design	Kind of probiotic	Dosage	Time of treatment	No. of subjects	Settings	Country
Savino F. et al., 2007	RCT	<i>L. reuteri</i> ATCC 5530	10 ⁸ cfu in 5 drops once per day	28 days	90 exclusively breastfed infants	Department of Pediatrics, University of Turin, Children Hospital	Italy
Savino F. et al., 2010	RCT-DB-PC	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu or placebo daily	21 days	46 exclusively breastfed infants (<i>L. reuteri</i> group: 25; placebo group: 21) completed the trial	Department of Pediatrics, University of Turin, Children Hospital	Italy
Szajewska H. et al., 2013	RCT-DB-PC	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu or placebo daily	21 days	80 infants	Family primary care practice in Warsaw	Poland
Sung V. et al., 2014	RCT-DB-PC	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu versus placebo daily	1 month	167 breastfed infants or formula fed infants aged less than 3 month	Royal Children's Hospital	Australia
Chau K. et al., 2015	RCT-DB-PC	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu in 5 drops once per day	28 days	52 infants (28 in the placebo group and 24 in the <i>L. reuteri</i> group)	The Hospital for Sick Children and in Pediatric care practices in Toronto, Ontario, Canada	Canada
Mi G.L. et al., 2015	RCT-PC	<i>L. reuteri</i> DSM 17938	10 ⁸ cfu or placebo daily	21 days	Exclusively breastfed 42 infants	Outpatient clinic of Hospital Children's of Zhengzhou China	China
Partty A. et al., 2015	RCT-DB-PC	<i>L. rhamnosus</i> GG	4.5*10 ⁹ cfu or placebo daily	28 days	30 infants during the first 6 wk of life	Department of Pediatrics, University of Turku and Turku University Hospital	Finland

RCT: randomized clinical trial; DB: double blind; PC: placebo-controlled; cfu: colony forming units.

for 3 weeks has been shown to be effective in reducing the duration and intensity of crying, with no serious reported side effects [40]. However, recently no significant usefulness of acupuncture in the treatment of infantile colic has been reported and the Authors suggest employing it only in clinical trials [41]. More researches are necessary in order to clarify and investigate its employment for the treatment of infantile colic.

- Behavioural interventions: “infant massage” is proposed by many studies but it does not significantly improve symptoms. A recent Cochrane Database Systematic Review reports that “there is some evidence of benefits on mother-infant interaction, sleeping and crying, and on hormones influencing stress levels.

Further research is needed”. A recent study proposes an approach based on regularity in infant’s daily care and feeding, accompanied by instructions to wrap during sleep. The purpose consists in helping the infant in establishing a regular sleep-wake rhythm and consequently reducing parental distress and improving parental life quality [42, 43].

Conclusions

The first approach is to reassure parents highlighting the favourable and self-limiting nature of this condition. The data available in the literature are not yet totally organized in a great exhaustive systematic review. Overall, most of the trials were not adequately sized, did not provide long-term

outcomes, suffered from poor reporting of a number of methodological quality items such as parental quality life and are often founded on low quality evidence-based medicine and are inconsistent with GRADE guidance [44, 45].

Recently, a Cochrane review concerning manipulative treatment has been published [39]. Cochrane reviews concerning the employment of other treatments (probiotics, pain-relieving agents and dietary treatment) are in progress.

Continued efforts toward research and discovery will be essential to increase knowledge concerning the administration of effective and safe treatments.

More research is recommended in order to i) investigate the long-term benefits of treatments (including the different subgroups of subjects, for example, breastfed versus formula fed); ii) identify which psychological factors have the strongest influence on parents experience of infantile colic and which of these factors can be utilized as appropriate outcome measures; iii) to promote more specifically targeted interventions which might have the potential to achieve stronger treatment effects, especially in order to produce meta-analysis based on a GRADE approach [46].

Declaration of interest

The Authors have no conflicts of interest to declare.

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