Infant colic: mechanisms and management

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Abstract | Infant colic is a commonly reported phenomenon of excessive crying in infancy with an enigmatic and distressing character. Despite its frequent occurrence, little agreement has been reached on the definition, pathogenesis or the optimal management strategy for infant colic. This Review aims to delineate the definitional entanglement with the Rome IV criteria, which were published in 2016, as the leading, most recent diagnostic criteria. Moreover, neurogenic, gastrointestinal, microbial and psychosocial factors that might contribute to the pathophysiology of infant colic are explored. This Review underlines that a comprehensive medical history and physical examination in the absence of alarm symptoms serve as guidance for the clinician to a positive diagnosis. It also highlights that an important aspect of the management of infant colic is parental education and reassurance. Management strategies, including behavioural, dietary, pharmacological and alternative interventions, are also discussed. Owing to a lack of large, high-quality randomized controlled trials, none of these therapies are strongly recommended. Finally, the behavioural and somatic sequelae of infant colic into childhood are summarized.

Crying is one of the earliest and most powerful forms of communication for newborn infants. At this early stage in their development, infants are not yet able to meet their own needs. Crying connects them to their caregivers, who are their primary source for protection and nurture, and this evolutionarily selected behaviour probably increases infants' chances of survival[1,2]. The amount and pattern of crying is age-dependent and changes during the first months of life. Despite considerable variation in crying among individuals during this period, a clear trend in the amount and pattern of crying is present, a feature described as the 'normal crying curve' in infants[2,3]. In a study published in 1962, caregivers kept daily diaries to record their infants' crying and fussing time during the first 12 weeks of life. In this study, fussing was defined as a type of crying displayed during discrete periods of the day, with a cyclic character because of its regular occurrence, which was heightened by environmental tension and not eliminated by obvious methods of relief offered by typical mothers[4]; a 2016 article alternatively defined fussing as "behaviour that is not quite crying but not awake and content either" (REF.[5]). The diaries demonstrated increased duration of crying in the first weeks of life, reaching a maximum between 6 and 8 weeks of age and then declining to more stable levels around 12 weeks of age[4] (FIG. 1). Other North American studies found similar crying curves and showed that after the crying decreases around 12 weeks of age, a period of fairly stable, low-level crying is present until the end of the first year[6,7] (FIG. 1). A meta-analysis published in 2017, which included 28 diary studies covering 8,690 infants, reported a mean daily fuss and cry duration of 117–133 min in the first 6 weeks of life, followed by a decline in crying time to a mean of 68 min per day by 10–12 weeks of age[8]. Infant crying has a diurnal pattern, with a typical clustering of crying during the late afternoon and the evening[4,6,9]. The pattern of early crying (during the first 3 months of life) is not modified by caretaking style, in contrast to the amount of crying later in the first year of life[4,9–12]. Therefore, the crying of infants during the first months of life is considered to reflect physiological maturational shifts in neurobehavioural development[9].

When the crying of otherwise healthy and well-fed babies gains a more persistent, inconsolable, excessive and unexplained character, it is often referred to as infant colic or excessive crying. Although infant colic is a benign and usually self-limiting condition, it is a source of major distress for the infant, parents, family and health-care givers[13]. Moreover, the perception of parents with respect to the cause of crying and the way they deal with these prolonged periods of crying might influence their affection for their child even long after the excessive crying has stopped[14,15]. At present, the cause of infant colic is poorly understood, leaving clinicians with the challenge of finding strategies to manage this phenomenon.

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Key points

- Infant colic is a common phenomenon in infancy with an enigmatic and distressing character.
- Infant colic is most often defined according to the Wessel criteria or according to the Rome criteria.
- The pathogenesis of infant colic remains unclear and is thought to be multifactorial; however, a growing body of evidence suggests that the gut microbiome contributes to development of the condition.
- The cornerstones in the management of infant colic are parental reassurance and education.
- Owing to a lack of large, high-quality randomized controlled trials, none of the behavioural, dietary, pharmacological or alternative interventions are strongly recommended.

This Review is designed to provide clinicians with guidance in the challenging management process of infant colic. As such, we provide an overview of the terminology, prevalence, pathophysiology, diagnostic work-up, management and possible long-term consequences of infant colic.

Definition

Most of the available definitions for infant colic focus on the duration of crying and/or on the effect it has on caregivers[16]. A systematic review on definitions and outcome measures in trials of infant colic reported the current variability in defining infant colic, which parallels the non-uniformity of measuring the condition[17]. Twenty different definitions for infant colic were used in 39 trials, and most of these definitions were based on Wessel's criteria[10] or the Rome III criteria[18]. Wessel's criteria, also known as the 'rule of threes', defines colic as paroxysms of irritability, fussing or crying lasting ≥3 hours per day on ≥3 days per week in any 1 week in an otherwise healthy baby aged 2 weeks to 4 months. Furthermore, it requires severe colicky infants to have paroxysms for >3 weeks[10]. However, measuring the duration of crying can be challenging in the household and clinical setting. For example, observing a crying infant for 3 weeks without evaluation or intervention is unacceptable for most parents and clinicians[19]. For researchers, it is also difficult to precisely assess behaviour over a 3-week period, as they are forced to rely upon retrospective parental reports of the crying and fussing, making measuring infant colic more prone to error[20]. Therefore, the Wessel criteria were found to be too arbitrary[21], culturally dependent[20] and impractical to use[5], with too little focus on the unsoothable character of the crying[22] and with invalid use of the word 'paroxysmal' (REFS[23,24]). For these reasons, several modified versions of the Wessel criteria and new definitions of infant colic were developed[17,25–28]. The Rome IV criteria for functional gastrointestinal disorders in infants, which were launched in 2016 (REF.[5]) (BOX 1), differentiate between a definition of infant colic for general paediatricians and for clinical researchers[5].

Epidemiology

Infant colic is a common phenomenon in infancy. As a consequence of the various definitions that are used for infant colic, prevalence varies widely. A systematic review published in 2001, which included eight community-based prospective surveys conducted in Northern Europe and the UK, demonstrated that the prevalence of infant colic ranged from 3–28%[29]. When the authors evaluated only the two studies that stringently used Wessel's criteria, cumulative incidence rates of infant colic varied from 5–19%. A systematic review published in 2017 assessed the prevalence of colic according to the modified Wessel criteria (that is, crying for ≥3 hours per day on at least 3 days in any 1 week) at different age stages during the first 12 weeks of life[8]. After pooling data of 28 diary studies, overall prevalence of colic in the first 6 weeks of life ranged from 17–25%[8]. These rates dropped to 11% and 0.6% by 8–9 weeks of age and 10–12 weeks of age, respectively[8]. It seems as though no differences exist in prevalence rates of infant colic between boys and girls[29–31] or between breastfed and formula-fed infants[32]. However, lower prevalence rates of colic than overall weighted colic prevalence were found in infants aged 5–6 weeks who were bottle-fed or mixed-fed[8]. Prevalence rates based on the Rome III criteria for infant colic were assessed in two population-based survey studies conducted in the US and Colombia in 2015 and 2016, respectively. According to the reports of mothers of 1,447 infants in the USA, colic was present in 5.9% of their infants[30]. In Colombia, a prevalence of 10.4% was found among 1,231 infants aged 0–48 months presenting at primary care clinics[31].

The prevalence of infant colic might be affected by parental perceptions of the duration and intensity of the crying bouts of their infant[24]. In one study, only 35% of infants who were perceived as colicky infants by their mothers were found to be excessive criers according to the rule of threes when measured with a strict diary[25]. Moreover, several studies have shown that parental recall measures tend to overestimate the number of infants who cry ≥3 hours per day in comparison with the number measured directly with a validated diary[28,33–35].

Clinical features

To differentiate colic from other, more serious conditions, it should be characterized according to several clinical features[36]. Infant colic is often accompanied by flushing of the face, a frown, tensing of the abdomen, clenching of the fists and drawing up of the legs[37]. Important additional clinical features of infant colic are its prolonged, hard-to-soothe and unexplained nature[5]. The duration of crying bouts, in particular, inconsolable crying bouts, is associated with frustration in caregivers[22]. Particularly in the first 4 months of life, the hard-to-soothe character of infant colic is distressing for parents because parents are unable to control the crying[22,38,39]. Furthermore, one study found that the crying of infants with colic is at a higher fundamental frequency and is harsher sounding (increased dysphonation) than the crying of infants without colic[40]. Another study reported a higher jitter (that is, frequency instability), shimmer (that is, amplitude instability) and proportion of noise in the cries of infants with colic than in those without colic[41]. Conversely, other studies have found no differences in fundamental frequency and dysphonation between cries of infants with colic and infants without colic[42] nor in distinct cry features between colic cries and pre-feed cries[24,43].

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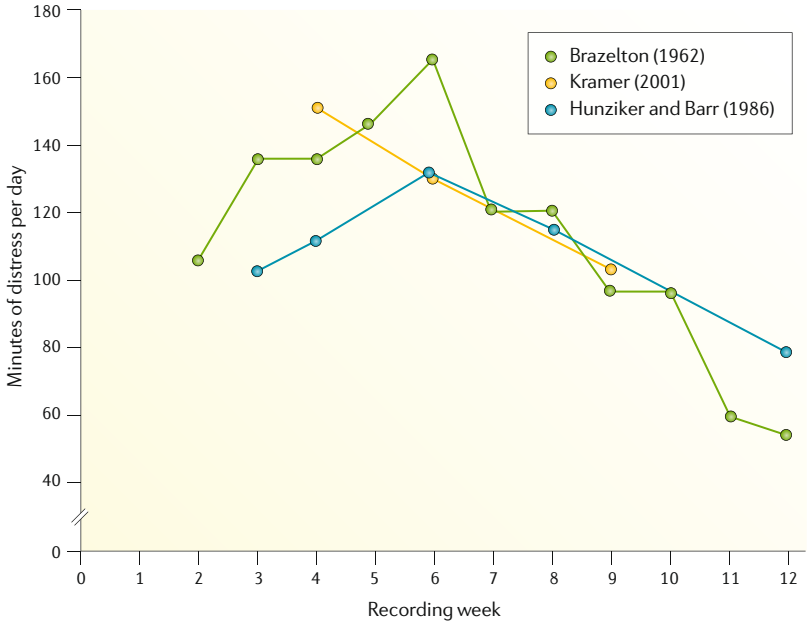

Fig. 1 | **Crying amounts and patterns from three North American studies[4,6,7] illustrating absence of a secular trend.** Adapted with permission from REF.[213], Elsevier.

Pathophysiology

The pathophysiological mechanisms underlying infant colic remain largely unclear. The term 'colic' stems from the Greek 'kolikos', the adjective of 'kolon', which means intestine[44]. This implied disturbance of the gastrointestinal tract was supported by Illingworth, who popularized the term 'colic' in 1954 (REF.[45]). Thereafter, he referred to this phenomenon as "pain that is obviously of intestinal origin" (REF.[37]). Currently, children with infant colic are sometimes referred to paediatric gastroenterologists, as it is frequently assumed by parents that crying reflects abdominal pain with a gastrointestinal origin[5,18]. However, it is arguable whether infant colic has a gastrointestinal origin[46]. In the following section, several factors are discussed that might contribute to the origin of infant colic, such as neurodevelopmental factors, the microbiome, gastrointestinal factors, the mode of feeding, psychosocial influences and serious underlying factors (FIG. 2).

Neurodevelopmental factors

A neurodevelopmental explanation has been suggested for the manifestation of infant colic[47]. For this explanation, it is important to dissociate the crying features frequency and bout length. This dissociation was first exemplified in a hunter–gatherer society in Botswana, the !Kung San[48], and was confirmed by others in Western societies[6,25,49]. The !Kung San caregiving style, characterized by close physical and temporal mother–infant contact, which is in contrast to Western practices[50], influenced only the duration of infant daytime crying and not the normal crying curve or the frequency of the crying bouts. In this context, it has been suggested that research on the neurodevelopmental explanation for colic should focus on the regulation of the crying state rather than on what causes the infant to cry[39,51]. This approach is reflected in one of the diagnostic criteria for infant colic, namely, inconsolability[5]. The unsoothable nature of crying bouts in infants with colic raises the question whether their sensory processing differs from that of infants who do not have colic. Indeed, infant colic was associated with crying that is easily triggered and a harder-to-soothe response following a neurobehavioural assessment[52]. This finding might imply a temporary lack of neurological control of behaviour during the developmental transition period, which normally occurs around the age of 2 months, in which brain systems are reorganized by replacing reflex mechanisms for behaviour control with cerebral cortex controlled systems[9,53]. In line with this hypothesis, a controlled clinical trial reported that infants with colic were less able to regulate their crying and were less effectively soothed following a sucrose stimulation than infants without colic, suggesting that the regulatory effects of sucrose taste are diminished in infants with colic[54]. One of the hypotheses underlying the soothing effect of sweet-tasting solutions is the endogenous opioid system, in which opioid receptors and their endogenous ligands exert a mediating stress effect in the central nervous system through a decreased release of excitatory neurotransmitters[55]. It is therefore suggested that the endogenous opioid system is altered in infants with colic, as they display a reduced effect of sucrose tasting[51,56].

Microbiota

Microbial patterns associated with infant colic. Gut microbial signatures from infants with colic differ from those from infants without colic in terms of microbial diversity, stability and colonization patterns[57–60]. These alterations indicate that a state of intestinal dysbiosis (defined as a microbial imbalance in the gastrointestinal tract) might play a role in the expression of infant colic symptoms[61] (FIG. 3). Crying behaviour as a result of intestinal dysbiosis would be facilitated by the microbiota–gut–brain axis that links the brain with peripheral intestinal functionalities in a bidirectional manner. Various signalling pathways are involved in this interaction, including neural, endocrine, immune and humoral signalling pathways[62,63]. Through this axis, intestinal dysbiosis can affect central and enteric neuronal function, such as detection of pain in infants[63,64], which could potentially have a role in excessive crying[65].

