

VIEWPOINT ARTICLE

Focus on infantile colic

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Abstract

Infantile colic is a widespread clinical condition in the first 3 months of life, which is easily recognized, but incompletely understood and difficult to solve. The available evidence suggests that infantile colic might have several independent causes. The medical hypotheses include food hypersensitivity or allergy, immaturity of gut function and dysmotility, and the behavioural hypotheses include inadequate maternal–infant interaction, anxiety in the mother and difficult infant temperament. Other recent hypotheses, such as hormone alterations and maternal smoking, still need confirmation, whereas the new concept of alterations in the gut microflora, have been reported. A number of interventions, including pharmacological agents, are discussed, but it is probable that infants with colic require a graded strategy.

Conclusion: Considering the favourable clinical course and the wide range of manifestations, a safe approach should be adopted, which is proportional to the intensity of the infantile colic. However, further research and guidelines are still needed.

INTRODUCTION

Infantile colic is a widespread clinical condition in infancy, which is observed in 10–30% of infants (1), in which a healthy infant suffers from paroxysms of excessive, high-pitched, inconsolable crying, frequently accompanied by flushing of the face, meteorism, drawing-up of the legs and the passing of gas. Even though infantile colic is a common disturbance, the aetiology is still not fully understood and the basis of the condition remains elusive. The classical and most often cited definition of infantile colic is based on the rule of threes, that is, periods of crying that last for 3 h or more per day, for 3 or more days per week and for a minimum of 3 weeks. The condition usually resolves spontaneously by the age of 3 months. The crying episodes tend to increase at 6 weeks of age and are most frequent in the late afternoon and evening hours. These characteristics help to differentiate colic from other more severe conditions (Table 1). Infantile colic is often described as mild, moderate or severe, but there are no set definitions for these grades. Further, colic affects infants of all socioeconomic strata in the same way without any evidence of family history, and there are no reported differences in prevalence between either boys and girls, or nursed and formula-fed infants.

Although there have been some recent progresses in understanding infantile colic, there has been little practical change in the clinical approach to these patients, and their condition continues to frustrate the health care provider and to produce parental anxiety and lack of confidence in the infant-caring capability of the parents. Clarification of the aetiopathogenesis and a better understanding of colic are needed to allow a more effective and precise management of the afflicted infant (and his/her exasperated caregiver). This viewpoint article examines the more recent scientific evidence supporting the various proposed organic aetiologies of infantile colic and discusses potential new remedies (Table 2).

LACTOSE INTOLERANCE

In recent decades, lactose intolerance due to a relative lactase deficiency has been identified as a possible causative factor in infant colic. The resulting failure to break down all the lactose in the food allows significant amounts to enter the large bowel, where it becomes a substrate for lactobacilli and bifidobacteria in the colon. Fermentation by these bacteria leads to production of lactic acid and hydrogen. The rapid production of hydrogen in the lower bowel

Table 1 Differential diagnosis between colic and clinical conditions

Common	Infrequent
Feeding disorders	Disaccharidase deficiency
Constipation	Renal pathology, including uretero-pelvic obstruction
Anal fissures	Biliary tree pathology, including stones
Gastro-oesophageal reflux disease	Acute abdomen diseases, including intussusception and volvulus
Infections, including otitis media	Incarcerated hernia
Cow's milk protein allergy	Occult fracture
Urinary tract infection	Neurological abnormalities, including Arnold–Chiari malformation
Rashes, including candidal dermatitis	Ocular foreign body or abrasions or infection
	Maternal drug effect (both illicit and prescription drugs)

Table 2 Infantile colic: aetiopathogenetic features

Lactose intolerance
Dysmotility
Gastro-oesophageal reflux
Gut hormones (motilin, ghrelin)
Gut microflora (<i>Lactobacillus spp.</i>)
Feeding disorders
Food hypersensitivity (cow's milk allergy)
Psychological factors (infant–parent interaction)

distends the colon, sometimes causing pain, whereas the osmotic pressures generated by the lactose and lactic acid in the colon cause an influx of water, leading to further distension of bowel.

