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Exploring Hypotheses and Rationale for Causes of Infantile Colic

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Abstract

Background—Infantile colic is a frequent problem in neonates and infants. This review addresses current management including the results for nutrient modifications, soy-based formulas, and prebiotics, probiotics and synbiotics.

Purpose—Given the evidence that there is still an unmet clinical need, as current treatments are incompletely efficacious, we have examined the evidence around three hypothetical mechanisms that could potentially be involved in etiopathogenesis of infantile colic: immaturity of bile acid mechanisms that alter intraluminal and absorptive mechanisms, immaturity in motility and alterations in the microbiome. Understanding these potential mechanisms may lead to the introduction of diagnostic procedures that should enhance the selection or individualization of therapy for infantile colic.

Keywords

nutrition; formulas; prebiotics; probiotics; synbiotics

Definition, Criteria and Causes of Infantile Colic

Infantile colic (IC) often results in excessive crying and accounts for 10–20% of pediatrician visits of infants aged 2 weeks to 3 months (1). In 2001, it was reported to cost the United Kingdom National Health Service in excess of £65 million per year (2). Infantile colic is a syndrome characterized by paroxysms of irritability and inconsolable crying and screaming, accompanied by clenched fists, drawn-up legs, and a red face. It presents typically in the second or third week after birth, and peaks at 5 to 8 weeks of age; it usually resolves

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spontaneously by 4 months of age. The prevalence is estimated to be between 5% and 28% (1). The currently used diagnostic criteria for IC are the Rome IV criteria, which include all of the followings: a) paroxysms of irritability with fussing or crying that start and stop without obvious causes; b) symptoms lasting ≥3 hours a day and occur ≥3 days a week for ≥1 week; c) absence of failure to thrive, in infants from birth to 5 months of age (1). These criteria are adapted from the "Rule of Three" originally proposed by Wessel and colleagues (3): 3 hours per day, ≥3 days per week, ≥3 weeks. An underlying organic cause for the colic is found in less than 5% of these infants. Thus, it is usually benign and self-limiting (4). Pathogenesis of IC is still unclear, but it has been associated with different causes, such as alterations in intestinal microflora and gut hormones, gas production, allergy to cow's milk proteins, behavioral problems (e.g. family tension and parental anxiety), increasing maternal age, first born status and maternal smoking (5). Moreover, it is also possible that IC represents the last stage of the physiological developmental "crying curve" of healthy infants, with no evidence that the crying is caused by pain in the abdomen or any other part of the body (1). Given these diverse associations, it is not surprising that treatment is non-specific and not driven by data.

Current Approaches to Treatment of IC

In this section we will summarize the findings of several systematic or narrative reviews that evaluated the different types of pharmacological, nutritional and behavioral interventions available for the treatment of IC. The role of probiotics, prebiotics, and synbiotics is discussed in the section on the hypothesis of alterations in the microbiota.

Pharmacological Approaches

Hall and colleagues (5) and Lucassen (6) systematically reviewed literature on treatments for IC. Considering pharmacological treatment, two different randomized controlled trials (RCTs) found no difference when **simethicone**, which prevents gas bubbles from forming in the gastrointestinal tract, was compared to placebo (7,8). On the contrary, one RCT found simethicone to be effective in the management of crying attacks (9). Nonetheless, this study was of poor-quality and the definition of colics was not clear (6). Regarding **dicyclomine hydrochloride**, an anticholinergic agent with a relaxing effect on smooth muscle, two different RCTs (10,11) found favorable results on crying time. However, due to reported side effects, such as dyspnea, respiratory collapse, apnea, asphyxia, pulse rate fluctuations, and muscular hypotonia, this drug is not approved for use in infants younger than 6 months of age (5). Finally, the last drug assessed for the management of IC is **cimetropium bromide**, a muscarinic antagonist with direct spasmolytic activity. There is only one RCT available, and the authors describe a significant decrease in the duration of colic episodes with cimetropium bromide compared to placebo (12). However, an increase in sleepiness is reported, and the level of evidence is poor because of methodological fails (6). Due to the uncertain efficacy for the management of IC and considering the possible adverse effects, this drug has never been approved for use in the U.S. and Canada. In conclusion, pharmacological treatment is not recommended for the management of infants with colics.

Nutrition Modification

Numerous studies have evaluated the efficacy of hydrolyzed formulas in bottle-fed infants or low-allergen maternal diets in breastfed infants. The effect of **casein hydrolysate milk** has been evaluated in several studies. In a recent review, Lucassen (13) identified two RCTs that demonstrated an effect of this intervention on infant distress and crying time. The first study from Hill et al. (14) compared the effects of maternal hypoallergenic diet/casein hydrolysate formula to standard care (breast milk or cow's milk formula), and found a significant reduction of infants' distress level in the active diet group compared to the standard care group. In the second study (15), Arikan et al. found that an hydrolyzed formula administered for 7 days was effective in reducing the duration of crying in colicky infants, compared with baseline. Nevertheless, for both studies, the level of evidence is very low, due to weak methods or incomplete reporting of the data (13). Moreover, a study by Jakobsson and colleagues (16) highlighted a reduction in crying duration using two types of casein hydrolyzed formulas versus cow's milk formula, while Forsyth (17) found no significant difference between casein hydrolysate and cow's milk formula. Also for these two last studies the level of evidence is poor due to unclear randomization and lack of calculation of patients needed to treat (5).

Similarly, another RCT (18) compared **whey hydrolysate milk** to cow's milk formula, and showed a reduction in crying from baseline. Yet, the quality of evidence is low due to unmasked blinding. Another study (19) highlighted a reduction in the number of colic episodes using a partially hydrolyzed whey formula with oligosaccharides, B-palmitic acid and low lactose. Nevertheless, the presence of several modified ingredients makes it difficult to evaluate the effects of whey hydrolysate alone (5).

Considering all the aforementioned evidence, the recommendation is to avoid changes in the type of formula if the child is thriving. However, in a selected subset of formula-fed infants, such as children with atopy, a trial with a hypoallergenic formula may be an effective treatment for IC (20,21), though it is important to highlight that this suggestion is not based on evidence from RCTs, but on clinical reasoning (13).

The benefits of **soy-based formulas** in treatment of IC are not supported by evidence of sufficient quality (13). In addition, due to the high phyto-oestrogen content that may affect long-term reproductive health, soy-based formulas are not recommended for use in healthy infants and should not be used during the first 6 months of life, as stated by the European Society of Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) Committee on Nutrition (22).

The use of **low-lactose milk** or **high-fiber formula** is ineffective and is not supported by evidence of sufficient quality (5,13).

Summary of nutrition modification

Changes in infant formula are often tried based on assumption that there may be intolerance or allergy, but this is seldom present, and it is important to emphasize avoiding changes in

the type of formula if the child is thriving and only consider a hypoallergenic formula if there is evidence of atopy.

Behavioral Approaches

Chiropractic manipulation helps some patients, but may be no more effective than a nurse's cuddling for 10 minutes. In a meta-analysis, when combining only those trials with a low risk of such performance bias, the results of manipulation did not reach statistical significance (23). Moreover, a case of death after manipulation of the cervical and thoracolumbar spine in a 3-months-old infant is reported. For this reason, considering the lack of evidence of safety and effectiveness, manipulation of the vertebral column is not recommended (13).