Distinct microbial patterns have been found in infants with colic up to 4 months of age. A lower diversity and stability of the intestinal microbiota was reported in infants with colic than in infants without colic during the first 2 weeks of life[57]. Other studies found that the presence of certain intestinal microorganisms was associated with increased amounts of crying in infants up to 3–4 months of age, including microorganisms belonging to the Proteobacteria phylum[57,58,66]. Within this phylum, the relative abundance of microorganisms belonging to the genera *Escherichia* and *Klebsiella* was increased in stool samples from infants with colic[57,58,66]. Moreover, differences regarding the presence of the Gram-negative bacterial genera *Serratia*, *Vibrio*, *Yersinia* and *Pseudomonas* (phylum Proteobacteria) were found in infants with colic compared with infants without colic

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Box 1 | **Rome IV criteria for infant colic**

Clinical purposes

Diagnostic criteria for clinical purposes must include all of the following:

- An infant who is <5 months of age when the symptoms start and stop
- Recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without obvious cause and cannot be prevented or resolved by caregivers
- No evidence of infant failure to thrive, fever or illness

Clinical research purposes

Diagnostic criteria for clinical research purposes must include the following:

- All of the preceding criteria
- Caregiver reports of infant crying or fussing for ≥3 hours per day during ≥3 more days in 7 days in a telephone or face-to-face screening interview with a researcher or clinician
- Total 24-hour crying plus fussing in the selected group of infants is confirmed to be 3 hours or more when measured by at least one prospectively kept, 24-hour behaviour diary

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at 2 or 4 weeks of age[57]. These observed microbial signatures, characterized by increased levels of potentially pathogenic Gram-negative bacteria, might result in increased intestinal pain and explain the excessive crying observed in colic[58,64–68].

One underlying mechanism would be excessive intestinal gas production, which can be caused by fermentation of lactose, carbohydrates and proteins by Proteobacteria[60,66]. Another important candidate mechanism is gut inflammation. Increased gut inflammation, as indicated by elevated concentrations of faecal calprotectin, a biomarker of intestinal neutrophilic infiltration, has been found in infants with colic[58]. More recently, it was shown that infants with colic had higher serum concentrations of pro-inflammatory cytokines and chemokines, including IL-8 and CC-chemokine ligand 4 (CCL4), than infants without colic, also indicating low-grade gut inflammation[67]. Gram-negative bacteria, such as species of *Escherichia* and Bacteroidetes, can induce gut inflammation through the presence of lipopolysaccharides (LPS) on their outer membrane[69] and might thus be pathogenically linked to colic. Pathogen-associated LPS can activate the production of pro-inflammatory cytokines and chemokines, consequently provoking a pro-inflammatory response in gut epithelial cells[70,71]. However, it remains to be established whether gut microbiota alternations in infants with colic cause gut inflammation or whether they are the result of intestinal inflammation[58,67]. Further potential (associated) mechanisms relating these microbial signatures to excessive crying are increased gut permeability and visceral hypersensitivity[65].

Certain microbial signatures have also been associated with decreased amounts of crying. Microorganisms from the phyla Bacteroidetes, Actinobacteria and Firmicutes were inversely associated with colic symptoms[57,58,66]. For example, gut microbiota from infants with colic had lower relative abundances of *Bifidobacterium* (phylum Actinobacteria) and *Lactobacillus* (phylum Firmicutes) than the microbiota of infants without colic within in the first 2 weeks after birth[57]. In accordance with these findings, an inverse association between the presence of *Bifidobacterium* and *Lactobacillus* in the stool samples of infants and crying time was reported during the first 3 months of life[72].

The negative associations between these microorganisms and infant crying can be explained by the fact that lactobacilli, or lactic acid bacteria, can have beneficial effects on the gut lumen, epithelial function, mucous barrier and gastrointestinal motility[73,74]. Moreover, specific *Bifidobacterium* spp. and *Lactobacillus* spp. might promote the appropriate functioning of the intestinal immune system[75,76]. Additionally, certain *Bifidobacterium* spp. and *Lactobacillus* spp. have the potential to exert antagonistic effects against gas-producing bacteria, including species of *Escherichia*, *Klebsiella* and *Enterobacter*[68].

Finally, three studies carried out in Egypt, Saudi Arabia and the Netherlands suggest a relationship between the presence of *Helicobacter pylori* in the gut and infantile colic[64,77,78]. In the study carried out in Egypt, *H. pylori* was significantly more prevalent in infants with colic than those without colic ($P<0.001$). In the study, 62% of infants with colic ($n=50$) and 20% of infants without colic ($n=50$) tested positive for *H. pylori*[78]. The other two studies reported similar findings with *H. pylori* or *Helicobacter*-related bacteria[64,77]. Given the low number of available studies and the fact that the prevalence of *H. pylori* varies geographically in infants and children, additional studies are warranted to confirm these findings[79].

Factors influencing infant microbiota and possibly contributing to infant colic. Within the first 2 weeks of life, preceding the peak of colic at 6 weeks, a distinct microbial pattern associated with infant colic can already be identified in the infant gut[57]. Moreover, as commensal microbiota colonization is suggested to start in utero, albeit with the most substantial colonization probably taking place at birth[80], the question is raised as to

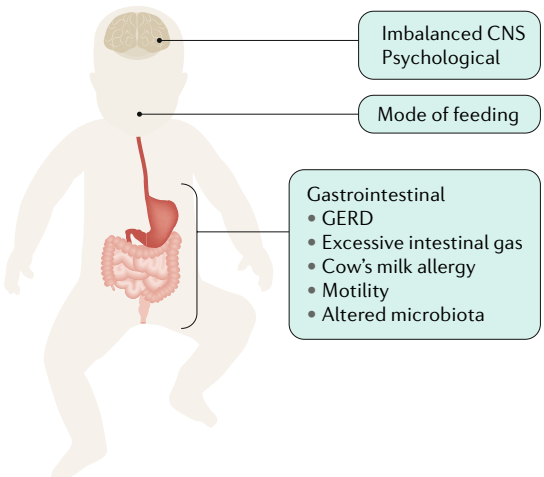

Fig. 2 | **Possible pathophysiological mechanisms contributing to the pathogenesis of infant colic.** Proposed factors include an imbalance of the central nervous system (CNS), several gastrointestinal factors, the mode of feeding and psychosocial factors.

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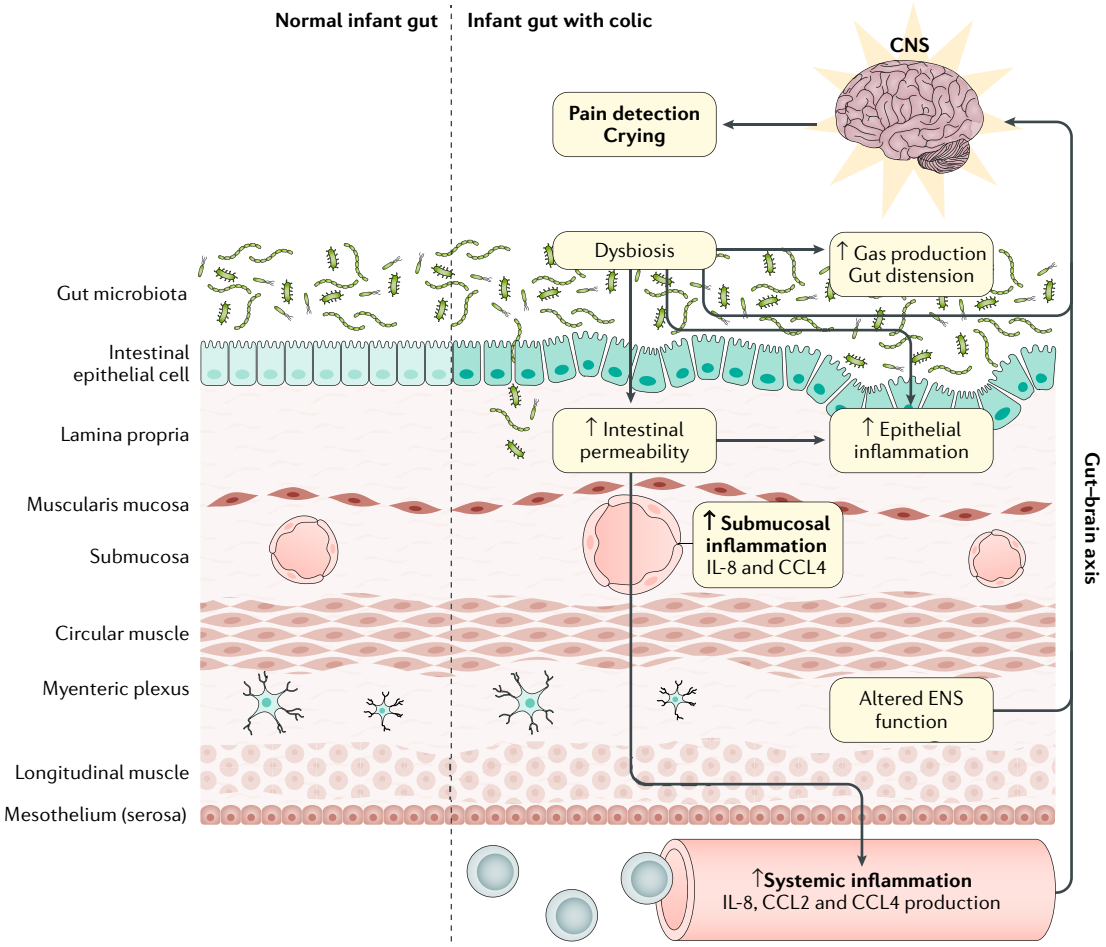

Fig. 3 | **Mechanisms through which bacterial dysbiosis can contribute to excessive crying in infant colic.** Alterations in microbial composition, diversity and stability, also referred to as intestinal dysbiosis, might be present in infants with colic. Intestinal dysbiosis might contribute to colic symptoms by increased fermentation of lactose, carbohydrates and proteins, resulting in increased gas production and gut extension. Increased gut permeability might facilitate increased low-grade mucosal, gut and systemic inflammation. Low-grade gut inflammation can result from elevated amounts of Gram-negative bacteria, including *Escherichia* spp., *Bacteroidetes* spp. and *Klebsiella* spp. Pathogen-associated lipopolysaccharide, present on the outer membranes of Gram-negative bacteria, can promote production of pro-inflammatory cytokines and chemokines, consequently provoking a pro-inflammatory response in gut epithelial cells. Increased serum concentrations of pro-inflammatory cytokines, including IL-8, CC-chemokine ligand 2 (CCL2) and CCL4, might reflect the low-grade gut inflammation in infant colic. Through the microbiota–gut–brain axis, intestinal dysbiosis might affect central and enteric neuronal function, including detection of pain and crying, in infants with colic. CNS, central nervous system; ENS, enteric nervous system.

whether aberrations in the early gut colonization process could be linked to infant colic. Colonization is influenced by a number of external factors, including maternal microbiota and health status, prenatal maternal stress, maternal medication use, environmental factors at home and in the hospital[81,82], infant antibiotic use, mode of delivery and infant feeding mode (breast milk versus formula feeding)[83,84]. However, there are no indications that these factors, at least separately, are associated with the development of infant colic[29,58,85–88] (FIG. 4). Thus, it is unlikely that these factors independently cause gut microbiota alterations that underlie infant colic.

In addition, studies have suggested that delayed or altered colonization by *Lactobacillus* spp. after birth, together with higher numbers of Enterobacteriaceae and *Enterococcus* spp., underlies the development of infant colic[89,90]. After parturition, the infant gut is colonized by Enterobacteria and *Enterococcus* spp., followed by colonization by *Bifidobacterium* spp. and *Lactobacillus* spp.[91]. This process might be affected in infants with colic; there is evidence that faecal samples from infants with colic might differ with regards to the presence of *Lactobacillus* spp. For example, faecal samples from infants with colic only contained *Lactobacillus brevis* and *Lactobacillus lactis*, whereas samples from healthy infants only contained *Lactobacillus acidophilus*[89]. However, the role of *Lactobacillus* spp. in the development of infant colic remains elusive. Some probiotic intervention studies in infants with colic investigating the efficacy of administering *Lactobacillus* spp., including *Lactobacillus rhamnosus* and *Lactobacillus reuteri*, after birth reported increased *Lactobacillus* spp. abundance and decreased *Escherichia coli* abundance in stool samples of infants with colic before the intervention[88,92,93].

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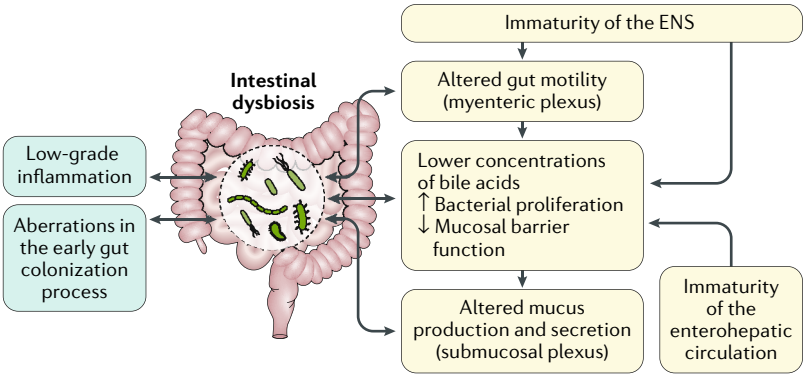

Fig. 4 | **Hypothesized mechanisms possibly leading to bacterial dysbiosis in infants.** Low-grade gut inflammation, as observed in infants with colic, might alter the composition of the gut microbiota. Conversely, gut microbiota alternations could induce gut inflammation in infant colic. Delayed or altered colonization by *Lactobacillus* spp. or *Bifidobacterium* spp. could contribute to intestinal dysbiosis. Immaturity of parts of the enterohepatic circulation might lead to reductions in bile acid production, potentially leading to reduced concentrations of bile acids, which is associated with increased bacterial proliferation, reduced mucosal barrier function and increased colonic contraction (which can be associated with pain). Reduced amounts of bile acids and/or the immature infant enteric nervous system (ENS) might alter gut motility, which is primarily controlled by the myenteric plexus. In addition, these factors might influence mucus production, which is mainly controlled by the submucosal plexus. On the other hand, intestinal dysbiosis might also influence the amount of bile acids, mucus production and secretion and gut motility.

In addition to bacterial colonization processes, a second factor hypothesized to indirectly lead to infant colic is the physiology of bile acid production and regulation during the first few postnatal months of age[94]. Bile acids, or bile salts when ionized in the gut, are produced in the liver and reabsorbed by the intestines and returned to the liver as part of the enterohepatic circulation[95]. Bile acids have important functions in the intestinal lumen. They exert bacteriostatic effects on gut microorganisms, influence bacterial proliferation and mucus production and promote mucosal barrier function[96]. Reduced intraluminal levels of bile acids in the infant gut can result in malabsorption of fat and nutrients and in alterations in gut microbiota composition, which could contribute to the manifestation of infant colic[58,64,66,94].