In the first period of life, a large number of infants may display partial malabsorption of dietary carbohydrate present in breast milk or formulas and thus a physiological insufficiency of gut enzyme systems may be one reason for the development of colic. Studies measuring hydrogen in the breath of colicky infants have produced inconsistent results, although increases in breath hydrogen levels have been reported. Recently, the hypothesis that colic symptoms could be relieved by reducing the lactose content of the infant's feed has been tested once again in a small double-blind study in which the feed of colicky babies was preincubated with lactase (2). The interesting results were, however, limited by the trial size, which prevented any formal proof of effect. In a similar, more recent study, Kanabar et al. found a significant difference in both crying time and breath hydrogen in those infants who used the lactase-treated feed, supporting the idea that symptoms could be relieved by reducing the lactose content of a lactose-intolerant infant's feed, but infants whose colic is caused by other factors can expect no relief (3).

MOTILITY

Transient dysregulation of the nervous system during development may cause intestinal hypermotility in infants with colic, particularly during the first few weeks of life. Radio-

logical studies performed many years ago stated that most cases of infantile colic could be explained by colonic hyperperistalsis and increased rectal pressure. There may, however, be some bias in these studies.

Predominance of the parasympathetic as well as the sympathetic nervous system has also been investigated. The early literature refers to colic as 'hypertonia of infancy', which was thought to be a consequence of vagotonia. This concept is supported by the documented beneficial effects of drugs with antispasmodic effects, such as dicyclomine hydrochloride (4), and by the relief of high motilin levels in colicky infants (5,6). However, whether dicyclomine exerts its effect via the relief of intestinal spasm by a direct relaxant effect on the colonic smooth muscle or through sedative central nervous system effects, remains unclear. Today, the use of this drug is limited in infants due to its known central effects and the potential to cause respiratory depression (7). Recently, a double-blind, placebo-controlled clinical trial was performed to investigate the effectiveness of another drug, cimetropium bromide (a quaternary ammonium semisynthetic derivative of the belladonna alkaloid scopolamine), in the treatment of infants with colic crisis (8). Thus drug acts through the competitive antagonism of muscarinic receptors of the visceral smooth muscles and a direct myolytic activity. This trial suggested that cimetropium bromide might significantly decrease the duration of crying, but not the number of crises. As far as conventional therapies are concerned, the anticholinergic and antiadrenergic activity of some herbal teas or drugs, such as fennel, lemon balm and camomile, has been also proposed (9). We have already suggested that a phytotherapeutic agent with *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis* improved colic in infants through its antispasmodic and antimetereic activity (10).

The findings of Kirjavainen et al. suggest that an imbalance between the parasympathetic and the sympathetic nervous system is not associated with infantile colic (11).

GASTRO-OESOPHAGEAL REFLUX (GOR)

It is appealing to explore whether there is a cause-effect relationship between GOR and infantile colic, especially in view of the prevalence of GOR during infancy. In my opinion, GOR and infantile colic are two different clinical conditions. The confusion arises when GOR does not show its typical symptoms but is rather only characterized by excessive crying, similar to colicky infants (12). Thus, particular care must be taken in the differential diagnosis of these two conditions.

Few studies have examined the role of gastric emptying and pathological GOR in colicky infants and the conclusions are controversial. The results suggest that, in the absence of regurgitation and vomiting, GOR is not a common cause of infantile irritability, and pathological GOR is only implicated in a small subset of young infants with severe colicky symptoms. Some clinicians suggest a defined antireflux pharmacotherapy in these selected cases (13), but a recent review stresses that a direct causal relationship between acid reflux and infantile colic appears unlikely (14).

GUT HORMONES

The gastrointestinal tract contains a wide variety of hormones involved in the regulation of intestinal motility, and these include vasoactive intestinal peptide (VIP), gastrin, motilin and the newly discovered ghrelin. Lothe et al. (5) found that VIP and gastrin levels were raised in children with other gastrointestinal disorders, but not in infantile colic. Further, formula-fed colicky infants had higher gastrin levels than breastfed ones. They also reported an increased basal motilin concentration in colicky infants. Motilin appears to play an interesting role in the aetiopathogenesis of infantile colic. It has been hypothesized that motilin enhances gastric emptying, which increases small-bowel peristalsis and decreases transit time.

More recently, it has been shown that colicky infants also have higher serum levels of ghrelin compared to their healthy counterparts, even though it is not clear whether the high values observed are a cause or a consequence of infantile colic. Ghrelin is thus thought to be implicated in promoting abnormal hyperperistalsis and increased appetite, typical of colicky patients. It can be considered a mediator between gut and brain (6).