The advice to **increase** carrying (24), to **reduce stimulation of the child** by not lifting and patting the baby (25), to use a car ride simulator or the counselling of the mother about specific management techniques (26) are not proven to be effective, and the level of quality of evidence is low (13).

Summary of the Evidence

It is important to highlight that a recent systematic review from Steutel and colleagues (27) showed a general lack of agreement about definitions, primary outcome measures, and instruments used in intervention trials on IC. Therefore, this lack of uniformity makes it difficult to evaluate and compare the results of the different trials. Even with the limitations associated with the lack of uniformity, the systematic analyses of the trials generally reach the same conclusion, that is, that none of the currently available treatments appears to be effective in the management of IC. For this reason, given the unmet clinical need, we explored alternative hypotheses that could lead to the identification of the mechanism(s) of IC, and may lead to opportunities for individualizing treatment of IC in the future.

Hypotheses

Given the prevailing timing of IC, which presents typically in the second or third week after birth, peaks at 5 to 8 weeks of age, and usually resolves spontaneously by 4 months of age, we explored three hypotheses:

First, immaturity of hepatic synthesis, reduced intraluminal levels of bile acids, and impaired ileal absorption of bile acids in the neonate result in malabsorption of fat and other nutrients, with potential for secondary effects on colonic microbial flora.

Second, the colonic microbial flora are abnormal and result in increased nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon.

Third, immaturity of the enteric nervous system leads to abnormal motor and sensory functions of the intestine and colon.

Overall, the literature provides evidence for interaction among these three mechanisms, and this review highlights the interplay among these mechanisms and the potential for their identification that may lead to novel approaches to the management of IC.

Literature Supporting the Hypothesis of Bile Acid Immaturity

There are several elements in the enterohepatic circulation that are immature in the neonate, based on animal and human studies. The evidence is summarized here:

Abnormal levels and composition of bile in the alimentary tract and serum

Reductions in bile salt pool size, synthesis, and intestinal concentrations have been demonstrated in neonates (28,29); maturity may be influenced by dexamethasone or phenobarbital administered to the mother prior to delivery. In addition, Kawasaki and colleagues (30) showed that serum concentrations of primary and total bile acids increased gradually in the neonatal period, with peak serum levels reached at 1 month of age, with predominance of primary serum bile acids by 3 months of age, with a significant increase in the primary total bile acid ratio by 5 months of age and declining to the ratios observed in adults by 4–6 years of age.

Fasting duodenal aspirate bile acid

Measurements of fasting duodenal aspirate bile acid showed higher cholic acid (CA) to chenodeoxycholic acid (CDCA) ratio and higher glycine to taurine conjugates of the bile acids (both being 3-alpha-hydroxy bile acids) at younger postnatal age in human milk-fed preterm infants (31). These data suggest immaturity in the alternative pathway of bile acid synthesis, which requires 27 alpha hydroxylase steps in the biosynthesis from cholesterol. In addition, the increased glycine conjugation suggests failure of peroxisomal function, since the normal ratio of conjugates is 3:1 (glycine to taurine). Interestingly, there is a decline in the ratio of CA to CDCA and glycine to taurine conjugate ratio in most infants within about 4–5 months, which corresponds to the timing of resolution of IC.

Fetal gallbladder bile

Profiles (collected postmortem) of fetal gallbladder bile are similar to those in the intestine with the exception of sulfate conjugates (32) and the proportion of deoxycholic acid (DCA). Thus, one study noted that DCA was notably absent from the bile of infants and some children (33), and this may suggest that the dehydroxylation of CA by colonic bacteria may have contributed to the absence of DCA in the gallbladder bile; however, this was based on bile from gallbladders obtained post-mortem from 30 human subjects rather than from otherwise healthy subjects.

The significance of this finding relative to intestinal colic is unclear, although studies in infants and children with inborn errors of bile acid metabolism (such as defects in amidation) may present with fat-soluble vitamin deficiency (34) and illustrate the potential role of immaturities in bile acid synthesis in the neonate.

Immaturity in hepatic synthesis of bile acids

Immaturity in hepatic synthesis of bile acids is supported by evidence of abnormal levels of nuclear receptors in developing rat hepatocytes (35). Thus, bile acid transporters (FXR, PXR, LXR-alpha, PPAR-alpha, RAR-alpha, LRH1 and SHP) involved in bile acid formation are poorly developed in the fetal stage, but their expression gradually matures post-natally and reaches adult levels by 4weeks of age. This immaturity of hepatic synthesis might therefore be a factor in the IC observed in the first 4 weeks post-natally, but may be one of the factors that initiates the cascade of events leading to IC observed after 4 weeks of age.

Immaturity in intestinal absorption of bile salts

In a series of landmark studies, Lester and colleagues investigated immaturity in intestinal absorption of bile salts. They showed that the ileal mechanism for active transport of taurocholate was undeveloped in the fetus and newborn infant, leading to the conjecture that enterohepatic circulation of bile salt during the perinatal period is limited to that fraction of bile salt absorbed passively, thus resulting in loss of bile salt from the immature intestine that may contribute to steatorrhea and to the “diarrhea” of newborn infants (36,37); similar findings were observed in dogs (38). Lester (39) drew attention to the analogy between immaturity of bilirubin conjugation and excretion in neonatal jaundice that resolves itself in a few days, and immaturity in bile acid production and function, that resolves in a few weeks.

Steatorrhea in neonatal period

Watkins et al. (40) reported that total fecal lipid excretion is normal in infants 3 to 11 days and 23 to 72 days of age (n=4 in each group, median 11.65g [IQR 7.65, 17.2] in neonates, 6.6 [5.7, 15.9] in older infants, p=0.49); however, they demonstrated that, the presence of increase in neutral fecal lipid (e.g. monoglycerides) in neonates may reflect either defective lipolysis in newborn infants (which may result in insufficient lipid micellization and/or mucosal transport for optimal lipid absorption) or colonic bacterial hydrolysis of triglycerides (40).

In addition, steatorrhea often occurs during the first month, and decreases during the first post-natal month (as shown by the fall in the steatocrit curve from 7th to 28th day) and, by 45 days, few babies have steatorrhea (41).

In the next section, we discuss the potential relationship between changes in bile acids and the microbiome, to which one can also add the potential that steatorrhea in the neonate could result in additional perturbation that may lead to IC, for example in the presence of high concentrations of fatty acids or bile acids in the infant’s colon. Although such studies have not been conducted in infants or children, it has been demonstrated in adults that higher concentrations of long chain and short chain fatty acids, and even relatively low concentrations of the bile acid, chenodeoxycholic acid (1mM infused into the distal colon), can induce high amplitude propagated contractions (42,43) that are frequently sensed or may be associated with pain.