Two mechanisms have been postulated to cause reductions in bile acids in infants. First, immaturity of parts of the enterohepatic circulation, including not fully functioning bile acid transporters and enzymes, might lead to reductions in bile acid production. Interestingly, the maturation in the hepatic system during the first few postnatal months corresponds with the development and resolution of infant colic[94]. Second, immaturity of the small intestines during the neonatal period might also lead to a reduced level of gut bile acids. Studies published in the 1970s found that ileal immaturity can lead to a decrease in active absorption of bile salts in the gut, resulting in a loss of these compounds in the enterohepatic circulation and their accumulation in the gastrointestinal tract[97,98]. In adults, low concentrations of bile acids, together with elevated concentrations of long and short-chain fatty acids, can produce colonic contractions[99,100] that can be associated with pain[94].

Although bile acids can influence the gut microbiota composition, the converse is also true: intestinal dysbiosis can influence the available amount of bile acids in the gut lumen[94]. About 5–10% of the bile acids present in the gut are degraded into secondary bile acids by specific bacterial groups, mainly anaerobic bacteria of the genera *Bacteroides*, *Eubacterium* and *Clostridium*, through the action of bile salt hydrolases. These secondary bile acids are then reabsorbed by enterocytes[101,102]. Thus, intestinal dysbiosis can interfere with normal degradation and uptake of bile acids in the intestines, possibly leading to decreased amounts of bile acids in the gut in some cases[94].

A third and final factor that could indirectly have a role in infant colic is immaturity of the enteric nervous system (ENS), which leads to abnormal gut motility and sensory functions[94]. The ENS, together with extrinsic innervation, controls motility and mucus secretion in the intestines[103]. Two neural networks form the ENS: the myenteric plexus and the submucosal plexus. The myenteric plexus, located between the circular and longitudinal layers of the muscularis propria, is primarily involved in coordination of gut motility. The submucosal plexus mainly controls mucosal secretion and absorption[103]. Immaturity of the ENS might contribute to infant colic in two ways. Gut dysmotility, together with altered mucus secretion, might alter the gastrointestinal environment in which bacteria reside. The altered gastrointestinal environment might consequently influence microbial composition[104], possibly contributing to infant colic through the proposed mechanisms described in the previous paragraphs.

Second, ENS immaturity might cause the transient dysregulation of small intestinal motility, which could result in intestinal dysmotility in infants with colic, thus contributing to pain and crying behaviour[94]. Owing to the lack of evidence in infant colic, this hypothesis is supported by studies in premature infants and neonates showing that immaturity of interstitial cells of Cajal (myenteric cells functioning as pacemakers of the bowel) can result in abnormal patterns of motility in the gut[105]. Indeed, preterm infants show delays in gastric emptying together with a clear pattern of gastrointestinal maturation in the first weeks after birth[106]. Moreover, infants born premature or small for gestational age also show an increased risk of excessive crying during the first postnatal months[107].

More evidence for the association between dysregulation of the intestinal tract motility and intestinal microbiota originates from intervention studies using prebiotics and probiotics[108,109]. For example, preterm infants who were fed with prebiotics (a mixture of short-chain galactooligosaccharides (scGOS) and long chain fructooligosaccharides (lcFOS)) and probiotics (*L. reuteri*) for one month had faster gastrointestinal motility, as measured by gastric emptying rate and electrogastrogram slow-wave propagation, than exclusively breastfed preterms[109].

Translating these findings to infant colic, *L. reuteri* has also been shown effective in relieving colicky symptoms[61]. Seven randomized controlled trials (RCTs) were included in a systematic review that concluded that

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L. reuteri DSM 17938 can be beneficial in reducing symptoms of infant colic, especially in breastfed infants[61]. These trials indicate that there might be a relation between gut dysmotility and intestinal dysbiosis in infant colic.

In conclusion, the literature provides evidence for an interplay between infant colic and intestinal dysbiosis, gut inflammation, altered hepatic bile acid production and regulation, and ENS immaturity, which is facilitated by the microbiota–gut–brain axis[64,67,94]. Further research is necessary to clarify these theories and to further unravel the potential underlying mechanisms.

Gastrointestinal factors

Several other gastrointestinal factors have been proposed to contribute to the pathogenesis of infant colic. These factors have been elucidated in TABLE 1. The most evidence exists for an association between cow's milk protein intolerance and infant colic on the basis of positive results of trials with soy and extensively hydrolysed formulas in infants with colic[110–112]. Some evidence supports the contribution of excessive intestinal gas and gut hormones to the aetiology of infant colic[113,114]. Evidence for a causative role of gastro-oesophageal reflux disease (GERD) or lactose intolerance in infant colic is weak (TABLE 1).

Mode of feeding

Similar prevalence, amount and pattern of crying are reported between infants fed with human milk, formula or formula-supplemented milk, suggesting that protein hypersensitivity in diet is not related to colic in otherwise healthy infants[40,115–117]. Contrarily, one study found a higher prevalence of colic symptoms in formula-fed infants than in breastfed infants[118]. A prospective study comparing the effect of prolonged emptying of one breast at each feed (the experimental group) with an equal emptying of both breasts at each feed (the control group) in 302 mother–child dyads showed a lower incidence of infant colic in the experimental group, suggesting that prolonged feeding from one breast decreases colic in infants[119].

Psychosocial influences

Whether crying is defined as a problem is determined by the perception of the parents of what they experience as excessive and inconsolable crying. Furthermore, family stress, maternal anxiety and the transmission of tension from mother to infant might play a role in the aetiology of infant colic[10,120–122]. Indeed, maternal anxiety disorders were a robust predictor for infant colic, even after controlling for potential confounders such as maternal age, education and parity[122]. Furthermore, mothers with a high trait anxiety score had a twofold higher risk of having an infant with colic than mothers with low trait anxiety scores[123]. By contrast, a prospective study of 378 infants did not find a relationship between maternal emotional factors and excessive infant crying[120]. Maternal self-efficacy (the belief about one's own parenting capabilities) during pregnancy mediated the postpartum effect of prenatal stress, as infants of mothers with high levels of prenatal stress and high levels of self-efficacy demonstrated reduced crying[124].

Finally, a population-based cohort study of 3,555 fathers showed an association between paternal depressive symptoms during pregnancy and the excessive crying of their infant at 2 months of age, independent of maternal depressive symptoms and other relevant confounders, such as maternal age, education level and ethnicity[121]. In summary, these findings indicate an important role for parental factors in the aetiology of infant colic. However, it remains a challenge to determine the causal relationship between infant colic and family stress as both factors influence the parental perception of crying.

Serious underlying condition

It is important to stress that in most cases of infant colic, no underlying organic cause is found. This aspect is exemplified by a retrospective review of 237 afebrile infants under 1 year of age who presented at an emergency department with a chief complaint of crying, irritability, screaming, colic or fussiness[125]. Only 12 infants (5.1%) had serious underlying aetiologies, with urinary tract infection as the most prevalent disorder ($n = 3$)[125].

Risk factors

A number of studies have found that mothers who smoked during pregnancy have an approximately twofold increased risk of having an infant with colic[126–129]. In addition, an equally increased risk of colic was found in infants of mothers who underwent nicotine replacement therapy during pregnancy, suggesting a role for nicotine in the pathogenesis of infant colic[129]. The same authors also assessed the relationship between gestational age and infant colic in a cohort of 62,761 live-born singletons in Denmark and found an increased risk of infant colic with decreasing gestational age, even after adjusting for covariates. Infants born before 32 completed gestational weeks had the highest risk of infant colic (OR 1.5, 95% CI 1.0–2.2)[130].

Evaluation

The cornerstone of the diagnostic work-up (FIG. 5) of infant crying typically includes a careful history and physical examination to exclude identifiable organic causes[125]. A thorough history examination should include a history of sleeping, nutrition, defecation and urination patterns; prenatal and perinatal problems; and a history of psychosocial problems, with special attention for parent–infant interactions[131]. In addition, a careful physical examination should comprise assessment of weight gain, vital signs, hydration and subcutaneous fat[131]. A list of key clinical clues, also termed 'red flags', might identify organic causes for crying or can be seen as alarming symptoms in the diagnostic process for colic[132–135] (BOX 2). When one of these alarm symptoms is discovered, further assessment is required[135]. It is usually unnecessary to perform laboratory testing or radiographic imaging if the infant with colic is gaining weight normally and has a normal physical examination[136]. A thorough and careful history and physical examination is reassuring to parents. FIGURE 5 shows the diagnostic work-up. With the introduction of the Rome IV criteria for infant colic in 2016, the assessment of the amount of

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Table 1 | **Possible gastrointestinal factors contributing to the pathophysiology of infant colic**

Gastrointestinal factor	Possible mechanisms	Evidence
CMPI	Allergic reaction: cow's milk protein is one of the first foods an infant is exposed to after birth. Allergic reactions following the introduction of this protein are suggested as a cause of infant colic[156]	• Three studies support the contribution of CMPI - Elimination of cow's milk protein in maternal diet improved symptoms in one-third of breastfed infants with colic[110] - There was symptom resolution in infants with colic after switching from a cow's-milk protein-based formula to soy protein-based formula[168] - There was a benefit of whey hydrolysate formula over standard formula for reduced crying duration in infants with colic[111] • One systematic review supports the contribution of CMPI - Breastfed infants: hypoallergenic maternal diet might be beneficial in decreasing colicky symptoms[112] - Formula-fed infants: hydrolysate formula might ameliorate symptoms in infants with colic[112] • One study argues against the contribution of CMPI - There was only a temporary improvement in the duration of crying after casein hydrolysate formula instead of a cow's milk-containing formula; this effect diminished with time and was not reproducible[163]
Excessive intestinal gas	Bacterial fermentation: incomplete absorption of carbohydrates in the small intestine results in bacterial fermentation, which might be related to intestinal immaturity[113]	• Two studies support the contribution of excessive intestinal gas - There is increased breath hydrogen in infants with colic compared with infants without colic, suggesting differences in colonic bacterial fermentation[114,228] • One study argues against the contribution of excessive intestinal gas - No differences in breath hydrogen excretion were seen between infants with or without colic[229]
Lactose intolerance	• Ingesting carbohydrates during the day leads to prolonged crying and abdominal pain, and crying peaks in late afternoon • Physiological malabsorption due to enzyme insufficiency, which has a tendency to resolve by the age of 3 months because of the increased gut lactase enzyme expression. This period coincides with the age that infant colic usually resolves[230,231]	• Two studies support the contribution of lactose intolerance - Infants with colic produced more breath hydrogen after intake of feedings containing lactose than infants without colic[114] - There was a minor improvement of symptoms in infants with colic after treatment with pre-incubated feeds with lactase[232] • Two studies argue against the contribution of lactose intolerance - There was no symptom improvement after lactase supplementation in breastfed or formula-fed infants with colic[233,234]
GER(D)	GER(D) has a relationship with infant colic because of overlapping symptoms in both entities, such as crying, irritability and restlessness[235]	• One study supports the contribution of GER - 16/26 infants with colic were found to have 'pathological GER' (on the basis of an oesophageal pH <4) after pH monitoring during infant colic attacks[236] • Six studies argue against the contribution of GER - Only 1/24 excessively crying infants younger than 3 months of age with presumptive GER had pathological GER on the basis of pH-monitoring results[237] - Treatment with anti-reflux medication in irritable and crying infants was not superior to placebo and did not reduce crying[238,239] - No correlation was found between duration of crying and fussing per day and the number of reflux episodes[240] - In sum, the evidence of a cause–effect relationship between GER(D) and infant colic is weak, and it seems unlikely that GER has a causative role in colic[241,242]
Gut hormones	• Disturbed gastrointestinal motility: motilin and appetite-regulating hormone affect gastric emptying and intestinal peristalsis, resulting in intestinal pain and hyperperistalsis[243,244] • Serotonin might lead to infant colic by affecting gastrointestinal motility, pain conduction and pain sensation[56]	• Two studies support the contribution of gut hormones - There are higher levels of appetite-regulating hormone and motilin in infants with colic than in infants without colic[243] - Higher levels of serotonin were found in infants with colic than in infants without colic[245]

The greatest evidence exists to support an association between intolerance of cow's milk protein and infant colic. By contrast, some evidence supports the contribution of excessive intestinal gas and gut hormones to the manifestation of infant colic. Evidence that GERD or lactose intolerance is causative of infant colic is weak. CMPI, cow's milk protein intolerance; GER(D), gastroesophageal reflux (disease).

crying in infants suspected of infant colic has become less important in the clinical diagnostic process[5]. Nevertheless, this assessment can help to reassure parents. In addition, it might provide parents with extra information on how much their infant is actually crying, as it is plausible that caregiver vulnerabilities, such as depression or absence of social support, affect their perception of the amount and duration of their infants' crying and misrepresent the behaviour of their infant[35]. An accurate and validated tool to assess infant crying is the Baby Day Diary[137]. In this diary, parents typically report the cry and fuss behaviour of their infant, in addition to sleeping, feeding and sucking behaviours, during 24 hours for a minimum of 3 consecutive days.

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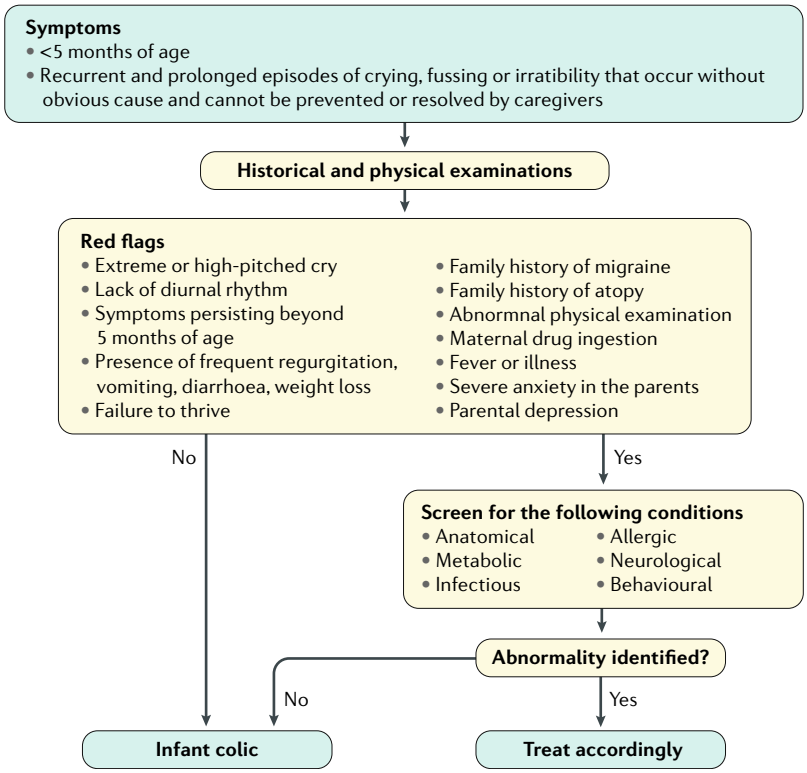

Fig. 5 | **Suggested diagnostic algorithm for infant colic.** After symptom identification, the diagnostic work-up of infant colic should include a careful history and physical examination to exclude identifiable organic causes. A list of alarming symptoms might help to identify these causes. If one of the alarming symptoms is found, further assessment is required.