GUT MICROFLORA

Among the organic hypotheses, the role of intestinal microflora in the aetiopathogenesis of infantile colic has been re-proposed recently. In 1994, Lehtonen first suggested that an aberrant gut microbial composition in the first months of life, such as inadequate lactobacilli levels, may affect intestinal fatty acid profiles and could thereby favour the development of infantile colic (15). Indeed, intestinal colonization by lactobacilli may be a prerequisite for normal mucosal immune function.

Lactobacilli are nonpathogenic, anaerobic, Gram-positive bacteria that play an important role in the development of local and systemic immune responses (16), and are thus attractive candidates for exogenous supply to infants. We found not only lower counts of intestinal lactobacilli in colicky infants compared to healthy ones (17), but also that *Lactobacillus brevis* and *L. lactis lactis* might even be involved in the pathogenesis of infantile colic by increasing meteorism and abdominal distension. Our findings led to the hypothesis that differences in the composition of intestinal lactobacilli might influence the aetiopathogenesis of infantile colic (18). An inadequate balance of lactobacilli in colicky infants might underlie immaturity in the gut barrier and lead to aberrant antigen transfer and immune responses, and increased vulnerability to the breakdown of oral tolerance. A recently published study examined the hypothesis that modulating the intestinal microflora of colicky infants by administering a probiotic would alleviate colic symptoms (19). In this prospective study, a cohort of 90 breastfed colicky infants was randomly assigned to treatment with the probiotic *Lactobacillus reuteri* or simethicone. Infants in the *L. reuteri*-treated-group showed significantly reduced crying compared to the simethicone group, supporting the hypothesis that probiotic supplementation could provide health ad-

vantages in colic through intestinal microfloral changes and thereby alter gut motility and/or immune responses. It has been demonstrated that luminal endogenous flora can influence the processes of bacteria-induced innate and adaptive host responses through the activation of toll-like receptors and nucleotide oligomerization domain receptors in intestinal epithelial cells. In experimental models, cytokines can initiate a hyper-reflex response of the enteric neuromusculature through neuro-immune and myo-immune interactions. Inappropriate interactions between the intestinal microflora and toll-like receptors might affect gut motor function, leading to abdominal dysmotility and perhaps colic symptoms. The mechanism that *L. reuteri* acts through on colic symptoms in breast-fed infants remains to be clarified.

FEEDING DIFFICULTIES

Infants with colic usually display feeding-related problems, such as disorganized feeding behaviour, less rhythmic nutritive and non-nutritive sucking, more discomfort following feeding and lower responsiveness during feeding interactions. It is possible that disorganized feeding patterns in infants with colic are indicative of an underlying disorder in behavioural regulation. Present knowledge underlines the impact of these difficulties on parental and infant interactions and suggests the potential for ongoing regulatory problems in these infants (20). Evans et al. compared the effect of two methods of breastfeeding (prolonged emptying of one breast at each feed vs. both breasts equally drained at each feed) on breast engorgement, mastitis, infantile colic and duration of breast feeling. The former group had a lower incidence of breast engorgement in the first week and of colic over the first 6 months, but the majority of mothers in this group felt it necessary to offer the second breast at the end of a feed to satisfy their infant's hunger (21).

FOOD HYPERSENSITIVITY

There is increased evidence that infantile colic is related to food allergy and sometimes it is the first clinical manifestation of atopic disease. Approximately 25% of infants with moderate or severe symptoms have cow's milk-dependent colic (22,23). The immunological model of colic focuses on possible allergens, such as cow milk proteins, in breast milk or infant formula as the cause of the colic (24).

In a recent systematic review, Lucassen et al. confirmed that hypoallergenic formulas were effective in the treatment of colic in some formula-fed infants (7). Jakobsson and Lindberg have previously reported that exclusion of cow's milk protein from the diet of mothers of nursed infants with colic resulted in colic resolution. Similar efficacy was shown in a trial using casein-hydrolyzed formula as a substitute for cow's milk. Lindberg (25) is also of the opinion that infants with moderate or severe colic respond favourably to a diet free of cow's milk protein. More recently, Lucassen et al. randomized Dutch infants with colic to either a whey-hydrolysate formula or a standard formula and suggested that substitution of cow's milk formula by an extensively hydrolyzed whey formula could be effective in the treatment of

infantile colic. However, considering the favourable clinical course of infantile colic and the fact that many but not all the affected infants have symptoms related to cow's milk allergy, the majority of the studies on dietary interventions, particularly in formula-fed infants, concluded that further research is necessary (26). A recent trial suggests that a new formula with partially hydrolyzed proteins, a low amount of lactose, and the addition of a mixture of galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS), led to a significant improvement in symptoms of the lower gastrointestinal tract, such as infantile colic (27).