Literature Supporting Microbial Alterations in the Neonate

Immediately after birth, a diverse flora of staphylococci, streptococci, enterococci and enterobacteriaceae colonizes the sterile gut. Anaerobic colonization occurs in the second day of life starting with bifidobacteria (44). Infants receive their 'original inoculum' of bacteria prenatally with the transfer of bacteria through umbilical blood, by contact with vaginal and intestinal microbiota during birth and by skin contact and milk during breast-feeding. This colonization may be essential for the maturation of the gut-associated lymphoid tissue, and intestinal epithelial homeostasis (44–46). In 14 healthy, full-term infants followed from birth to 12 months of age, the composition of the microbiota varied widely from baby to baby, but within an individual baby, there were recognizable features of the microbial community for months, and the intestinal microbiota began developing towards an adult profile 5 days after birth and had evolved towards the characteristics of the adult gastrointestinal microbial profile by one year of age (47). Nevertheless, more recent studies showed that the adult GI microbial profile is not yet reached by one year of age (48,49). Two important principles regarding the gastrointestinal microbiota in infants are the transfer from mother to infant during the perinatal period (50) and adaptation to the specific environment of the child, as demonstrated by comparisons of the gut microbiota of 6-month-old infants who were breast-fed and received an age-appropriate diet typical for each area living in rural Malawi (higher proportions of *Bifidobacteria* and *Bacteroides/Prevotella* group bacteria) compared to urban Finland (*Clostridium perfringens* and *Staphylococcus aureus*) (51). While both the type of feed and the mode of delivery at the birth of the infant have major impact on gut microbiome, the literature does not provide strong evidence that infants that are breastfed compared to formula fed, or those born by vaginal delivery compared to Caesarian section have differences in the prevalence of infantile colic.

Association of changes in microbiota and IC

In earlier studies, colicky infants were more frequently colonized with *Clostridium difficile* during the time of colic than were the age-matched controls; this difference disappeared by age 3 months, when it was noted that stool fatty-acid profiles were different between the infants who had suffered from severe colic and the control infants. The fatty-acid profiles were also influenced by the age of the infant, the mode of delivery, antimicrobial drugs taken by the mother during delivery, and breast-feeding and type of feeding (52). Fecal samples were found to have higher counts of coliform bacteria and lower counts of lactobacilli in infants with colic symptoms compared with children not suffering from colic (53,54); moreover, different colonization patterns of lactobacilli were found among colicky and healthy infants: *Lactobacillus brevis* and *L. lactis* were found only in colicky infants, whereas *L.acidophilus* was found only in healthy infants (55). Interestingly, *L. delbrueckii* subsp. delbrueckii DSM 20074 and *L. plantarum* MB 456 had anti-microbial effects against six species of gas-forming coliforms isolated from colicky infants (56). These interesting studies on different *Lactobacillus* species need replication by other research groups.

In other studies, *Klebsiella* species were more prevalent in colic patients than in control patients, whereas *Enterobacter/Pantoea* species were detected only in the control patients; in the same study, fecal calprotectin levels were 2-fold higher in infants with colic than in

control infants (57). The proportion of *Bifidobacterium* counts to total bacterial counts and to a lesser extent, the frequency of *Lactobacillus* spp. at the age of 3 weeks were inversely associated with the amount of crying and fussing during the first 3 months (58). A probiotic *Bifidobacterium breve* B632 species inhibited growth of gas-forming Enterobacteriaceae in fecal microbiota cultures from a colicky infant (59).

Using phylogenetic microarray for studying the human gastrointestinal microbiota (the human intestinal tract chip [HITChip] assay), infants with colic showed lower microbial diversity and stability than control infants in the first weeks of life; there were also differences in the abundance of certain bacteria at 2 weeks suggesting that microbial signatures may explain the colic phenotype (60). The colic phenotype correlated positively with specific groups of proteobacteria, including bacteria related to *Escherichia, Klebsiella, Serratia, Vibrio, Yersinia*, and *Pseudomonas*, but negatively with bacteria belonging to the Bacteroidetes and Firmicutes phyla. The latter phyla include some lactobacilli and canonical groups known to produce butyrate and lactate (61).

It has been postulated that early increased levels of pathogenic bacteria and reductions of lactobacilli, bifidobacteria or butyrate-producing bacteria produce intestinal pain and inflammation in the infant, and that this in turn causes excessive crying (62).

Trials of prebiotics, probiotics and synbiotics in IC

Given the potential effects of prebiotics, probiotics and synbiotics on intestinal motility and sensory neurons, contractile activity of the intestine, anti-inflammatory effects and alterations of the microbiome, several studies have explored their potential clinical benefit (Tables 1 and 2) (63–71) and have also been evaluated in three recent systematic reviews (72–74). Although *Lactobacillus reuteri* may be effective as a treatment strategy for crying in exclusively breastfed infants with colic, the evidence supporting probiotic use for the treatment of IC or crying in formula-fed infants remains unresolved. The administration of *L. reuteri DSM 17938* at a dose of 10^8 CFU once a day appears to reduce crying times in infants with IC, especially in exclusively or predominantly breastfed infants (72–74). Nevertheless, these industry-sponsored trials require replication, particularly in formula-fed patients.

Relationship of microbiome to bile acids

Perturbations of the microbiota shape the bile acid pool and modulate the activity of bile acid-activated receptors. Bile acids, in turn, can also regulate the composition of the gut microbiome at the highest taxonomic levels (75). Several molecules made or modified by the microbiota including short-chain fatty acids, succinate, mucin O-glycans, secondary bile acids, and the AI-2 quorum sensing auto-inducer affect the growth and virulence of pathogens (76).

Literature Supporting Immaturity of Intestinal Motility in Neonate and Infancy

There is evidence of transient dysregulation of the repertoire of small intestinal motility that facilitates normal propulsion and depends on the function of the extrinsic and enteric neural control. Thus, it is postulated that immaturity of the enteric nervous system during development may cause intestinal hypermotility in infants with colic, particularly during the first few weeks of life. There are no formal motility studies to support abnormal gastrointestinal motility in patients with infant colic; the circumstantial evidence supporting this hypothesis is based on the evidence of immaturity of normal patterns of motility in prematurity and neonates, and evidence of postnatal, delayed maturation of interstitial cells of Cajal (pacemakers in the intestine) in cases of neonatal pseudo-obstruction (77).

In the following sections, we review the normal development of the neural control of gut motor functions [reviewed in detail elsewhere (78)], abnormal motor repertoire associated with prematurity, and potential therapeutic approaches to normalize the dysfunction.

Ontogeny of neural control of intestinal motility

The enteric nervous system (ENS) develops in utero by migration of neural crest cells to the developing alimentary canal. The ENS cells are derived from precursor cells from three axial levels of the neural crest. Vagal neural crest cells from the developing hindbrain colonize the gut by migration in a rostro-caudal direction; whereas, enteric neurons arrive in the hindgut from the lumbosacral level via a caudo-rostral wave of colonization. Movement of the neural crest cells through the gut mesenchyme, survival in the gut, and differentiation into mature cells are influenced by the microenvironment within the developing gut. Thus, migration of neural crest cells and the sequence of innervation of different levels of the gut are regulated by specific signaling molecules that include transcription factors, neurotrophic factors [e.g., the glial-derived neurotrophic factor (GDNF) and its receptor subunits], and the neuregulin signaling system. These facilitate the growth, differentiation, and persistence of the migrating nerve cells once they arrive in the gut. Neuregulins are structurally related signaling proteins, which are likely to have important roles in the development, maintenance, and repair of the nervous system and other selected tissues.