Management

The clinical management of infant colic is often guided by experience rather than based on evidence. When colic is not accompanied with alarming signs or other symptoms, this self-limiting condition should at first be treated with empathy and reassurance. Additionally, various treatment options have been suggested for infant colic, and several of these treatments have been assessed in RCTs. However, many of these studies have methodological shortcomings that legitimize careful conclusions and recommendations. Furthermore, management should always be individualized, as each family approaches the crying problem in a different way. This context leaves the treating clinician with a challenging task.

Behavioural interventions

Parental education and reassurance. Parents of infants with colic are challenged with less sleep and with concerns and feelings of frustration and failure because they are not able to soothe their baby. Therefore, key factors in the management of infant colic are parental education, reassurance and empathy provided by the physician[138]. The first step consists of a detailed physical examination and discussion of differential diagnoses with the parents. It might be helpful to assure parents that an organic cause is found in only 5% of infants with colic[125]. Furthermore, parents should be educated on the normal crying curve[9] and the importance of understanding that crying is not always a way of expressing pain but is also a form of communication[138]. Moreover, it should be explained to parents that excessive crying is something that healthy infants do, rather than the result of a condition an infant has[51]. It is essential for the clinician to acknowledge parental stress and fatigue, to identify the insecurities of the caregivers about their nurturing abilities and to reassure the parents that these feelings are normal. Parental vulnerabilities might have a negative influence on outcomes, and it is therefore important to see infant crying as a social and family problem rather than an infant medical condition[47]. It is of the utmost importance for the treating clinician to evaluate the parents' state of mind concerning their ability to soothe the crying infant[139]. Unsoothable crying is associated with caregiver frustration, which might increase the risk of shaken baby syndrome or other forms of abuse[22,140,141] (FIG. 6). When the clinician estimates this risk to be too high, infant colic should then be considered as a clinical emergency. Two RCTs evaluated education materials for caregivers on knowledge of infant crying and shaken baby syndrome. Results of these studies demonstrated that these educational materials, compared with control materials, improved parents' knowledge of their infants' crying and of the dangers of shaking their baby and increased the information-sharing of parents with other caregivers regarding walking away when frustrated by unsoothable crying[142,143]. Hence, these results seem to warrant including these education materials in prenatal or postnatal parenting classes.

Behaviour modification

Following parental education and reassurance, a management strategy incorporating modification of infant care and environmental routines should be considered. Home-based treatment programmes that emphasize the individual needs and unique features of the family to establish regularity and predictability in sleeping, feeding and activity routines for the benefit of the children and parents have been found to be effective in treating infant colic[34]. Reducing and regulating the infant's level of arousal during a 4-week home-based intervention

Box 2 | **Red flags in infant colic**[121,132–135]

- Extreme or high-pitched cry
- Lack of diurnal rhythm
- Symptoms after 4 months of age
- Presence of frequent regurgitation, vomiting, diarrhoea and/or weight loss
- Failure to thrive
- Family history of migraine
- Family history of atopy
- Abnormal physical examination
- Maternal drug ingestion
- Fever or illness
- Severe anxiety in the parents
- Parental depression

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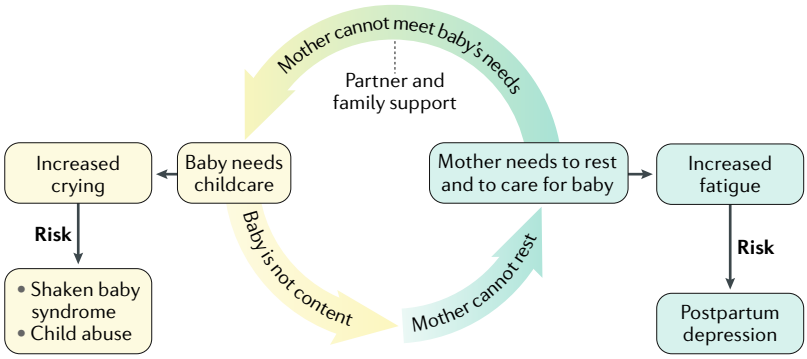

Fig. 6 | **The vicious circle of infant crying and maternal fatigue and adverse events.** Adapted with permission from REF.[141], Elsevier.

carried out by a nurse who focused on reassurance, empathy, support and time out (REST programme) decreased infant crying by 1.7 hours compared with the group who received routine care[144]. Furthermore, extensive parental counselling on effective coping strategies for excessive crying, consisting of several instructions on how to respond to infant crying, resulted in crying decreasing from 2.6 to 0.8 hours per day in one study[145] and was more effective than dietary changes in another[146]. An RCT evaluating the effect of family-based treatment, consisting of intensive support by a behavioural paediatrician and a mental health clinician, demonstrated a positive effect of this treatment on crying reduction[147].

Video home training

Video feedback intervention to promote positive parenting (VIPP), in which parental behaviours are videotaped in order to increase parents' sensitivity to signals from their children, was developed for caregivers who experience parenting stress or have parenting questions[148]. Furthermore, this training increases the empowerment and confidence of parents and reduces the adverse consequences of crying on the interaction between parent and child[148]. However, no specific studies have been conducted on the use of VIPP in families with an infant with colic and, therefore, further research is warranted.

Swaddling

The effect of swaddling, whereby cloth wrappings are used to bind the infant's arms and shoulders tightly but leg flexion and abduction is permitted, as a therapeutic strategy for infant colic was assessed in a Dutch RCT of 398 infants with excessive crying[34]. Infants were randomly assigned to a behavioural intervention consisting of regularity, predictability and stimuli reduction in baby care in combination with swaddling or without swaddling[34]. No differences were found between the two treatment groups[34]. However, infants of both groups did demonstrate a 42% reduction of crying after 1 week of intervention[34]. The behavioural and swaddling interventions were well accepted by parents and provided parental support, which is an important cornerstone in the management of infant colic.

Baby massage

Baby massage might be beneficial for infants with colic as it improves the early mother–child relationship and provides sensory stimulation inducing pacifying effects in infants in general[149–151]. A large Dutch study conducted in a multicultural population found that 50% of 1,142 mothers used massage as a soothing technique for infants with excessive crying[152]. By contrast, a Cochrane review concluded that weak evidence exists that baby massage might benefit the mother–child interaction, sleeping patterns and crying[153]. However, the quality of the included studies was poor, and many did not address the biological mechanisms by which effects of the treatments might be exerted. Clearly, more high-quality studies are needed before this intervention can be recommended in the treatment of infant colic.

Carrying

A few studies have assessed the effect of increased carrying by mothers on infant crying in general and on the relief of symptoms in infants with colic in particular. However, results are conflicting. One study showed a decrease in total daily duration of crying in infants who received additional carrying from their mothers, but no effect was found on the frequency of the crying bouts[6]. By contrast, two RCTs did not observe differences in duration or frequency of crying in infants who were carried more often than in infants who received standard care[154,155].

Dietary interventions

Breastfed infants. It remains a matter of debate whether cow milk proteins excreted in breast milk lead to symptoms of infant colic[156]. Nevertheless, a systematic review published in 2012 reported that elimination of cow milk protein from the maternal diet is a common strategy in the management of infant colic[112]. In a trial of 66 mothers of breastfed infants, colic disappeared in 35 infants after the mother followed a diet free from cow milk protein and reappeared in 23 infants after reintroduction of cow milk to the maternal diet[157]. This finding was not supported by another RCT ($n = 20$) in which no effect on the duration of persistent crying was found in breastfed infants after elimination of cow milk from the maternal diet[158]. The effect of a more extensive maternal low-allergen diet was assessed in a high-quality RCT among exclusively breastfed infants with colic. Infants of mothers who excluded cow's milk, eggs, peanuts, tree nuts, wheat, soy and fish from their diet demonstrated a reduction in the cry and fuss duration compared with the infants of mothers without this diet[159]. On the basis of these results, one can conclude that maternal low-allergen diets might be beneficial in reducing infant colic in breastfed infants. However, the results should be interpreted with caution, as they are not conclusive enough to recommend diet changes in all breastfeeding mothers of infants with colic. Furthermore, it should be noted that these dietary interventions can be quite intensive and might lead to increased stress in an already tense environment.

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Formula-fed infants. The use of partially, extensively or completely hydrolysed formulas for formula-fed infants with colic has been subject to a variety of studies. Four RCTs evaluating the effect of an extensively hydrolysed formula in infants with colic showed a decrease in the duration of crying[111,160–162]. One study reported that a change from a formula containing cow's milk to a casein hydrolysate formula led to only a temporary reduction in crying, which diminished with time and was not reproducible[163]. An RCT of 432 healthy infants published in 2017 demonstrated that a combination of fermented formula with scGOS–lcFOS decreased the incidence of infant colic (8%) compared with scGOS–lcFOS (20%) or fermented formula (20%) alone[164]. Taken together, these results suggest that the use of hydrolysate formulas for the reduction of crying symptoms in formula-fed infants with colic could be effective[112,165,166].

The use of soy-based formula has been studied in four small RCTs of low quality[167–170] and in one long-term prospective study[171]. The results indicated improvement of crying symptoms after introduction of formula based on soy milk in infants with colic. However, it is debatable whether the above-mentioned results are related to the use of soy milk rather than to the elimination of cow milk protein. The use of soy protein formula for the management of infant colic is therefore not recommended by the Nutrition Committee of the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[172].

Probiotics. Probiotics have been defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (REF.[173]). Because emerging evidence suggests that the intestinal microbiota has a role in the pathogenesis of infant colic, probiotic bacteria have been proposed as a promising treatment option for colic[57,61,64,174]. *Lactobacillus* spp. and *Bifidobacterium* spp. are the most commonly used probiotics in infants with colic, particularly *L. reuteri*[61].

A systematic review and meta-analysis, pooling results from seven RCTs, concluded that *L. reuteri* DSM 17938 could be considered in the treatment of infant colic[61]. Five of the seven included studies evaluated the efficacy of *L. reuteri* DSM 17938. In three of those studies, the infants were exclusively or predominantly breastfed (>50% breastfed)[93,175,176]. In the remaining two studies, infants received either formula or breast milk[177,178]. Daily intake of *L. reuteri* DSM 17938 (1×10^8 colony forming units) for 21 or 28 days, compared with placebo, reduced crying time by almost 50 min (mean difference (MD) −50 min, 95% CI −66 min to −33 min) and was mostly found efficacious in exclusively breastfed infants[61]. Data from a meta-analysis pooling raw participant-level data from four double-blind RCTs confirmed this finding, suggesting that *L. reuteri* DSM 17938 is effective in treating breastfed infants with colic, but not formula-fed infants, and that this probiotic can be recommended to breastfed infants with colic[179]. Formula-fed and breastfed infants have different gut microbial compositions[64,180], and this might explain the increased effectiveness of *L. reuteri* in breastfed infants.

Other probiotic strains have also been investigated in the clinical trial setting. One RCT evaluated the efficacy of *L. rhamnosus* GG in infants with colic and found no difference in daily crying time between infants ($n = 15$) receiving the probiotic and infants receiving placebo ($n = 15$) (MD 1 min, 95% CI −62 min to 60 min)[61,92]. In another RCT, a synbiotic containing *Lactobacillus casei*, *L. rhamnosus*, *Streptococcus thermophilus*, *Bifidobacterium breve*, *L. acidophilus*, *Bifidobacterium longum* subsp. *infantis*, *Lactobacillus delbrueckii* subsp. *bulgaricus* and fructooligosaccharides was compared with placebo in 50 breastfed infants with colic. After 7 and 30 days of treatment, statistically significant differences in treatment success (defined as >50% reduction in daily crying time) were found between the groups. At day 7, treatment success was 82.6% and 35.7% in the synbiotic group and placebo group, respectively ($P < 0.05$). At day 30, treatment success was also higher in the synbiotic group (87%) than in the placebo group (46%; $P < 0.01$)[181].

Finally, a large RCT including 589 healthy full-term breastfed and formula-fed infants evaluated the prophylactic use of *L. reuteri* DSM 17938 in preventing infant colic. Daily administration of *L. reuteri* DSM 17938 from birth reduced crying time by ~51 min per day at 1 month and ~33 min per day at 3 months compared with infants receiving placebo[182].

Several mechanisms of action have been proposed for the effectiveness of probiotics in reducing infant crying. These mechanisms include the reduction of gut inflammation by modulation of Toll-like receptors and pro-inflammatory cytokine levels[183–186], the preservation of the mucosal gut barrier and gut epithelial function[73,187] and the reduction of bacterial translocation from the intestinal lumen to mesenteric lymph nodes or other extra-intestinal sites[188,189]. In addition, probiotics might increase production of short-chain fatty acids that improve epithelial barrier function[190], modulate visceral sensitivity and gut-mediated pain perception[191,192], compete with colonic pathogens for adhesion on gut epithelial cells[193,194] and reduce gastric distension by changing gut motility[109,195,196]. Additionally, certain probiotic strains can exert bactericidal effects on bacterial pathogens[197,198]. For example, *L. reuteri* can inhibit pathogens, such as *E. coli*, *Klebsiella* spp. and *Enterobacter* spp., that might be associated with infant colic[66,68,88,197,199].

Pharmacological treatment

The pharmacological treatments available for infant colic are presented in TABLE 2. Data on the effect of the various pharmacological agents are scarce, and evidence for the use of one of those agents in infant colic is weak owing to bias and methodological limitations. Therefore, treatment with pharmacological agents is not supported[174,200].