For colicky breastfed infants, research has shown that simply modifying the mother's diet could be also effective (28). Estep et al. has even proposed that a brief intervention with amino-acid-based formula, coupled with strict maternal avoidance of milk and dairy products under direct supervision of a lactation consultant, may be an effective treatment for colic in some breast-milk-fed infants (29). This kind of approach can, however, have a negative effect on maternal anxiety and the duration of breast feeding, and, because there is no doubt that human milk is superior food for all infants, I believe that I would never suggest that human milk be avoided at all in infants with colic (30).

PSYCHOSOCIAL FACTORS

Colic has also been suggested to be a personality disorder in the child. Colicky infants are often considered irritable and hypersensitive, with a 'difficult' temperament. However, temperament does not provide an explanation for most of the features of persistent infant crying, but can only be considered a contributing factor.

It is a frequently held view that colic results from an unfavourable climate created by inexperienced and anxious parents, in particular mothers, and that behavioural problems could result from a less than optimal parent–infant interaction. The quality of infant–parent interactions is of growing interest to those studying excessively crying and irritable infants. In particular, the relationship between the mothers and their persistently crying infants appeared mildly or significantly distressed. Few studies have focused on the role of the fathers and the whole family unit limiting our understanding of these factors. Recently, an observational study showed that excessive crying in infants is clearly associated with less than optimal parental and father–infant interaction. However, most of these problems are limited to the severely colicky group of infants (31).

MANAGEMENT OF INFANTILE COLIC

Over the years, both behavioural to pharmacological remedies have been studied and proposed as treatments for colic, although few have been confirmed through rigorous scientific evaluation in the form of randomized control trials (RCT). Despite the favourable clinical course of infantile colic (most infants being free from symptoms by the age of 4–5 months), many parents seek medical help. Moreover, serious somatic problems are absent in most cases, but still

doctors and nurses believe something has to be done to assist parents who are experiencing considerable stress.

I think the most effective treatment could be given by first grading the colic as mild, moderate or severe, but there is no consensus on the definition of each grade (32). The foregoing discussion demonstrates that the management of a colicky infant remains a frustrating problem for both carers and paediatricians.

Behavioural interventions

The first step in treating a child with infantile colic is to give general advice and reassurance for the parents. One should inform them that infantile colic is a self-limiting condition that is not due to a disease or to anything the parents have done or omitted to do to their infants. Second, the attentiveness of the parents should be stimulated by teaching them to give more appropriate responses to their infants, including less overstimulation and more effective soothing. At the same time, the parents should be advised not to exhaust themselves and, if possible, to leave their infants with others (7).

Herbal formulation

Herbal teas containing mixtures of vervain, camomile, fennel, liquorice and lemon balm have been shown to decrease crying in infants with colic through their antispasmodic activity (9). Products contain a variety of herbs and herbal oil and they are thought to provide relief from flatulence and indigestion. They are not entirely without risk, however, as they contain sugar and alcohol. Given the multiplicity of herbal products, the lack of standardization of strength and dosage and the potential interference with normal feeding, parents should be cautioned about their use for infantile colic. A recent study showed that colic in the breastfed infant could improve within 1 week of treatment with an extract based on *Matricariae recutita*, *Foeniculum vulgare* and *Melissa officinalis*. The phytotherapeutic agent tested in this study contained a high, standardized concentration of three herbs with the added advantage of defined dosage without the need for increased fluid intake (10).