Evidence of immature small intestinal motility

The Berseth group conducted an extensive series of studies of antral and small intestinal motility in preterm and term infants (79–82).

Duodenal motility patterns—In preterm and term infants, dudodenal motility patterns differ. Intestinal motor characteristics are more immature in preterm than term infants; clustered phasic contractions occur more frequently and are of shorter duration and lower amplitude. Duodenal clusters are significantly less common, but their amplitudes increase with increasing gestational age (81).

Antral motility—Antral motility consists of isolated single contractions and clustered phasic contractions in term and preterm infants, with no differences in the occurrence or

amplitude of antral activity between the two groups of infants and with no change of antral motor activity with advancing gestational age (79). The proportion of antral clusters that was temporally associated with duodenal activity was significantly lower in preterm infants than in term infants ($p<0.001$). Moreover, the degree of association of antral and duodenal activity increased significantly with gestational age.

These data show that fasting antral motor activity is comparable in preterm and term infants, and the temporal coordination of antral and duodenal activity develops in association with progressive changes in duodenal motor activity in the preterm infant. One way to enhance the functional maturation of these motor functions is enteral feeding. Thus, early-fed infants were able to tolerate full oral nutrition sooner, had fewer days of feeding intolerance, and had shorter hospital stays in preterm infants (81). This is also achieved with intragastric feeding (79), and the effect is specific for motor, rather than mucosal, maturation (82). In part, this maturation is also enhanced by the post-natal development of gut neuroendocrine signals (80). Thus, fasting plasma gastrin and peptide YY levels were low in the preterm human (n=19) and canine neonate during the first post-natal week, but the plasma levels of both increased with post-natal age. Motor quiescence during fasting (in contrast to the excessive incoordinated contractile activity manifested as clustered phasic contractions) becomes a more prominent feature of newborn intestinal motor functions post-natally (75). The inhibition of this contractile activity appears to coincide with the level of peptide YY, which generally reduces contractile activity and is a major factor in mediating the ileal brake in the mature gut (83,84). Conversely, the motilin receptor agonist, erythromycin, is able to induce phase III migrating motor complexes after 32 weeks' gestation, suggesting that early use of erythromycin as a prokinetic agent may not be useful in early preterm infants, may be partially useful in older preterm infants, and may be most useful in full-term infants (85). Finally, the relevance of the maturation of the motor repertoire is confirmed by experience showing that assessment of intestinal motility serves as a useful clinical guide in the feeding management of the newborn (86). These observations provide the basis for the hypothesis that enteric motor immaturity may conceivably result in infantile colic.

Therapeutic Opportunities for Immaturity of Motor Function

The extrinsic parasympathetic and sympathetic nerves serve to modulate the pre-programmed functions controlled by the enteric nervous system. The peristaltic reflex involves an afferent component that is mediated by intrinsic primary afferent neurons, ascending contractions (e.g., cholinergic and tachykininergic neurons), and descending relaxation [nitrergic or vasoactive intestinal peptidergic (VIPergic) neurons]. The observation of normal variability in heart rate in children with colic suggests that extrinsic parasympathetic control of viscera is normal (87). Overall, the hypothesis that IC may be a disorder of gastrointestinal motor function requires further support through measurements of motility in infants with IC. Meanwhile, the studies of the ontogeny of the enteric neural control and maturation of the repertoire in small intestinal motility provide support for the concept that dysregulation and immaturity of intestinal motility contribute to the development of infantile colic (88,89).

Irrespective of the precise mechanism, there appears to be incoordination or spasm of intestinal motility, and this has led to the use of antispasmodic drugs, such as dicyclomine (11) or cimetropium bromide (12), which are generally muscarinic cholinergic antagonists. In addition, development of interdigestive migrating motor complexes appears to be associated with relief of colic. Such complexes are associated with high motilin levels (90,91). Beneficial effects are reported with some herbal teas, such as fennel, lemon balm and chamomile, or with phytotherapeutic agents (92,93), though the mechanisms and potential effects of all of these therapies on motor incoordination are unclear..

Potential Interactions between Three Hypothetical Mechanisms in Infantile Colic and Conclusion

Overall, the literature provides evidence for interaction among these three mechanisms, and this review highlights the interplay among these mechanisms and the potential for their identification that may lead to novel approaches to the management of infantile colic. The immaturity of hepatic bile acid synthesis, intraluminal levels, and ileal absorption of bile acids in the neonate result in malabsorption of fat, with potential for secondary effects on colonic microbial flora. The latter changes may result in increased nutrient fermentation and reduced levels of dehydroxylated bile acids in the colon, where the contractile activities may be significantly altered, based on studies of the effects of primary (dehydroxylated) bile acids in the human adult colon exposed to estimated loads of ~1mM chenodeoxycholate (43). These levels are likely to be achieved in the neonatal colon. However, no such studies are available to assess whether the immaturity of the enteric nervous system and the increase in intracolonic bile acid and fat content increases the propensity to abnormal motor and sensory functions of the intestine and colon in the neonate or infant with IC. Further research on these three, potentially interacting mechanisms may lead to novel approaches to more specific diagnosis and management of infantile colic. Thus, with the availability of noninvasive tests that assess hepatic synthesis of bile acids (serum 7αC4) (94), gastric emptying in neonates using breath test measurements (95), and stool microbiome studies (including phylogenetic microarray by HITChip assay), it is conceivable that there may be opportunities for individualizing therapy based on objective biomarker(s) in infants whose colic does not respond to the customary first line therapies.

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References

1. Benninga MA, Nurko S, Faure C, Hyman PE, St. James Roberts I, Schechter NL. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016; 150:1443–1455.
2. Morris S, James-Roberts IS, Sleep J, Gillham P. Economic evaluation of strategies for managing crying and sleeping problems. Arch Dis Child. 2001; 84:15–19. [PubMed: 11124777]
3. Wessel MA, Cobb JC, Jackson EB, Harris GS Jr, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. Pediatrics. 1954; 14:421–435. [PubMed: 13214956]