Complementary treatment

Many families use alternative and complementary interventions for the management of infant colic, as there is no widely accepted conventional treatment for infant colic. TABLE 3 illustrates possible complementary management strategies for infant colic. Some evidence indicates that certain herbal preparations containing

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Table 2 | **Pharmacological management strategies for infant colic**

Treatment	Mechanism	Evidence
Sucrose	Administration of oral sucrose to produce a calming effect or to yield pain relief[246]	• Two RCTs demonstrated a transitory reduction in crying in infants with colic[54,247] • Two SRs (three included studies) found weak evidence for a beneficial effect of sucrose on the reduction of crying in infants with colic[174,200]
Simethicone	Non-absorbable de-foaming agent that decreases the surface tension of gut mucus, allowing gas bubbles within the gut to coalesce and promoting easier expulsion of intestinal air[248]	• One RCT reported fewer episodes of crying following the administration of simethicone than placebo in infants with colic (no details on the definition of infant colic were given)[249] • Two RCTs reported no benefit of simethicone[250,251] • One SR (four included studies) found no evidence to support the use of simethicone as a pain-relieving agent for infant colic[200]
Lactase	Administered to treat lactose intolerance	• One RCT found greater reduction of crying in a subset of infants with colic treated with pre-incubated feeds with lactase compared with the placebo group in a crossover trial[232] • Two RCTs examining the effect of lactase supplementation in breastfed or formula-fed infants with colic demonstrated a lack of response to treatment[233,234] • One SR (one included study) found weak evidence for the use of lactase in infants with colic[174]

Evidence supporting pharmacological management strategies in infants with colic is weak. Of the three interventions assessed in randomized controlled trials (RCTs), the most evidence is available for sucrose administration, followed by simethicone and then by lactase. However, owing to bias and methodological limitations, all evidence is very weak and treatment of infant colic with a pharmacological agent can therefore not be supported. SR, systematic review.

fennel, among other components, might reduce crying time in infant colic[200,201] (TABLE 3). However, owing to a limited number of studies and low methodological quality, these results should be interpreted carefully. Furthermore, little evidence exists for the effectiveness of acupuncture as a management strategy for infant colic[202,203] (TABLE 3). The quality of this evidence is also poor, and further research is needed before recommendations can be made. Finally, conclusions about efficacy of manipulative therapies or reflexology cannot be made as a result of methodological shortcomings, especially performance bias, and scarce evidence[204,205] (TABLE 3).

Follow-up

Short-term consequences

In the majority of infants, excessive crying resolves spontaneously after 3 months of age[51,154]. However, the effects of infant colic on the development of the child or the family structure might persist and can negatively affect both the child and the family. Vik et al. assessed 1,015 mother–infant dyads on infant crying and maternal depression scores[206]. They found that infant colic at the age of 2 months increased the risk of maternal depression 4 months later by almost fourfold[206]. Moreover, a cohort study showed an association between inconsolable infant crying as experienced by the mother and measured with the Baby Day Diary[137] and postpartum depressive symptoms[207]. Infant colic was also found to be associated with maternal depression, but this association was weaker[207]. Two other observational studies confirmed these findings[208,209].

In the short term, infant colic might also lead to early cessation of breastfeeding. This finding was demonstrated in a large cohort of 700 breastfed infants and their mothers who were followed up from birth to 12 months of age[210]. Results indicated an inverse association between infant colic and breastfeeding duration[210]. In a few cases, infant colic was associated with more severe outcomes such as child abuse or shaken baby syndrome[211,212]. A community-based study of 3,259 infants and their parents assessed the actions parents would take to stop their infant from crying[211]. In infants aged 6 months, 5.6% of the parents reported having shaken, smothered or slapped their baby to stop it from crying. One in five of these parents had taken more than one of these three actions[211]. In addition, Barr et al.[213] also highlighted the possibility of an association between infant crying and shaken baby syndrome by showing a similarity between the age-related incidence curve of shaken baby syndrome and the normal infant crying curve.

Long-term consequences

Several studies have linked infant colic to behavioural problems, migraine, abdominal pain or family functioning later in life. Different outcomes are reported for excessive crying that resolves at 3 months of age (transient infant colic) compared with excessive crying that persists after 3 months of age.

Behavioural. The sequelae of infant colic with regard to behavioural problems during childhood or adolescence have been the subject of many studies. In a follow-up study of infants with colic in the first 3 months of life, mothers reported their 4-year-old children to be much more emotional according to a temperament questionnaire than children who had not had colic[214]. Similar findings were reported in a Finnish cohort of 865 infants with colic who were monitored until the age of 3 years[215]. These 3-year-olds had more sleeping problems and more frequent temper tantrums as measured with questionnaires than children who had not had colic during infancy. Moreover, the parents of infants who had a history of colic were more often unsatisfied with the arrangement of daily family responsibilities and had decreased shared leisure time compared with parents of children who had not had infant colic[215]. A follow-up study of 3,369 children demonstrated that excessive crying in infants at 12 weeks of age increased the risk of maternally reported conduct problems, hyperactivity, mood problems and overall problem behaviour at the age of 5–6 years by twofold[216]. Lastly, infants who had a history of colic were more aggressive and had more feelings of supremacy when they were 10 years of age than children who had not had colic as infants[217].

Assessing the relations between persistent infant colic and later development, a prospective cohort study of 327 infants found that children who exhibited prolonged excessive crying as infants had an increased risk of lower IQ scores, hyperactivity and discipline problems at 5 years of age, whereas transient infant colic was not associated with cognitive problems at this age[218].

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Table 3 | **Possible complementary management strategies for infant colic**

Treatment	Mechanism	Evidence
Herbal remedies	The use of herbal remedies in the form of fennel, chamomile, gripe water or vervain might have antispasmodic action and relieve colic symptoms[138]	• Three RCTs supported the use of herbal remedies as a complementary management strategy for infant colic - One study reported a greater reduction in crying time in infants treated with a phytotherapeutic agent containing fennel (ColiMil; Humana, Portugal) than in infants treated with placebo[252] - Two other RCTs demonstrated a possible benefit of fennel seed oil emulsion or herbal tea with chamomile, licorice, vervain, fennel and balm mint versus placebo in reducing the crying time in infants with colic[253,254] • One SR (five included studies) somewhat supported the use of herbal remedies as a complementary management strategy for infant colic - Some evidence exists for the effectiveness of different fennel preparations[201]. Results have to be interpreted carefully because of the limited number of studies and low study quality • One SR (five included studies) argued against the use of herbal remedies as a complementary management strategy for infant colic - Some evidence indicated that herbal agents might reduce crying time compared with placebo or no treatment. However, results should be interpreted with great caution, as the quality of the evidence is very poor and the magnitude of the benefit is variable. Therefore, treatment with herbal remedies cannot be recommended[200] - The use of herbal products is not standardized, and the benefits do not outweigh the potential risks of the use of these products, such as contamination with bacteria or toxins[255,256]
Acupuncture	Acupuncture might attenuate symptoms of infant colic because of its inhibiting effect on somatic and visceral pain[257] and its effect on the autonomic nervous system[258]	• Two RCTs supported the use of acupuncture as a complementary management strategy for infant colic - Minimal acupuncture on one point in the hand of infants with colic reduced crying intensity and duration compared with the control group (standard care without needling)[202] - A single-blind randomized study of infants with colic compared two styles of acupuncture with no acupuncture and found a greater reduction in the amount of crying in both acupuncture groups than in the control group[203] • One RCT argued against the use of acupuncture as a complementary management strategy for infant colic - This study failed to show a difference in crying time reduction between the acupuncture and the control group[259] - Acupuncture might be an effective and safe treatment option for infant colic, but further research is needed to optimize the needling location and stimulation[203,260]
Manipulative therapies	Manipulative therapies might alleviate biomechanical distress that originates during the birth process, which might have led to colicky symptoms by cranial moulding or cervical dysfunction[204]	• One SR (six included studies) argue against the use of manipulative therapies as a complementary management strategy for infant colic - It stated that it is impossible to achieve a definitive conclusion about the efficacy of manipulative therapies for infant colic owing to methodological shortcomings, especially performance bias, despite a greater proportion of parents reporting fewer hours crying per day than parents whose infants did not receive the therapy[204]
Reflexology	The mechanism underlying reflexology is unknown, but many believe that the effect is caused by an improvement of blood flow that encourages relaxation	• One RCT somewhat supported the use of reflexology as a complementary management strategy for infant colic - One study comparing specific and nonspecific reflexology with observation only found a better effect in the reflexology groups than in the observation only group. No difference between the two reflexology groups was found[205]. Methodological quality was low • Definitive conclusions about the effectiveness of reflexology are precluded because evidence is scarce and the methodology is impaired

Some evidence suggests that certain herbal preparations containing fennel, among other supplements, might reduce crying time in infants with colic, although studies are limited in number and poor in quality. Little evidence is available to support acupuncture, manipulative therapies or reflexology in the management of infant colic. RCT, randomized controlled trial; SR, systematic review.

In line with these findings, an increased risk of hyperactivity problems and academic difficulties was reported in children aged 8–10 years who had persistently cried as infants (when this crying lasted beyond the age of 3 months) compared with classmates who had not persistently cried during infancy[219]. Finally, in a meta-analysis of 22 longitudinal studies on regulatory problems (that is, crying, sleeping and/or feeding problems), of which 10 studies evaluated the consequences of excessive crying, a strong association was found between crying problems during infancy and behavioural problems during childhood in the form of externalizing problems and attention-deficit hyperactivity disorder[220].

Somatic. In support of the gastrointestinal explanation for the pathogenesis of infant colic, it is hypothesized that this condition might be an early manifestation of functional gastrointestinal disorders (FGIDs) diagnosed during childhood or adolescence. Indeed, one study demonstrated that more children with a history of infant colic developed an FGID by the time they were 13 years old than children who had not had colic during infancy[221]. This finding was in concordance with an earlier follow-up study that showed an association between infant colic and recurrent abdominal pain at the age of 10 years[217]. Furthermore, it has been suggested that infant colic is a precursor of childhood

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migraine. A retrospective case–control study found that children aged 6 to 18 years with migraine, as diagnosed according to the International Classification of Headache Disorders Second Edition Revised (ICHD-II), displayed a sixfold higher risk of a history of infant colic than children without migraine[222]. A systematic review confirmed the relation between infant colic and childhood migraine but concluded that the results have to be interpreted with caution owing to the retrospective character of the included studies, which makes them prone to recall bias[223]. In a prospective follow-up study of 1,267 infants, infant colic was found to be a predictor of migraine without aura, even after multivariate analysis[224]. This association was not proved for migraine with aura[224]. Whether infant colic is an early expression of migraine itself, or only a marker for the genetics of migraine, still has to be elucidated[225]. Finally, infant colic has been linked to the development of asthma or atopic disease during childhood. However, results of prospective studies are not unequivocal. An observational study followed up 116 infants from birth until the age of 2 years and found an association between colic during the twelfth week of age and atopic disease at 2 years of age[226]. Similarly, a higher prevalence of allergic rhinitis, asthma, pollinosis, atopic eczema and food allergy was found in 10-year-old children who had a history of infant colic than in children without infant colic in their history[217]. By contrast, a follow-up study of 983 infants who were monitored until the age of 11 years failed to demonstrate an increased risk of allergic disease or atopy as a consequence of infant colic[227].

Conclusions

In summary, infant colic is a common and distressing problem during infancy with effects on the infant, the parents and health-care professionals. It is mostly defined according to Wessel's rule of three or according to the Rome criteria, of which the latest revisions focus on the unsoothable character of the crying rather than the amount of crying. Several pathophysiological theories, including neurodevelopmental, microbial, gastrointestinal, nutritional and psychosocial mechanisms, have been proposed to contribute to infant colic. However, owing to methodological shortcomings, no firm conclusions can be drawn, paving the way for a multifactorial explanation for this entity. When no alarm signs or red flags are present, infant colic should first be treated with reassurance and explanation for the parents. Moreover, parental support during this challenging period is one of the important cornerstones in the management of infant colic. At present, high-quality therapeutic trials are scarce. Some evidence supports the use of the probiotic *L. reuteri* DSM 17938 in the treatment of colic in breast-fed infants in addition to rest and predictability in infant care practices. However, large, well-designed trials with clear definitions, predefined outcome measures and appropriate sample sizes are warranted. BOX 3 delineates clinical questions relating to infant colic that might give an indicator of the outlook for the field and summarizes expert insights into where research should be directed.

Box 3 | Conclusions

Open clinical questions include the following:

- What are the pathophysiological mechanisms underlying infant colic?
- What is the role of the microbiome in the pathophysiology of infant colic?
- How can we offer better support to families that have an excessively crying infant? Should we intensify the focus on multidisciplinary care?

Where should research be directed?

- There is a need for objective methods to measure infant crying and associated behavioural symptoms
- Larger, high-quality randomized controlled trials (RCTs) are needed to assess management strategies for infant colic
- Large multicentre RCTs with (novel) probiotic strains using validated outcome measures and metabolomic microbial analysis are required to increase understanding of the relationship between metabolomic profiles and infant colic and to develop therapeutic strategies

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1. Zeifman, D. M. An ethological analysis of human infant crying: answering Tinbergen's four questions. *Dev. Psychobiol.* **39**, 265–285 (2001).
2. deVries, M. W. Temperament and infant mortality among the Masai of East Africa. *Am. J. Psychiatry* **141**, 1189–1194 (1984).
3. St James-Roberts, I. & Halil, T. Infant crying patterns in the first year: normal community and clinical findings. *J. Child Psychol. Psychiatry* **32**, 951–968 (1991).
4. Brazelton, T. B. Crying in infancy. *Pediatrics* **29**, 579–588 (1962).
5. Benninga, M. A. et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* **150**, 1443–1455.e2 (2016).
6. Hunziker, U. A. & Barr, R. G. Increased carrying reduces infant crying: a randomized controlled trial. *Pediatrics* **77**, 641–648 (1986).
7. Kramer, M. S. et al. Pacifier use, early weaning, and cry/fuss behavior: a randomized controlled trial. *JAMA* **286**, 322–326 (2001).
8. Wolke, D., Bilgin, A. & Samara, M. Systematic review and meta-analysis: fussing and crying durations and prevalence of colic in infants. *J. Pediatr.* **185**, 55–61.e4 (2017).
9. Barr, R. The normal crying curve: what do we really know? *Dev. Med. Child Neurol.* **32**, 356–362 (1990).
10. Wessel, M. A., Cobb, J. C., Jackson, E. B., Harris, G. S. & Detwiler, A. C. Paroxysmal fussing in infancy, sometimes called colic. *Pediatrics* **14**, 421–435 (1954).
11. Emde, R. N., Gaensbauer, T. J. & Harmon, R. J. Emotional expression in infancy; a biobehavioral study. *Psychol. Issues* **10**, 1–200 (1976).
12. Bell, S. M. & Ainsworth, M. D. Infant crying and maternal responsiveness. *Child Dev.* **43**, 1171–1190 (1972).
13. James-Roberts, I. S. in *New Evidence on Unexplained Early Infant Crying: Its Origins, Nature and Management*. (eds Barr, R. G, St James-Roberts, I. & Keefe, M. R.) 5–24 (Johnson & Johnson Pediatric Institute, Skillman, New Jersey, 2001).
14. Forsyth, B. W. & Canny, P. F. Perceptions of vulnerability 3 1/2 years after problems of feeding and crying behavior in early infancy. *Pediatrics* **88**, 757–763 (1991).
15. Lehtonen, L. A. in *New Evidence on Unexplained Early Infant Crying: Its Origins, Nature and Management*. (eds Barr, R. G, St James-Roberts, I. & Keefe, M. R.) 259–271 (Johnson & Johnson Pediatric Institute, Skillman, New Jersey, 2001).
16. Reijneveld, S. A., Brugman, E. & Hirasing, R. A. Excessive infant crying: the impact of varying definitions. *Pediatrics* **108**, 893–897 (2001).
17. Steutel, N. F., Benninga, M. A., Langendam, M. W., de Kruijff, I. & Tabbers, M. M. Reporting outcome measures in trials of infant colic. *J. Pediatr. Gastroenterol. Nutr.* **59**, 341–346 (2014).
18. Hyman, P. E. et al. Childhood functional gastrointestinal disorders: neonate/toddler. *Gastroenterology* **130**, 1519–1526 (2006).
19. Gormally, S. M. & Barr, R. G. Of clinical pies and clinical clues: proposal for a clinical approach to complaints of early crying and colic. *Ambulatory Child Health.* **2**, 137–153 (1997).
20. Wolke, D. in *New Evidence on Unexplained Early Infant Crying: Its Origins, Nature and Management*. (eds Barr, R. G, St James-Roberts, I. & Keefe, M. R.) 187–208 (Johnson & Johnson Pediatric Institute, Skillman, New Jersey, 2001).
21. Barr, R. in *Handbook of Development Psychopathology* (eds Sameroff, A. J., Lewis, M. & Miller, S. M.) 327–350 (Kluwer Academic/Plenum Publishers, New York, 2000).