Dietary intervention

1. Breast-fed infants. A strict cow's milk-free diet for the mother (with an extra supplement of calcium) may be suggested. Recently, Hill et al. found a therapeutic benefit in eliminating dairy products, eggs, wheat and nuts from the diet of breast-feeding mothers while advising them to ensure a well-balanced diet and an adequate calcium intake (28). Dietary interventions in mothers should be strictly monitored and continued only if they are effective.
2. Formula-fed infants. Hypoallergenic formulas, mainly extensively hydrolysed formulas based on casein or whey, are effective in the treatment of infantile colic (see recent reviews by Lucassen and Garrison (7,26)). It is not so long ago that even soy-based formulas were used in the treatment of infantile colic. Recently, the ESPGHAN Committee on Nutrition has recommended that soy protein formula should not be used in infants with food al-

lergy during the first 6 months of life, stressing that there is no evidence supporting their use in the management of infantile colic (33). In view of the wide range of severity of infantile colic discussed above, and that many infants without cow's milk allergy have colic, extensively protein hydrolyzed formulas might not consider the first dietary approach. On the other hand, a new formula based on partially hydrolysed proteins, low amounts of lactose and supplemented with FOS and GOS was effective (27,34). Finally, the large number of new formulas containing functional nutrients for gut well-being indicates the need for further research to define the best and first dietary approach for colicky infants.

Hypertonic glucose solution

A randomized clinical trial (RCT) performed by Barr et al. found that infants with and without colic responded to sucrose but not to placebo. The response in the colicky infants lasted on average <3 min whereas the infants with colic were less effectively calmed by sucrose. In contrast, Akcam et al. observed that 30% glucose solution might be used as a safe, effective, easily achievable and well-tolerated alternative method in the treatment of infantile colic and that the placebo effect was worthy of note (35). Again, further research is needed before this remedy can be suggested in clinical practice.

Pharmaceutical interventions

Simethicone, a defoaming agent, has been promoted as an effective treatment for colicky infants. It is safe and may reduce meteorism. However, a recent meta-analysis revealed that out of three RCTs using simethicone, only one showed any potential benefit (7,26).

Systematic reviews of anticholinergic drugs in infantile colic found them to be more effective than placebo. The most commonly used agent, dicyclomine, has, however, adverse effects and is now contraindicated in infants <6 months old (26). Nevertheless, we have shown that cimetropium bromide is effective in reducing crying during the colic episodes (8).

Probiotics

Recently, a randomized, controlled study demonstrated that *Lactobacillus reuteri* improved colicky symptoms in breast-fed infants more than simethicone, supporting the hypothesis that probiotic supplementation could lead to health advantages in colic (1,26). This is the first study performed to evaluate the efficacy of probiotic agents for colicky infants, and additional research, from clinical observation to microbiologic analysis, is needed to confirm the beneficial effects of *L. reuteri*. Moreover, since specific probiotic strains have specific properties and targets in the human intestinal flora, exerting differing health benefits, it remains to be seen whether other lactobacilli have similar effects. The mechanism by which *L. reuteri* reduces colic should be the subject of future clinical investigation to allow screening for even more effective probiotics for colic in the future (19).

LONG-TERM OUTCOMES

Infantile colic is characterized by a favourable clinical course and a self-limiting nature. The majority of colicky infants completely recover by the age of 4–5 months.

With regard to allergy, an association has been observed between colic and atopic eczema, food allergy, and respiratory and ocular allergies (23) although one study did not obtain such results (36).

Concerning psychological problems, Rautava et al. determined that families that had colicky infants exhibited more dissatisfaction with the daily functioning of their family life. Canivet et al. performed a follow-up study of colicky infants and controls when they reached 4 years of age and showed that former colicky children displayed more negative emotions and more negative moods during meals.

Our recent prospective 10-year study reported that susceptibility to recurrent abdominal pain, allergic and psychological disorders in childhood may be significantly increased in subjects who suffered from infantile colic (37). Thus, infantile colic might be an early expression of some of the most common disorders in childhood, although other long-term follow-up studies are still needed to confirm these links.

CONCLUDING REMARK

There is no scientifically defined cause for infantile colic, a behavioural clinical condition, in which an otherwise healthy infant cries frequently and inconsolably for an extended period of time for no discernable reason. The self-limiting nature of colic has precluded the use of invasive investigations to establish a pathophysiological model *in vivo*. Nevertheless, there is a complex relationship between the intestinal immune system and the commensal flora and motility, which requires further research. As colic frequently resolves spontaneously, dietary intervention might be more appropriate than pharmacological treatment.

Considering the favourable clinical course of infantile colic, the range of ways in which it manifests itself and the day-to-day variability of crying time, a safe therapeutic approach should be adopted and appropriate guidelines could be useful. However, as ever, there is still a need for further research and modification of current remedies.

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