4. Akhnikh S, Engelberts AC, van Sleuwen BE, L'Hoir MP, Benninga MA. The excessively crying infant: etiology and treatment. Pediatr Ann. 2014; 43:e69–e75. [PubMed: 24716561]
5. Hall B, Chesters J, Robinson A. Infantile colic: a systematic review of medical and conventional therapies. J Paediatr Child Health. 2012; 48:128–137. [PubMed: 21470331]
6. Lucassen P. Colic in infants. BMJ Clin Evid. 2010 Feb 5.:0309.
7. Danielsson B, Hwang CP. Treatment of infantile colic with surface active substance (simethicone). Acta Paediatr Scand. 1985; 74:446–450. [PubMed: 3890465]
8. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. Pediatrics. 1994; 94:29–34. [PubMed: 8008533]
9. Sethi KS, Sethi JK. Simethicone in the management of infant colic. Practitioner. 1988; 232:508. [PubMed: 3064072]
10. Hwang CP, Danielsson B. Dicyclomine hydrochloride in infantile colic. Br Med J (Clin Res Ed). 1985; 291(6501):1014.
11. Weissbluth M, Christoffel KK, Davis AT. Treatment of infantile colic with dicyclomine hydrochloride. J Pediatr. 1984; 104:951–955. [PubMed: 6374085]
12. Savino F, Brondello C, Cresi F, Oggero R, Silvestro L. Cimetropium bromide in the treatment of crisis in infantile colic. J Pediatr Gastroenterol Nutr. 2002; 34:417–419. [PubMed: 11930101]
13. Lucassen P. Colic in infants. BMJ Clin Evid. 2015 Aug 11.:0309.
14. Hill DJ, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. J Allergy Clin Immunol. 1995; 96:886–892. [PubMed: 8543745]
15. Arikan D, Alp H, Gözüm S, Orbak Z, Cifçi EK. Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic. J Clin Nurs. 2008; 17:1754–1761. [PubMed: 18592627]
16. Jakobsson I, Lothe L, Ley D, Boerschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. ActaPaediatr. 2000; 89:18–21.
17. Forsyth BWC. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. J Pediatr. 1989; 115:521–526. [PubMed: 2677292]
18. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. Pediatrics. 2000; 106:1349–1354. [PubMed: 11099588]
19. Savino F, Palumeri E, Castagno E, Cresi F, Dalmasso P, Cavallo F, Oggero R. Reduction of crying episodes owing to infantile colic: A randomized controlled study on the efficacy of a new infant formula. Eur J Clin Nutr. 2006; 60:1304–1310. [PubMed: 16736065]
20. Shergill-Bonner R. Infantile colic: practicalities of management, including dietary aspects. J Fam Health Care. 2010; 20:206–209. [PubMed: 21319674]
21. Vandenplas Y, Gutierrez-Castrellon P, Velasco-Benitez C, Palacios J, Jaen D, Ribeiro H, Shek LP, Lee BW, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. Nutrition. 2013; 29:184–194. [PubMed: 23137717]
22. Agostoni C, Axelsson I, Goulet O, Koletzko B, Michaelsen KF, Puntis J, Rieu D, Rigo J, et al. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr. 2006; 42:352–361. [PubMed: 16641572]
23. Dobson D1, Lucassen PL, Miller JJ, Vlieger AM, Prescott P, Lewith G. Manipulative therapies for infantile colic. Cochrane Database Syst Rev. 2012 Dec 12.12:CD004796. [PubMed: 23235617]
24. Barr RG, McMullan SJ, Spiess H, Leduc DG, Yaremko J, Barfield R, Francoeur TE, Hunziker UA. Carrying as colic "therapy": a randomized controlled trial. Pediatrics. 1991; 87:623–630. [PubMed: 2020506]
25. McKenzie S. Troublesome crying in infants: effect of advice to reduce stimulation. Arch Dis Child. 1991; 66:1416–1420. [PubMed: 1776889]
26. Parkin PC, Schwartz CJ, Manuel BA. Randomized controlled trial of three interventions in the management of persistent crying of infancy. Pediatrics. 1993; 92:197–201. [PubMed: 8337017]

27. Steutel NF, Benninga MA, Langendam MW, de Kruijff I, Tabbers MM. Reporting outcome measures in trials of infant colic. J Pediatr Gastroenterol Nutr. 2014; 59:341–346. [PubMed: 24796800]
28. Watkins JB, Ingall D, Szczepanik P, Klein PD, Lester R. Bile-salt metabolism in the newborn - measurement of pool size and synthesis by stable isotope technic. N Engl J Med. 1973; 288:431–434. [PubMed: 4683916]
29. Watkins JB, Szczepanik P, Gould JB, Klein P, Lester R. Bile salt metabolism in the human premature infant. Preliminary observations of pool size and synthesis rate following prenatal administration of dexamethasone and phenobarbital. Gastroenterology. 1975; 69:706–713. [PubMed: 1158088]
30. Kawasaki H, Yamanishi Y, Miyake M, Mura T, Ikawa S. Age- and sex-related profiles of serum primary and total bile acids in infants, children and adults. Tohoku J Exp Med. 1986; 150:353–357. [PubMed: 3824379]
31. Boehm G, Braun W, Moro G, Minoli I. Bile acid concentrations in serum and duodenal aspirates of healthy preterm infants: effects of gestational and postnatal age. Biol Neonate. 1997; 71:207–214. [PubMed: 9129789]
32. Naritaka N, Suzuki M, Sato H, Takei H, Murai T, Kurosawa T, Iida T, Nittono H, et al. Profile of bile acids in fetal gallbladder and meconium using liquid chromatography-tandem mass spectrometry. Clin Chim Acta. 2015; 446:76–81. [PubMed: 25887994]
33. Bongiovanni AM. Bile acid content of gallbladder of infants, children and adults. J Clin Endocrinol Metab. 1965; 25:678–685. [PubMed: 14313762]
34. Heubi JE, Setchell KD, Jha P, Buckley D, Zhang W, Rosenthal P, Potter C, Horslen S, Suskind D. Treatment of bile acid amidation defects with glycocholic acid. Hepatology. 2015; 61:268–274. [PubMed: 25163551]
35. Balasubramaniyan N, Shahid M, Suchy FJ, Ananthanarayanan M. Multiple mechanisms of ontogenic regulation of nuclear receptors during rat liver development. Am J Physiol. 2005; 288:G251–G260.
36. de Belle RC, Vaupshas V, Vitullo BB, Haber LR, Shaffer E, Mackie GG, Owen H, Little JM, et al. Intestinal absorption of bile salts: immature development in the neonate. J Pediatr. 1979; 94:472–476. [PubMed: 423038]
37. Lester R. Diarrhea and malabsorption in the newborn. N Engl J Med. 1977; 297:505–507. [PubMed: 887132]
38. Lester R, Smallwood RA, Little JM, Brown AS, Piasecki GJ, Jackson BT. Fetal bile salt metabolism. The intestinal absorption of bile salt. J Clin Invest. 1977; 59:1009–1016. [PubMed: 863998]
39. Lester R. Introduction. Bile acid metabolism in the newborn. J Pediatr Gastroenterol Nutr. 1983; 2:335–336. [PubMed: 6875759]
40. Watkins JB, Bliss CM, Donaldson RM Jr, Lester R. Characterization of newborn fecal lipid. Pediatrics. 1974; 53:511–515. [PubMed: 4823327]
41. Iacono G, Carroccio A, Cavataio F, Montalto G, Mancuso C, Balsamo V, Notarbartolo A. Steatocrit test: normal range and physiological variations in infants. J Pediatr Gastroenterol Nutr. 1990; 11:53–57. [PubMed: 2388133]
42. Bampton PA, Dinning PG, Kennedy ML, Lubowski DZ, Cook IJ. The proximal colonic motor response to rectal mechanical and chemical stimulation. Am J Physiol Gastrointest Liver Physiol. 2002; 282:G443–G449. [PubMed: 11841994]
43. Spiller RC, Brown ML, Phillips SF. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. Gastroenterology. 1986; 91:100–107. [PubMed: 3710059]
44. Gueimonde M, Laitinen K, Salminen S, Isolauri E. Breast milk: a source of bifidobacteria for infant gut development and maturation? Neonatology. 2007; 92:64–66. [PubMed: 17596738]
45. Jiménez E, Fernández L, Marín ML, Martín R, Odriozola JM, Nueno-Palop C, Narbad A, Olivares M, et al. Isolation of commensal bacteria from umbilical cord blood of healthy neonates born by cesarean section. Curr Microbiol. 2005; 51:270–274. [PubMed: 16187156]