© 2018 Macmillan Publishers Limited, part of Springer Nature. All rights reserved.

22. Fujiwara, T., Barr, R. G., Brant, R. & Barr, M. Infant distress at five weeks of age and caregiver frustration. *J. Pediatr.* **159**, 425–430.e2 (2011).
23. Gustafson, G., Wood, R. & Green, J. A. in *Crying as a Sign, a Symptom, and a Signal*. (eds Barr, R. G., Hopkins, B. & Green, J. A.) 8–22 (Mac Keith Press, London, 2000).
24. James-Roberts, I. S., Conroy, S. & Wilsher, K. Bases for maternal perceptions of infant crying and colic behaviour. *Arch. Dis. Child.* **75**, 375–384 (1996).
25. Barr, R. G., Rotman, A., Yaremko, J., Leduc, D. & Francoeur, T. E. The crying of infants with colic: a controlled empirical description. *Pediatrics* **90**, 14–21 (1992).
26. St James-Roberts, I., Hurry, J. & Bowyer, J. Objective confirmation of crying durations in infants referred for excessive crying. *Arch. Dis. Child.* **68**, 82–84 (1993).
27. Räihä, H., Lehtonen, L. & Korvenranta, H. Family context of infantile colic. *Infant Ment. Health J.* **16**, 206–217 (1995).
28. Lehtonen, L. & Korvenranta, H. Infantile colic. Seasonal incidence and crying profiles. *Arch. Pediatr. Adolesc. Med.* **149**, 533–536 (1995).
29. Lucassen, P. L. et al. Systematic review of the occurrence of infantile colic in the community. *Arch. Dis. Child.* **84**, 398–403 (2001).
30. van Tilburg, M. A. L. et al. Prevalence of functional gastrointestinal disorders in infants and toddlers. *J. Pediatr.* **166**, 684–689 (2015).
31. Chogle, A. et al. A population-based study on the epidemiology of functional gastrointestinal disorders in young children. *J. Pediatr.* **179**, 139–143.e1 (2016).
32. Clifford, T. J., Campbell, M. K., Speechley, K. N. & Gorodzinsky, F. Infant colic: empirical evidence of the absence of an association with source of early infant nutrition. *Arch. Pediatr. Adolesc. Med.* **156**, 1123–1128 (2002).
33. Canivet, C., Hagander, B., Jakobsson, I. & Lanke, J. Infantile colic — less common than previously estimated? *Acta Paediatr.* **85**, 454–458 (1996).
34. van Sleuwen, B. E. et al. Comparison of behavior modification with and without swaddling as interventions for excessive crying. *J. Pediatr.* **149**, 512–517 (2006).
35. Zwart, P., Vellema-Goud, M. G. A. & Brand, P. L. P. Characteristics of infants admitted to hospital for persistent colic, and comparison with healthy infants. *Acta Paediatr.* **96**, 401–405 (2007).
36. Lester, B. M., Boukydis, C. F. Z., Garcia-Coll, C. T. & Hole, W. T. Colic for developmentalists. *Infant Ment. Health J.* **11**, 321–333 (1990).
37. Illingworth, R. S. Infantile colic revisited. *Arch. Dis. Child.* **60**, 981–985 (1985).
38. James-Roberts, I. S., Conroy, S. & Wilsher, K. Clinical, developmental and social aspects of infant crying and colic. *Infant Child Dev.* **4**, 177–189 (1995).
39. Barr, R. G., Paterson, J. A., MacMartin, L. M., Lehtonen, L. & Young, S. N. Prolonged and unsoothable crying bouts in infants with and without colic. *J. Dev. Behav. Pediatr.* **26**, 14–23 (2005).
40. Lester, B. M., Zachariah Boukydis, C. F., Garcia-Coll, C. T., Hole, W. & Peucker, M. Infantile colic: acoustic cry characteristics, maternal perception of cry, and temperament. *Infant Behav. Dev.* **15**, 15–26 (1992).
41. Fuller, B. F., Keefe, M. R., Curtin, M. & Garvin, B. J. Acoustic analysis of cries from "normal" and "irritable" infants. *West. J. Nurs. Res.* **16**, 243–253 (1994).
42. Zeskind, P. S. & Barr, R. G. Acoustic characteristics of naturally occurring cries of infants with "colic". *Child Dev.* **68**, 394–403 (1997).
43. St James-Roberts, I. What is distinct about infants' "colic" cries? *Arch. Dis. Child.* **80**, 56–61; discussion 62 (1999).
44. Carey, W. B. Colic - primary excessive crying as an infant-environment interaction. *Pediatr. Clin. North Am.* **31**, 993–1005 (1984).
45. Illingworth, R. S. Three-months' colic. *Arch. Dis. Child.* **29**, 165–174 (1954).
46. Shamir, R. et al. Infant crying, colic, and gastrointestinal discomfort in early childhood; a review of the evidence and most plausible mechanisms. *J. Pediatr. Gastroenterol. Nutr.* **57**, S1–S45 (2013).
47. James-Roberts, I. S. & Alvarez, M. Emergence of a developmental explanation for prolonged crying in 1-to 4-month-old infants: review of the evidence. *J. Pediatr. Gastroenterol. Nutr.* **57**, S30–S36 (2013).
48. Barr, R. G., Konner, M., Bakeman, R. & Adamson, L. Crying in!Kung San infants: a test of the cultural specificity hypothesis. *Dev. Med. Child Neurol.* **33**, 601–610 (1991).
49. Barr, R. G., Paterson, J. A., MacMartin, L. M., Calinoiu, N. & Young, S. N. 'What is colic?': a test of the early difficult temperament hypothesis. *Pediatr. Res.* **47**, 23A (2000).
50. Barr, R. G. The early crying paradox: a modest proposal. *Hum. Nat.* **1**, 355–389 (1990).
51. Barr, R. G. in *New Evidence On Unexplained Early Crying: Its Origins, nature, and management*. (eds Barr, R. G, St James-Roberts, I. & Keefe, M. R.) 87–104 (Johnson & Johnson Pediatric Institute, Skillman, New Jersey, 2001).
52. St James-Roberts, I., Goodwin, J., Peter, B., Adams, D. & Hunt, S. Individual differences in responsivity to a neurobehavioural examination predict crying patterns of 1-week-old infants at home. *Dev. Med. Child Neurol.* **45**, 400–407 (2003).
53. Trevarthen, C. & Aitken, K. J. in *Regression Periods in Human Infancy* (ed. Heimann, M.) 107–184 (Lawrence Erlbaum Associates, Mahwah, New Jersey, 2003).
54. Barr, R. G., Young, S. N., Wright, J. H., Gravel, R. & Alkawaf, R. Differential calming responses to sucrose taste in crying infants with and without colic. *Pediatrics* **103**, e68 (1999).
55. Marsh, D. F., Hatch, D. J. & Fitzgerald, M. Opioid systems and the newborn. *Br. J. Anaesth.* **79**, 787–795 (1997).
56. Leuchter, R. H.-V., Darque, A. & Hüppi, P. S. Brain maturation, early sensory processing, and infant colic. *J. Pediatr. Gastroenterol. Nutr.* **57**, S18–S25 (2013).
57. de Weerth, C., Fuentes, S., Puylaert, P. & de Vos, W. M. Intestinal microbiota of infants with colic: development and specific signatures. *Pediatrics* **131**, e550–e558 (2013).
58. Rhoads, J. M. et al. Altered fecal microflora and increased fecal calprotectin in infants with colic. *J. Pediatr.* **155**, 823–828.e1 (2009).
59. Roos, S. et al. 454 Pyrosequencing analysis on faecal samples from a randomized DBPC trial of colicky infants treated with *Lactobacillus* reuteri DSM 17938. *PLoS ONE* **8**, e56710 (2013).
60. Savino, F. et al. Comparison of formula-fed infants with and without colic revealed significant differences in total bacteria, *Enterobacteriaceae* and faecal ammonia. *Acta Paediatr.* **106**, 573–578 (2017).
61. Dryl, R. & Szajewska, H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. *Arch. Med. Sci.* https://doi.org/10.5114/aoms.2017.66055 (2017).
62. Clarke, G. et al. The microbiome-gut-brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. *Mol. Psychiatry* **18**, 666–673 (2013).
63. Mayer, E. A. et al. Gut/brain axis and the microbiota. *J. Clin. Invest.* **125**, 926–938 (2015).
64. de Weerth, C., Fuentes, S. & de Vos, W. M. Crying in infants: on the possible role of intestinal microbiota in the development of colic. *Gut Microbes* **4**, 416–421 (2013).
65. Eutamène, H. et al. Luminal contents from the gut of colicky infants induce visceral hypersensitivity in mice. *Neurogastroenterol. Motil.* **29**, e12994 (2017).
66. Savino, F. et al. Molecular identification of coliform bacteria from colicky breastfed infants. *Acta Paediatr.* **98**, 1582–1588 (2009).
67. Pärtty, A., Kalliomäki, M., Salminen, S. & Isolauri, E. Infantile colic is associated with low-grade systemic inflammation. *J. Pediatr. Gastroenterol. Nutr.* **64**, 691–695 (2017).
68. Savino, F. et al. Antagonistic effect of *Lactobacillus* strains against gas-producing coliforms isolated from colicky infants. *BMC Microbiol.* **11**, 157 (2011).
69. Vatanen, T. et al. Variation in microbiome LPS immunogenicity contributes to autoimmunity in humans. *Cell* **165**, 842–853 (2016).
70. Nanthakumar, N. N., Fusunyan, R. D., Sanderson, I. & Walker, W. A. Inflammation in the developing human intestine: a possible pathophysiologic contribution to necrotizing enterocolitis. *Proc. Natl Acad. Sci. USA* **97**, 6043–6048 (2000).
71. He, Y. et al. The human milk oligosaccharide 2′-fucosyllactose modulates CD14 expression in human enterocytes, thereby attenuating LPS-induced inflammation. *Gut* **65**, 33–46 (2016).
72. Pärtty, A. et al. Compositional development of Bifidobacterium and *Lactobacillus* microbiota is linked with crying and fussing in early infancy. *PLoS ONE* **7**, e32495 (2012).
73. Ewaschuk, J. B. et al. Secreted bioactive factors from Bifidobacterium infantis enhance epithelial cell barrier function. *Am. J. Physiol. Gastrointest. Liver Physiol.* **295**, G1025–G1034 (2008).
74. Chichlowski, M., De Lartigue, G., German, J. B., Raybould, H. E. & Mills, D. A. Bifidobacteria isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function. *J. Pediatr. Gastroenterol. Nutr.* **55**, 321–327 (2012).
75. Liu, Y., Fatheree, N. Y., Mangalat, N. & Rhoads, J. M. Human-derived probiotic *Lactobacillus* reuteri strains differentially reduce intestinal inflammation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **299**, G1087–G1096 (2010).
76. Smits, H. H. et al. Selective probiotic bacteria induce IL-10–producing regulatory T cells in vitro by modulating dendritic cell function through dendritic cell–specific intercellular adhesion molecule 3–grabbing nonintegrin. *J. Allergy Clin. Immunol.* **115**, 1260–1267 (2005).
77. Ali, A. M. *Helicobacter pylori* and infantile colic. *Arch. Pediatr. Adolesc. Med.* **166**, 648–650 (2012).
78. Ali, A. S. A. & Borei, M. B. M. Helicobacter pylori and Egyptian infantile colic. *J. Egypt. Soc. Parasitol.* **43**, 327–332 (2013).
79. Carreira, H., Bastos, A., Peleteiro, B. & Lunet, N. Breast-feeding and *Helicobacter pylori* infection: systematic review and meta-analysis. *Public Health Nutr.* **18**, 500–520 (2015).
80. Rautava, S., Collado, M. C., Salminen, S. & Isolauri, E. Probiotics modulate host-microbe interaction in the placenta and fetal gut: a randomized, double-blind, placebo-controlled trial. *Neonatology* **102**, 178–184 (2012).
81. Rautava, S., Luoto, R., Salminen, S. & Isolauri, E. Microbial contact during pregnancy, intestinal colonization and human disease. *Nat. Rev. Gastroenterol. Hepatol.* **9**, 565–576 (2012).
82. Zijlmans, M. A. C., Korpela, K., Riksen-Walraven, J. M., de Vos, W. M. & de Weerth, C. Maternal prenatal stress is associated with the infant intestinal microbiota. *Psychoneuroendocrinology* **53**, 233–245 (2015).
83. Penders, J. et al. Factors influencing the composition of the intestinal microbiota in early infancy. *Pediatrics* **118**, 511–521 (2006).
84. Rutayisire, E., Huang, K., Liu, Y. & Tao, F. The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. *BMC Gastroenterol.* **16**, 86 (2016).
85. Aloisio, I. et al. Influence of intrapartum antibiotic prophylaxis against group B *Streptococcus* on the early newborn gut composition and evaluation of the anti-*Streptococcus* activity of Bifidobacterium strains. *Appl. Microbiol. Biotechnol.* **98**, 6051–6060 (2014).
86. Clifford, T. J., Campbell, M. K., Speechley, K. N. & Gorodzinsky, F. Sequelae of infant colic: evidence of transient infant distress and absence of lasting effects on maternal mental health. *Arch. Pediatr. Adolesc. Med.* **156**, 1183–1188 (2002).
87. Corvaglia, L. et al. Influence of intrapartum antibiotic prophylaxis for group B *Streptococcus* on Gut microbiota in the first month of life. *J. Pediatr. Gastroenterol. Nutr.* **62**, 304–308 (2016).
88. Mentula, S., Tuure, T., Koskenala, R., Korpela, R. & Könönen, E. Microbial composition and fecal fermentation end products from colicky infants – a probiotic supplementation pilot. *Microb. Ecol. Health Dis.* **20**, 37–47 (2008).
89. Savino, F. et al. Bacterial counts of intestinal *Lactobacillus* species in infants with colic. *Pediatr. Allergy Immunol.* **16**, 72–75 (2005).
90. Savino, F. et al. Intestinal microflora in breastfed colicky and non-colicky infants. *Acta Paediatr.* **93**, 825–829 (2004).
91. Adlerberth, I. Establishment of the gut microbiota in Western infants. *Acta Pædiatr.* **98**, 229–238 (2009).
92. Pärtty, A., Lehtonen, L., Kalliomäki, M., Salminen, S. & Isolauri, E. Probiotic *Lactobacillus rhamnosus* GG therapy and microbiological programming in infantile colic: a randomized, controlled trial. *Pediatr. Res.* **78**, 470–475 (2015).
93. Savino, F. et al. *Lactobacillus* reuteri DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. *Pediatrics* **126**, e526–e533 (2010).
94. Camilleri, M., Park, S.-Y., Scarpato, E. & Staiano, A. Exploring hypotheses and rationale for causes of infantile colic. *Neurogastroenterol. Motil.* **29**, e12943 (2017).
95. Hofmann, A., F. in *Enterohepatic Circulation of Bile Acids. Comprehensive Physiology* 567–596 (John Wiley & Sons, USA, 2011).
96. Pavlidis, P. et al. Systematic review: bile acids and intestinal inflammation- luminal aggressors or

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regulators of mucosal defence? *Aliment. Pharmacol. Ther.* **42**, 802–817 (2015).
97. Lester, R. Diarrhea and malabsorption in the newborn. *N. Engl. J. Med.* **297**, 505–507 (1977).
98. Lester, R. et al. Fetal bile salt metabolism. The intestinal absorption of bile salt. *J. Clin. Invest.* **59**, 1009–1016 (1977).
99. Bampton, P. A., Dinning, P. G., Kennedy, M. L., Lubowski, D. Z. & Cook, I. J. The proximal colonic motor response to rectal mechanical and chemical stimulation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **282**, G443–G449 (2002).
100. Spiller, R. C., Brown, M. L. & Phillips, S. F. Decreased fluid tolerance, accelerated transit, and abnormal motility of the human colon induced by oleic acid. *Gastroenterology* **91**, 100–107 (1986).
101. Dawson, P. A., Lan, T. & Rao, A. Bile acid transporters. *J. Lipid Res.* **50**, 2340–2357 (2009).
102. Ridlon, J. M., Kang, D.-J. & Hylemon, P. B. Bile salt biotransformations by human intestinal bacteria. *J. Lipid Res.* **47**, 241–259 (2005).
103. Wood, J. D. Enteric nervous system: reflexes, pattern generators and motility. *Curr. Opin. Gastroenterol.* **24**, 149–158 (2008).
104. Dinan, T. G. & Cryan, J. F. Regulation of the stress response by the gut microbiota: implications for psychoneuroendocrinology. *Psychoneuroendocrinology* **37**, 1369–1378 (2012).
105. Kenny, S. E. et al. Delayed maturation of the interstitial cells of Cajal: a new diagnosis for transient neonatal pseudoobstruction. Report of two cases. *J. Pediatr. Surg.* **33**, 94–98 (1998).
106. Riezzo, G. et al. Gastric electrical activity and gastric emptying in term and preterm newborns. *Neurogastroenterol. Motil.* **12**, 223–229 (2000).
107. Halpern, R. & Coelho, R. Excessive crying in infants. *J. Pediatr. (Rio. J.).* **92**, S40–S45 (2016).
108. Indrio, F. et al. The effects of probiotics on feeding tolerance, bowel habits, and gastrointestinal motility in preterm newborns. *J. Pediatr.* **152**, 801–806 (2008).
109. Indrio, F. et al. Effects of probiotic and prebiotic on gastrointestinal motility in newborns. *J. Physiol. Pharmacol.* **60** (Suppl. 6), 27–31 (2009).
110. Jakobsson, I. & Lindberg, T. Cow's milk as a cause of infantile colic in breast-fed infants. *Lancet* **2**, 437–439 (1978).
111. Lucassen, P. L., Assendelft, W. J., Gubbels, J. W., van Eijk, J. T. & Douwes, A. C. Infantile colic: crying time reduction with a whey hydrolysate: a double-blind, randomized, placebo-controlled trial. *Pediatrics* **106**, 1349–1354 (2000).
112. Iacovou, M., Ralston, R. A., Muir, J., Walker, K. Z. & Truby, H. Dietary management of infantile colic: a systematic review. *Matern. Child Health J.* **16**, 1319–1331 (2012).
113. Jones, P. M. & Gupta, S. K. in *Pediatric Gastrointestinal and Liver Disease* (eds Wyllie, R., Hyams, J. S. & Kay, M.) 115–123 (Elsevier Health Sciences, 2015).
114. Moore, D. J., Robb, T. A. & Davidson, G. P. Breath hydrogen response to milk containing lactose in colicky and noncolicky infants. *J. Pediatr.* **113**, 979–984 (1988).
115. Thomas, D. W., McGilligan, K., Eisenberg, L. D., Lieberman, H. M. & Rissman, E. M. Infantile colic and type of milk feeding. *Am. J. Dis. Child.* **141**, 451–453 (1987).
116. Ståhlberg, M. R. Infantile colic: occurrence and risk factors. *Eur. J. Pediatr.* **143**, 108–111 (1984).
117. Barr, R. G., Kramer, M. S., Pless, I. B., Boisjoly, C. & Leduc, D. Feeding and temperament as determinants of early infant crying/fussing behavior. *Pediatrics* **84**, 514–521 (1989).
118. Lucas, A. & St James-Roberts, I. Crying, fussing and colic behaviour in breast- and bottle-fed infants. *Early Hum. Dev.* **53**, 9–18 (1998).
119. Evans, K., Evans, R. & Simmer, K. Effect of the method of breast feeding on breast engorgement, mastitis and infantile colic. *Acta Paediatr.* **84**, 849–852 (1995).
120. Søndergaard, C. et al. Psychosocial distress during pregnancy and the risk of infantile colic: a follow-up study. *Acta Paediatr.* **92**, 811–816 (2003).
121. van den Berg, M. P. et al. Paternal depressive symptoms during pregnancy are related to excessive infant crying. *Pediatrics* **124**, e96–e103 (2009).
122. Petzoldt, J. et al. Maternal anxiety disorders predict excessive infant crying: a prospective longitudinal study. *Arch. Dis. Child.* **99**, 800–806 (2014).
123. Canivet, C. A., Ostergren, P.-O., Rosén, A.-S., Jakobsson, I. L. & Hagander, B. M. Infantile colic and the role of trait anxiety during pregnancy in relation to psychosocial and socioeconomic factors. *Scand. J. Public Health* **33**, 26–34 (2005).
124. Bolten, M. I., Fink, N. S. & Stadler, C. Maternal self-efficacy reduces the impact of prenatal stress on infant's crying behavior. *J. Pediatr.* **161**, 104–109 (2012).
125. Freedman, S. B., Al-Harthy, N. & Thull-Freedman, J. The crying infant: diagnostic testing and frequency of serious underlying disease. *Pediatrics* **123**, 841–848 (2009).
126. Reijneveld, S. A., Brugman, E. & Hirasing, R. A. Infantile colic: maternal smoking as potential risk factor. *Arch. Dis. Child.* **83**, 302–303 (2000).
127. Søndergaard, C., Henriksen, T. B., Obel, C. & Wisborg, K. Smoking during pregnancy and infantile colic. *Pediatrics* **108**, 342–346 (2001).
128. Canivet, C. A., Ostergren, P.-O., Jakobsson, I. L., Dejin-Karlsson, E. & Hagander, B. M. Infantile colic, maternal smoking and infant feeding at 5 weeks of age. *Scand. J. Public Health* **36**, 284–291 (2008).
129. Milidou, I., Henriksen, T. B., Jensen, M. S., Olsen, J. & Søndergaard, C. Nicotine replacement therapy during pregnancy and infantile colic in the offspring. *Pediatrics* **129**, e652–e658 (2012).
130. Milidou, I., Søndergaard, C., Jensen, M. S., Olsen, J. & Henriksen, T. B. Gestational age, small for gestational age, and infantile colic. *Paediatr. Perinat. Epidemiol.* **28**, 138–145 (2014).
131. Douglas, P. & Hill, P. Managing infants who cry excessively in the first few months of life. *BMJ* **343**, d7772 (2011).
132. Gormally, S. in *New Evidence on Unexplained Early Crying: Its Origins, Nature, and Management*. (eds Barr, R. G, St James-Roberts, I. & Keefe, M. R.) 133–148 (Skillman, New Jersey: Johnson & Johnson Pediatric Round Table Series, 2001).
133. Vandenplas, Y. Algorithms for common gastrointestinal disorders. *J. Pediatr. Gastroenterol. Nutr.* **63** (Suppl. 1), S38–S40 (2016).
134. Vandenplas, Y. et al. Functional gastro-intestinal disorder algorithms focus on early recognition, parental reassurance and nutritional strategies. *Acta Paediatr.* **105**, 244–252 (2016).
135. Nurko, S. et al. in *Rome IV Pediatric Functional Gastrointestinal Disorders* (eds Di Lorenzo, C. et al.) 171–190 (The Rome Foundation, Raleigh, North Carolina, 2016).
136. Roberts, D. M., Ostapchuk, M. & O'Brien, J. G. Infantile colic. *Am. Fam. Physician* **70**, 735–740 (2004).
137. Barr, R. G., Kramer, M. S., Boisjoly, C., McVey-White, L. & Pless, I. B. Parental diary of infant cry and fuss behaviour. *Arch. Dis. Child.* **63**, 380–387 (1988).
138. Bellaïche, M., Levy, M. & Jung, C. Treatments for infant colic. *J. Pediatr. Gastroenterol. Nutr.* **57**, S27–S30 (2013).
139. Murray, L. & Cooper, P. in *New Evidence on Unexplained Early Infant Crying: Its Origins, Nature and Management*. (eds Barr, R. G, St James-Roberts, I. & Keefe, M. R.) 149–164 (Johnson & Johnson Pediatric Institute, Skillman, New Jersey, 2001).
140. Christian, C. W. & Block, R. Abusive head trauma in infants and children. *Pediatrics* **123**, 1409–1411 (2009).
141. Kurth, E., Kennedy, H. P., Spichiger, E., Hösli, I. & Stutz, E. Z. Crying babies, tired mothers: what do we know? A systematic review. *Midwifery* **27**, 187–194 (2011).
142. Barr, R. G. et al. Effectiveness of educational materials designed to change knowledge and behaviors regarding crying and shaken-baby syndrome in mothers of newborns: a randomized, controlled trial. *Pediatrics* **123**, 972–980 (2009).
143. Barr, R. G. et al. Do educational materials change knowledge and behaviour about crying and shaken baby syndrome? A randomized controlled trial. *Can. Med. Assoc. J.* **180**, 727–733 (2009).
144. Keefe, M. R. et al. Effectiveness of an intervention for colic. *Clin. Pediatr. (Phila).* **45**, 123–133 (2006).
145. Taubman, B. Clinical trial of the treatment of colic by modification of parent-infant interaction. *Pediatrics* **74**, 998–1003 (1984).
146. Taubman, B. Parental counseling compared with elimination of cow's milk or soy milk protein for the treatment of infant colic syndrome: a randomized trial. *Pediatrics* **81**, 756–761 (1988).
147. Salisbury, A. L. et al. A randomized control trial of integrated care for families managing infant colic. *Infant Ment. Health J.* **33**, 110–122 (2012).
148. Juffer, F., Bakermans-Kranenburg, M. J. & van Ljzendoorn, M. H. *Promoting Positive Parenting: an Attachment-Based Intervention*. (Lawrence Erlbaum Associates, 2008).
149. White-Traut, R. & Nelson, M. N. Maternally administered tactile, auditory, visual, and vestibular stimulation: relationship to later interactions between mothers and premature infants. *Res. Nurs. Health* **11**, 31–39 (1988).
150. Brackbill, Y. Cumulative effects of continuous stimulation on arousal level in infants. *Child Dev.* **42**, 17–26 (1971).
151. Brackbill, Y. Continuous stimulation reduces arousal level: stability of the effect over time. *Child Dev.* **44**, 43–46 (1973).
152. van der Wal, M. F., van den Boom, D. C., Pauw-Plomp, H. & de Jonge, G. A. Mothers' reports of infant crying and soothing in a multicultural population. *Arch. Dis. Child.* **79**, 312–317 (1998).
153. Bennett, C., Underdown, A. & Barlow, J. Massage for promoting mental and physical health in typically developing infants under the age of six months. *Cochrane Database Syst. Rev*. https://doi.org/10.1002/14651858 (2013).
154. Parkin, P. C., Schwartz, C. J. & Manuel, B. A. Randomized controlled trial of three interventions in the management of persistent crying of infancy. *Pediatrics* **92**, 197–201 (1993).
155. Barr, R. G. et al. Carrying as colic therapy: a randomized controlled trial. *Pediatrics* **87**, 623–630 (1991).
156. Heine, R. G. Cow's-milk allergy and lactose malabsorption in infants with colic. *J. Pediatr. Gastroenterol. Nutr.* **57**, S25–S27 (2013).
157. Jakobsson, I. & Lindberg, T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics* **71**, 268–271 (1983).
158. Evans, R. W., Fergusson, D. M., Allardyce, R. A. & Taylor, B. Maternal diet and infantile colic in breast-fed infants. *Lancet* **1**, 1340–1342 (1981).
159. Hill, D. J. et al. Effect of a low-allergen maternal diet on colic among breastfed infants: a randomized, controlled trial. *Pediatrics* **116**, e709–e715 (2005).
160. Lothe, L. & Lindberg, T. Cow's milk whey protein elicits symptoms of infantile colic in colicky formula-fed infants: a double-blind crossover study. *Pediatrics* **83**, 262–266 (1989).
161. Jakobsson, I., Lothe, L., Ley, D. & Borschel, M. W. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatr.* **89**, 18–21 (2000).
162. Arikan, D., Alp, H., Gözüm, S., Orbak, Z. & Cifçi, E. K. Effectiveness of massage, sucrose solution, herbal tea or hydrolysed formula in the treatment of infantile colic. *J. Clin. Nurs.* **17**, 1754–1761 (2008).
163. Forsyth, B. W. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. *J. Pediatr.* **115**, 521–526 (1989).
164. Vandenplas, Y. et al. Randomised controlled trial demonstrates that fermented infant formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides reduces the incidence of infantile colic. *Acta Paediatr.* **106**, 1150–1158 (2017).
165. Hall, B., Chesters, J. & Robinson, A. Infantile colic: a systematic review of medical and conventional therapies. *J. Paediatr. Child Health* **48**, 128–137 (2012).
166. Lucassen, P. L. et al. Effectiveness of treatments for infantile colic: systematic review. *BMJ* **316**, 1563–1569 (1998).
167. Lothe, L., Lindberg, T. & Jakobsson, I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics* **70**, 7–10 (1982).
168. Campbell, J. P. Dietary treatment of infant colic: a double-blind study. *J. R. Coll. Gen. Pract.* **39**, 11–14 (1989).
169. Oggero, R., Garbo, G., Savino, F. & Mostert, M. Dietary modifications versus dicyclomine hydrochloride in the treatment of severe infantile colics. *Acta Paediatr.* **83**, 222–225 (1994).
170. Berseth, C. L., Johnston, W. H., Stolz, S. I., Harris, C. L. & Mitmesser, S. H. Clinical response to 2 commonly used switch formulas occurs within 1 day. *Clin. Pediatr. (Phila).* **48**, 58–65 (2009).
171. Iacono, G. et al. Severe infantile colic and food intolerance: a long-term prospective study. *J. Pediatr. Gastroenterol. Nutr.* **12**, 332–335 (1991).
172. Agostoni, C. et al. Soy protein infant formulae and follow-on formulae. *J. Pediatr. Gastroenterol. Nutr.* **42**, 352–361 (2006).
173. Hill, C. et al. Expert consensus document: the international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Gastroenterol. Hepatol.* **11**, 506–514 (2014).
174. Harb, T., Matsuyama, M., David, M. & Hill, R. J. Infant colic — what works. *J. Pediatr. Gastroenterol. Nutr.* **62**, 668–686 (2016).
175. Chau, K. et al. Probiotics for infantile colic: a randomized, double-blind, placebo-controlled trial