46. Jiménez E, Marín ML, Martín R, Odriozola JM, Olivares M, Xaus J, Fernández L, Rodríguez JM. Is meconium from healthy newborns actually sterile? Res Microbiol. 2008; 159:187–193. [PubMed: 18281199]
47. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO. Development of the human infant intestinal microbiota. PLoS Biol. 2007; 5:e177. [PubMed: 17594176]
48. Hollister EB, Riehle K, Luna RA, Weidler EM, Rubio-Gonzales M, Mistretta TA, Raza S, Doddapaneni HV, et al. Structure and function of the healthy pre-adolescent pediatric gut microbiome. Microbiome. 2015; 3:36. [PubMed: 26306392]
49. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, Contreras M, Magris M, Hidalgo G, et al. Human gut microbiome viewed across age and geography. Nature. 2012; 486:222–227. [PubMed: 22699611]
50. Rautava S, Luoto R, Salminen S, Isolauri E. Microbial contact during pregnancy, intestinal colonization and human disease. Nat Rev Gastroenterol Hepatol. 2012; 9:565–576. [PubMed: 22890113]
51. Grzeskowiak L, Collado MC, Mangani C, Maleta K, Laitinen K, Ashorn P, Isolauri E, Salminen S. Distinct gut microbiota in southeastern African and northern European infants. J Pediatr Gastroenterol Nutr. 2012; 54:812–816. [PubMed: 22228076]
52. Lehtonen L, Korvenranta H, Eerola E. Intestinal microflora in colicky and noncolicky infants: bacterial cultures and gas-liquid chromatography. J Pediatr Gastroenterol Nutr. 1994; 19:310–314. [PubMed: 7815263]
53. Savino F, Cresi F, Pautasso S, Palumeri E, Tullio V, Roana J, Silvestro L, Oggero R. Intestinal microflora in breastfed colicky and non-colicky infants. Acta Paediatr. 2004; 93:825–829. [PubMed: 15244234]
54. Savino F, Cordisco L, Tarasco V, Calabrese R, Palumeri E, Matteuzzi D. Molecular identification of coliform bacteria from colicky breastfed infants. Acta Paediatr. 2009; 98:1582–1588. [PubMed: 19604166]
55. Savino F, Bailo E, Oggero R, Tullio V, Roana J, Carlone N, Cuffini AM, Silvestro L. Bacterial counts of intestinal Lactobacillus species in infants with colic. Pediatr Allergy Immunol. 2005; 16:72–75. [PubMed: 15693915]
56. Savino F, Cordisco L, Tarasco V, Locatelli E, Di Gioia D, Oggero R, Matteuzzi D. Antagonistic effect of Lactobacillus strains against gas-producing coliforms isolated from colicky infants. BMC Microbiol. 2011; 11:157. [PubMed: 21718486]
57. Rhoads JM, Fatheree NY, Norori J, Liu Y, Lucke JF, Tyson JE, Ferris MJ. Altered fecal microflora and increased fecal calprotectin in infants with colic. J Pediatr. 2009; 155:823–828. e1. [PubMed: 19628216]
58. Partty A, Kalliomaki M, Endo A, Salminen S, Isolauri E. Compositional development of Bifidobacterium and Lactobacillus microbiota is linked with crying and fussing in early infancy. PLoS One. 2012; 7:e32495. [PubMed: 22403665]
59. Simone M, Gozzoli C, Quartieri A, Mazzola G, Di Gioia D, Amaretti A, Raimondi S, Rossi M. The probiotic Bifidobacterium breve B632 inhibited the growth of Enterobacteriaceae within colicky infant microbiota cultures. Biomed Res Int. 2014; 2014:301053. [PubMed: 25309908]
60. Rajilić-Stojanović M, Heilig HG, Molenaar D, Kajander K, Surakka A, Smidt H, de Vos WM. Development and application of the human intestinal tract chip, a phylogenetic microarray: analysis of universally conserved phylotypes in the abundant microbiota of young and elderly adults. Environ Microbiol. 2009; 11:1736–1751. [PubMed: 19508560]
61. de Weerth C, Fuentes S, Puylaert P, de Vos WM. Intestinal microbiota of infants with colic: development and specific signatures. Pediatrics. 2013; 131:e550–e558. [PubMed: 23319531]
62. de Weerth C, Fuentes S, de Vos WM. Crying in infants: on the possible role of intestinal microbiota in the development of colic. Gut Microbes. 2013; 4:416–421. [PubMed: 23941920]
63. Chau K, Lau E, Greenberg S, Jacobson S, Yazdani-Brojeni P, Verma N, Koren G. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial investigating Lactobacillus reuteri DSM 17938. J Pediatr. 2015; 166:74–78. [PubMed: 25444531]

64. Dupont C, Rivero M, Grillon C, Belaroussi N, Kalindjian A, Marin V. Alpha-lactalbumin-enriched and probiotic-supplemented infant formula in infants with colic: growth and gastrointestinal tolerance. Eur J Clin Nutr. 2010; 64:765–767. [PubMed: 20517331]

65. Giovannini M, Verduci E, Gregori D, Ballali S, Soldi S, Ghisleni D, Riva E. PLAGOS Trial Study Group. Prebiotic effect of an infant formula supplemented with galacto-oligosaccharides: randomized multicenter trial. J Am Coll Nutr. 2014; 33:385–393. [PubMed: 25302927]

66. Kianifar H, Ahanchian H, Grover Z, Jafari S, Noorbakhsh Z, Khakshour A, Sedaghat M, Kiani M. Synbiotic in the management of infantile colic: a randomised controlled trial. J Paediatr Child Health. 2014; 50:801–805. [PubMed: 24962875]

67. Mi GL, Zhao L, Qiao DD, Kang WQ, Tang MQ, Xu JK. Effectiveness of Lactobacillus reuteri in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. Antonie van Leeuwenhoek. 2015; 107:1547–1553. [PubMed: 25876529]

68. Partty A, Luoto R, Kalliomaki M, Salminen S, Isolauri E. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: randomized, double-blind, placebo-controlled trial. J Pediatr. 2013; 163:1272–1277. e1–e2. [PubMed: 23915796]

69. Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. Lactobacillus reuteri (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: a prospective randomized study. Pediatrics. 2007; 119:e124–e130. [PubMed: 17200238]

70. Sung V, Hiscock H, Tang M, Mensah FK, Nation ML, Satzke C, Heine RG, Stock A, et al. Treating infant colic with the probiotic Lactobacillus reuteri: a randomised double-blind placebo-controlled trial. BMJ. 2014; 348:g2107. [PubMed: 24690625]

71. Szajewska H, Gyrczuk E, Horvath A. Lactobacillus reuteri DSM 17938 for the management of infantile colic in breastfed infants: a randomized, double-blind, placebo controlled trial. J Pediatr. 2013; 162:257–262. [PubMed: 22981952]

72. Anabrees J, Indrio F, Paes B, Al Faleh K. Probiotics for infantile colic: a systematic review. BMC Pediatr. 2013; 13:186. [PubMed: 24238101]

73. Harb T, Matsuyama M, David M, Hill R. Infant colic - what works: a systematic review of interventions for breastfed infants. J Pediatr Gastroenterol Nutr. 2016; 62:668–686. [PubMed: 26655941]

74. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the treatment of infantile colic: a systematic review. J Pharm Pract. 2016 Mar 2. 0897190016634516 (Epub ahead of print).

75. Fiorucci S, Distrutti E. Bile acid-activated receptors, intestinal microbiota, and the treatment of metabolic disorders. Trends Mol Med. 2015; 21:702–714. [PubMed: 26481828]

76. Vogt SL, Peña-Díaz J, Finlay BB. Chemical communication in the gut: Effects of microbiota-generated metabolites on gastrointestinal bacterial pathogens. Anaerobe. 2015; 34:106–115. [PubMed: 25958185]

77. Kenny SE, Vanderwinden JM, Rintala RJ, Connell MG, Lloyd DA, Vanderhaegen JJ, De Laet MH. Delayed maturation of the interstitial cells of Cajal: a new diagnosis for transient neonatal pseudoobstruction. Report of two cases. J Pediatr Surg. 1998; 33:94–98. [PubMed: 9473109]

78. Camilleri M. Enteric nervous system disorders: genetic and molecular insights for the neurogastroenterologist. Neurogastroenterol Motil. 2001; 13:277–295. [PubMed: 11576388]

79. al Tawil Y, Berseth CL. Gestational and postnatal maturation of duodenal motor responses to intragastric feeding. J Pediatr. 1996; 129:374–381. [PubMed: 8804326]

80. Baker J, Berseth CL. Postnatal change in inhibitory regulation of intestinal motor activity in human and canine neonates. Pediatr Res. 1995; 38:133–139. [PubMed: 7478806]

81. Berseth CL. Effect of early feeding on maturation of the preterm infant's small intestine. J Pediatr. 1992; 120:947–953. [PubMed: 1593357]

82. Owens L, Burrin DG, Berseth CL. Minimal enteral feeding induces maturation of intestinal motor function but not mucosal growth in neonatal dogs. J Nutr. 2002; 132:2717–2722. [PubMed: 12221235]

83. Spiller RC, Trotman IF, Higgins BE, Ghatei MA, Grimble GK, Lee YC, Bloom SR, Misiewicz JJ, et al. The ileal brake-inhibition of jejunal motility after ileal fat perfusion in man. Gut. 1984; 25:365–374. [PubMed: 6706215]
84. Spiller RC, Trotman IF, Adrian TE, Bloom SR, Misiewicz JJ, Silk DB. Further characterisation of the 'ileal brake' reflex in man-effect of ileal infusion of partial digests of fat, protein, and starch on jejunal motility and release of neurotensin, enteroglucagon, and peptide YY. Gut. 1988; 29:1042–1051. [PubMed: 3410330]
85. Jadcherla SR, Berseth CL. Effect of erythromycin on gastroduodenal contractile activity in developing neonates. J Pediatr Gastroenterol Nutr. 2002; 34:16–22. [PubMed: 11753158]
86. Berseth CL. Assessment in intestinal motility as a guide in the feeding management of the newborn. Clin Perinatol. 1999; 26:1007–1015. [PubMed: 10572734]
87. Kirjavainen J, Jahnukainen T, Huhtala V, Lehtonen L, Kirjavainen T, Korvenranta H, Mikola H, Kero P. The balance of the autonomic nervous system is normal in colicky infants. Acta Paediatr. 2001; 90:250–254. [PubMed: 11332162]
88. Shamir R, St James-Roberts I, Di Lorenzo C. Infant crying, colic, and gastrointestinal discomfort in early childhood: a review of the evidence and most plausible mechanisms. J Pediatr Gastroenterol Nutr. 2013; 57(Suppl 1):S1–S45. [PubMed: 24356023]
89. Vanderhoof JA, Murray ND, Young RJ. Infantile colic—a functional bowel disorder? Pract Gastroenterol. 1999; 23:39–41.
90. Lothe L, Ivarsson A, Lindberg T. Motilin, vasoactive intestinal peptide and gastrin in infantile colic. Acta Paediatr Scand. 1987; 76:316–320. [PubMed: 3591297]
91. Savino F, Grassino EC, Guidi C, Oggero R, Silvestro L, Miniero R. Ghrelin and motilin concentration in colicky infants. Acta Paediatr. 2006; 95:738–741. [PubMed: 16754557]
92. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (FoeniculumVulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. AlternTher Health Med. 2003; 9:58–61.
93. Savino F, Cresi F, Castagno E, Silvestro L, Oggero R. A randomized double-blind placebo controlled trial of a standardized extract of Matricariaerecutita, Foeniculumvulgare and Melissa officinalis (ColiMil) in the treatment of breastfed colicky infants. Phytother Res. 2005; 19:335–340. [PubMed: 16041731]
94. Freudenberg F, Gothe F, Beigel F, Rust C, Koletzko S. Serum 7-alpha-hydroxy-4-cholesten-3-one as a marker for bile acid loss in children. J Pediatr. 2013; 163:1367–1371. e1. [PubMed: 23968740]
95. Staelens S, Van den Driessche M, Barclay D, Carrié-Faessler AL, Haschke F, Verbeke K, Vandebroek H, Allegaert K, et al. Gastric emptying in healthy newborns fed an intact protein formula, a partially and an extensively hydrolysed formula. Clin Nutr. 2008; 27:264–268. [PubMed: 18280619]
96. Savino F, Cordisco L, Tarasco V, Palumeri E, Calabrese R, Oggero R, Roos S, Matteuzzi D. Lactobacillus reuteri DSM 17938 in infantile colic: a randomized, double blind, placebo-controlled trial. Pediatrics. 2010; 126:e526–e533. [PubMed: 20713478]

Key Points

- Infantile colic, typically manifested as excessive crying in infants, accounts for 10–20% of pediatrician visits of infants aged 2 weeks to 3 months
- The published literature (including systematic reviews) on therapy for infantile colic reveals significant unmet needs despite the use of specialty nutrition, milk formulas, prebiotics, probiotics, and synbiotics
- There is evidence in support of three mechanisms for infantile colic which are related to the transient immaturity of intestinal functions: the enterohepatic functions and bile acid homeostasis, gastrointestinal motility, and the colonic microbiome. Further integrated studies of these mechanisms are recommended to find novel approaches for diagnosis and therapy of this common and distressing condition.

Table 1

Trials with *L. reuteri* Strains in Infantile Colic

Author, Year (ref. #)	Type of Study/Study Population/Intervention	Outcomes	Results
Savino et al. 2007 (69)	- Prospective, open-label, randomized controlled trial. - 83 breastfed infants. - *L. reuteri* ATCC 55730 (10^8 CFU), once a day for 28 days vs. simethicone (60 mg/day), twice a day for 28 days.	- Reduction in daily average crying time.	- Significant reduction in daily median crying times in probiotic group vs. simethicone group at day 28 ($p<0.001$).
Savino et al. 2010 (96)	- Randomized, double-blind, placebo-controlled trial. - 46 exclusively breastfed infants - *L. reuteri* DSM 17938 vs. placebo, once a day for 21 days.	- Primary outcome: reduction of average crying time on day 21. - Secondary outcomes: number of "responders" (those who experienced a decrease in the daily average crying time of 50% from baseline) in each group on days 7, 14, and 21; effects on the intestinal microbiota.	- Significant reduction in daily median crying time in the probiotic group vs. placebo group ($p=0.22$), at day 21. - Significantly higher number of responders in the probiotic group compared with placebo group, at times 7, 14, and 21 ($p=0.006$, $p=0.007$, and $p=0.36$, respectively). - Significant increase in fecal *Lactobacilli* ($p=0.002$), and reduction in fecal *Escherichia coli* in the probiotic group ($p=0.001$). No differences for *Bifidobacteria* and *C. butyricum*.
Szajewska et al. 2013 (71)	- Randomized, double-blind, placebo-controlled trial. - 80 exclusively or predominantly (>50%) breastfed infants - *L. reuteri* DSM 17938 (10^8 CFU) vs. placebo, once a day for 21 days.	- Primary outcomes: "treatment success" (reduction in the daily average crying time ≥50%) at days 7, 14, 21 and 28; duration of crying (minutes/day). - Secondary outcomes: reduction in daily average crying time; persistence of IC after the intervention; parental perception of colic severity; parental/family quality of life.	- Treatment success significantly higher in the probiotic group vs. the placebo group, at all time points ($p<0.05$). - Significant reduction of median daily crying time in the probiotic group at days 14, 21 and 28 ($p<0.0001$). - Significant reduction in parental perception of colic severity, and improved parental/family quality of life in the probiotic group compared with the placebo group ($p<0.0001$).
Sung et al. 2014 (70)	- Randomized, double-blind, placebo-controlled trial. - 167 breastfed or formula-fed infants - *L. reuteri* DSM 17938 (10^8 CFU) vs. placebo (maltodextrin), once a day for 28 days.	- Primary outcome: daily duration of cry or fuss at 1 month - Secondary outcomes: duration of cry or fuss episodes; number of cry or fuss episodes; sleep duration of infants; maternal mental health; family functioning; parents quality of life; infants functioning; infant fecal microbiota; calprotectin levels.	- At 1 month, the probiotics group cried or fussed 49 minutes/day more than the placebo group ($p=0.02$). Difference mainly due to more fussing in the probiotic group ($p=0.002$). - No significant difference in all secondary outcomes.
Chau et al. 2015 (63)	- Randomized, double-blind, placebo-controlled trial. - 52 exclusively breastfed infants.	- Primary outcome: reduction in the duration of average crying and fussing times, from baseline to day 21, to <3 hours/day.	- Total average crying and fussing times shorter in the *L. reuteri* group vs. the placebo group ($p=0.028$).

Author, Year (ref. #)	Type of Study/Study Population/Intervention	Outcomes	Results
	- *L. reuteri* DSM 17938 (10^8 CFU) vs. placebo, once a day for 21 days.	- Secondary outcomes: number of "responders" to treatment (those who experienced a decrease in the daily average crying and/or fussing time ≥50% from baseline) on days 7, 14 and 21.	- Significantly greater reduction in daily crying and fussing times in the probiotic group vs. placebo group (p=0.045), at the end of the treatment.
Mi et al. 2015 (67)	- Randomized, single-blind, placebo-controlled trial. - 39 exclusively or predominantly breastfed infants. - *L. reuteri* DSM 17938 (10^8 CFU) vs. placebo, once a day for 28 days.	- Primary outcome: "treatment success" (reduction in the daily average crying time ≥50%). - Secondary outcomes: mean reduction of daily average crying time, parental satisfaction, and reduction in maternal depression.	- Treatment success in 100% of the probiotic group vs. 15.7% of placebo group (p<0.01), at the end of the treatment period. - Significant reduction in daily crying time in the probiotic group (p<0.01). - Significant improvement of parental satisfaction and maternal depression (p<0.01)

CFU: colony forming unit

Table 2

Trials with *L. rhamnosus GG*, Prebiotics and Synbiotics in Infantile Colic (CFU: colony forming unit)

Authors, Year (ref. #)	Type of Study/Study Population/ Intervention	Outcomes	Results
Dupont et al. 2010 (64)	- Randomized, multi-centre, double-blind, placebo-controlled trial. - 66 formula-fed infants. - Experimental formula (enriched with alpha-lactalbumin, *L. rhamnosus Bifidobacterium infantis*, reduced in protein and lactose contents, and thickened with corn starch) vs. control formula.	- Effects on and crying, irritability, and agitation without crying duration. - Effects on regurgitation, flatulence/gas, and vomiting.	- No differences between the two groups for crying duration. - Feeding-related GI side effects were significantly lower with the experimental formula (p=0.01).
Partty et al. 2013 (68)	- Randomized, double-blind, placebo-controlled trial. - 94 preterm infants. - Prebiotic mixture of galacto-oligosaccharides and polydextrose 1:1 (600 mg/day) vs. *L. rhamnosus* GG ATCC 53103 (10^9 CFU) vs. placebo (microcrystalline, cellulose and dextrose anydrate), once a day from days 1 to 30 and twice a day from days 31 to 60.	- Effects on infant crying, fussing, and irritability, and on microbiota development.	- Significantly less frequent excessive criers in the prebiotic and probiotic groups vs. the placebo group (p=0.02). - Higher proportion of *Lactobacillus-Lactococcus-Enterococcus* group relative to total bacterial count in stools of excessive criers vs. contented infants (p=0.005). - Lower proportion of *Clostridium histolyticum*-type bacteria to total bacterial count in the fecal samples of probiotic group compared to the prebiotic and placebo groups (p=0.047).
Giovannini et al. 2014 (65)	- Randomized, double-blind, parallel group trial. - 199 breastfed infants and 163 formula-fed. - Formula-fed infants randomized to either control formula or a GOS-supplemented formula (0.4 g/100 ml).	- Effects on GI symptoms (colic, stool consistency and frequency, regurgitation). - Effects on the intestinal microbiota.	- Supplemented group normal and soft stools in 89% of the episodes; significantly lower incidence of colic. - Supplemented group had lower count of *Clostridium* and higher count of *Bifidobacterium* compared to the control group.
Kianifar et al. 2014 (66)	- Randomized, double-blind, placebo-controlled trial. - 50 breastfed infants - Synbiotic mixture (1 billion CFU of 7 probiotics: *L. casei, L. rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, L. acidophilus, B. infantis, L. Bulgaricus*; and fructo-oligo-saccharides) vs. placebo, once a day for 30 days.	- Primary outcome: "treatment success" (reduction in the daily average crying time >50%). - Secondary outcomes: symptom resolution (reduction in daily crying time >90%); duration of colic (minutes/day); weight.	- Treatment success higher in the synbiotic group compared with placebo group, at days 7 (p<0.005) and 30 (p<0.01). - Symptom resolution higher in the synbiotic group vs. the placebo group at day 7 (p<0.03) but not at day 30.