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investigating *Lactobacillus* reuteri DSM 17938. *J. Pediatr.* **166**, 74–78 (2015).
176. Mi, G.-L. et al. Effectiveness of *Lactobacillus* reuteri in infantile colic and colicky induced maternal depression: a prospective single blind randomized trial. *Antonie Van Leeuwenhoek* **107**, 1547–1553 (2015).
177. Sung, V. et al. Treating infant colic with the probiotic Lactobacillus reuteri: double blind, placebo controlled randomised trial. *BMJ* **348**, g2107 (2014).
178. 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.* **162**, 257–262 (2013).
179. Sung, V. et al. *Lactobacillus* reuteri to treat infant colic: a meta-analysis. *Pediatrics* **141**, e20171811 (2018).
180. Rautava, S., Kainonen, E., Salminen, S. & Isolauri, E. Maternal probiotic supplementation during pregnancy and breast-feeding reduces the risk of eczema in the infant. *J. Allergy Clin. Immunol.* **130**, 1355–1360 (2012).
181. Kianifar, H. et al. Synbiotic in the management of infantile colic: a randomised controlled trial. *J. Paediatr. Child Health* **50**, 801–805 (2014).
182. Indrio, F. et al. Prophylactic use of a probiotic in the prevention of colic, regurgitation, and functional constipation: a randomized clinical trial. *JAMA Pediatr.* **168**, 228–233 (2014).
183. Ganguli, K. et al. Probiotics prevent necrotizing enterocolitis by modulating enterocyte genes that regulate innate immune-mediated inflammation. *Am. J. Physiol. Gastrointest. Liver Physiol.* **304**, G132–G141 (2013).
184. Liu, Y., Fatheree, N. Y., Mangalat, N. & Rhoads, J. M. *Lactobacillus* reuteri strains reduce incidence and severity of experimental necrotizing enterocolitis via modulation of TLR4 and NF- B signaling in the intestine. *Am. J. Physiol. Gastrointest. Liver Physiol.* **302**, G608–G617 (2012).
185. Livingston, M., Loach, D., Wilson, M., Tannock, G. W. & Baird, M. Gut commensal *Lactobacillus* reuteri 100–123 stimulates an immunoregulatory response. *Immunol. Cell Biol.* **88**, 99–102 (2010).
186. Rodes, L. et al. Effect of probiotics *Lactobacillus* and Bifidobacterium on gut-derived lipopolysaccharides and inflammatory cytokines: an in vitro study using a human colonic microbiota model. *J. Microbiol. Biotechnol.* **23**, 518–526 (2013).
187. Penna, F. J., Péret, L. A., Vieira, L. Q. & Nicoli, J. R. Probiotics and mucosal barrier in children. *Curr. Opin. Clin. Nutr. Metab. Care* **11**, 640–4 (2008).
188. Mattar, A. F., Drongowski, R. A., Coran, A. G. & Harmon, C. M. Effect of probiotics on enterocyte bacterial translocation in vitro. *Pediatr. Surg. Int.* **17**, 265–268 (2001).
189. Sherman, M. P. New concepts of microbial translocation in the neonatal intestine: mechanisms and prevention. *Clin. Perinatol.* **27**, 565–579 (2010).
190. Kim, H. K. et al. Probiotic supplementation influences faecal short chain fatty acids in infants at high risk for eczema. *Benef. Microbes* **6**, 783–90 (2015).
191. Kamiya, T. et al. Inhibitory effects of *Lactobacillus* reuteri on visceral pain induced by colorectal distension in Sprague-Dawley rats. *Gut* **55**, 191–196 (2006).
192. Rousseaux, C. et al. *Lactobacillus acidophilus* modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat. Med.* **13**, 35–37 (2007).
193. Candela, M. et al. Interaction of probiotic *Lactobacillus* and Bifidobacterium strains with human intestinal epithelial cells: adhesion properties, competition against enteropathogens and modulation of IL-8 production. *Int. J. Food Microbiol.* **125**, 286–292 (2008).
194. Collado, M. C., Meriluoto, J. & Salminen, S. Role of commercial probiotic strains against human pathogen adhesion to intestinal mucus. *Lett. Appl. Microbiol.* **45**, 454–460 (2007).
195. Indrio, F. et al. Prebiotics improve gastric motility and gastric electrical activity in preterm newborns. *J. Pediatr. Gastroenterol. Nutr.* **49**, 258–261 (2009).
196. Indrio, F. et al. *Lactobacillus* reuteri accelerates gastric emptying and improves regurgitation in infants. *Eur. J. Clin. Invest.* **41**, 417–422 (2011).
197. Cleusix, V., Lacroix, C., Vollenweider, S., Duboux, M. & Le Blay, G. Inhibitory activity spectrum of reuterin produced by *Lactobacillus* reuteri against intestinal bacteria. *BMC Microbiol.* **7**, 101 (2007).
198. Spinler, J. K. et al. Human-derived probiotic *Lactobacillus* reuteri demonstrate antimicrobial activities targeting diverse enteric bacterial pathogens. *Anaerobe* **14**, 166–171 (2008).
199. Simone, M. et al. The probiotic Bifidobacterium breve B632 inhibited the growth of Enterobacteriaceae within colicky infant microbiota cultures. *Biomed. Res. Int.* **2014**, 301053 (2014).
200. Biagioli, E., Tarasco, V., Lingua, C., Moja, L. & Savino, F. Pain-relieving agents for infantile colic. *Cochrane Database Syst. Rev.* **9**, CD009999 (2016).
201. Anheyer, D. et al. Herbal medicines for gastrointestinal disorders in children and adolescents: a systematic review. *Pediatrics* **139**, e20170062 (2017).
202. Reinthal, M. et al. Effects of minimal acupuncture in children with infantile colic – a prospective, quasi-randomised single blind controlled trial. *Acupunct. Med.* **26**, 171–182 (2008).
203. Landgren, K. & Hallström, I. Effect of minimal acupuncture for infantile colic: a multicentre, three-armed, single-blind, randomised controlled trial (ACU-COL). *Acupunct. Med.* **35**, 171–179 (2017).
204. Dobson, D. et al. Manipulative therapies for infantile colic. *Cochrane Database Syst. Rev.* **12**, CD004796 (2012).
205. Bennedbaek, O. et al. [Infants with colic. A heterogenous group possible to cure? Treatment by pediatric consultation followed by a study of the effect of zone therapy on incurable colic]. *Ugeskr. Laeger* **163**, 3773–3778 (2001).
206. Vik, T. et al. Infantile colic, prolonged crying and maternal postnatal depression. *Acta Paediatr.* **98**, 1344–1348 (2009).
207. Radesky, J. S. et al. Inconsolable infant crying and maternal postpartum depressive symptoms. *Pediatrics* **131**, e1857–e1864 (2013).
208. Howell, E. A., Mora, P. & Leventhal, H. Correlates of early postpartum depressive symptoms. *Matern. Child Health J.* **10**, 149–157 (2006).
209. Akman, I. et al. Mothers' postpartum psychological adjustment and infantile colic. *Arch. Dis. Child.* **91**, 417–419 (2006).
210. Howard, C. R., Lanphear, N., Lanphear, B. P., Eberly, S. & Lawrence, R. A. Parental responses to infant crying and colic: the effect on breastfeeding duration. *Breastfeed. Med.* **1**, 146–155 (2006).
211. Reijneveld, S. A., van der Wal, M. F., Brugman, E., Sing, R. A. H. & Verloove-Vanhorick, S. P. Infant crying and abuse. *Lancet* **364**, 1340–1342 (2004).
212. Levitzky, S. & Cooper, R. Infant colic syndrome — maternal fantasies of aggression and infanticide. *Clin. Pediatr. (Phila.)* **39**, 395–400 (2000).
213. Barr, R. G., Trent, R. B. & Cross, J. Age-related incidence curve of hospitalized shaken baby syndrome cases: convergent evidence for crying as a trigger to shaking. *Child Abuse Negl.* **30**, 7–16 (2006).
214. Canivet, C., Jakobsson, I. & Hagander, B. Infantile colic. Follow-up at four years of age: still more "emotional". *Acta Paediatr.* **89**, 13–17 (2000).
215. Rautava, P., Lehtonen, L., Helenius, H. & Sillanpää, M. Infantile colic: child and family three years later. *Pediatrics* **96**, 43–47 (1995).
216. Smarius, L. J. C. A. et al. Excessive infant crying doubles the risk of mood and behavioral problems at age 5: evidence for mediation by maternal characteristics. *Eur. Child Adolesc. Psychiatry* **26**, 293–302 (2017).
217. Savino, F. et al. A prospective 10-year study on children who had severe infantile colic. *Acta Paediatr. Suppl.* **94**, 129–132 (2005).
218. Rao, M. R., Brenner, R. A., Schisterman, E. F., Vik, T. & Mills, J. L. Long term cognitive development in children with prolonged crying. *Arch. Dis. Child.* **89**, 989–992 (2004).
219. Wolke, D., Rizzo, P. & Woods, S. Persistent infant crying and hyperactivity problems in middle childhood. *Pediatrics* **109**, 1054–1060 (2002).
220. Hemmi, M. H., Wolke, D. & Schneider, S. Associations between problems with crying, sleeping and/or feeding in infancy and long-term behavioural outcomes in childhood: a meta-analysis. *Arch. Dis. Child.* **96**, 622–629 (2011).
221. Partty, A., Kalliomaki, M., Salminen, S. & Isolauri, E. Infant distress and development of functional gastrointestinal disorders in childhood. *JAMA Pediatr.* **167**, 977 (2013).
222. Romanello, S. et al. Association between childhood migraine and history of infantile colic. *JAMA* **309**, 1607 (2013).
223. Gelfand, A. A., Goadsby, P. J. & Allen, I. E. The relationship between migraine and infant colic: a systematic review and meta-analysis. *Cephalalgia* **35**, 63–72 (2015).
224. Sillanpää, M. & Saarinen, M. Infantile colic associated with childhood migraine: a prospective cohort study. *Cephalalgia* **35**, 1246–1251 (2015).
225. Gelfand, A. A. Infant colic — a baby's migraine? *Cephalalgia* **35**, 1243–1245 (2015).
226. Kalliomäki, M., Laippala, P., Korvenranta, H., Kero, P. & Isolauri, E. Extent of fussing and colic type crying preceding atopic disease. *Arch. Dis. Child.* **84**, 349–350 (2001).
227. Castro-Rodrīguez, J. A. et al. Relation between infantile colic and asthma/atopy: a prospective study in an unselected population. *Pediatrics* **108**, 878–882 (2001).
228. Miller, J. J., McVeagh, P., Fleet, G. H., Petocz, P. & Brand, J. C. Breath hydrogen excretion in infants with colic. *Arch. Dis. Child.* **64**, 725–729 (1989).
229. Hyams, J. S., Geertsma, M. A., Etienne, N. L. & Treem, W. R. Colonic hydrogen production in infants with colic. *J. Pediatr.* **115**, 592–594 (1989).
230. Barr, R. G., Hanley, J., Patterson, D. K. & Wooldridge, J. Breath hydrogen excretion in normal newborn infants in response to usual feeding patterns: evidence for "functional lactase insufficiency" beyond the first month of life. *J. Pediatr.* **104**, 527–533 (1984).
231. Douwes, A. C., Oosterkamp, R. F., Fernandes, J., Los, T. & Jongbloed, A. A. Sugar malabsorption in healthy neonates estimated by breath hydrogen. *Arch. Dis. Child.* **55**, 512–515 (1980).
232. Kanabar, D., Randhawa, M. & Clayton, P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J. Hum. Nutr. Diet.* **14**, 359–363 (2001).
233. Miller, J. J., McVeagh, P., Fleet, G. H., Petocz, P. & Brand, J. C. Effect of yeast lactase enzyme on colic in infants fed human milk. *J. Pediatr.* **117**, 261–263 (1990).
234. Ståhlberg, M. R. & Savilahti, E. Infantile colic and feeding. *Arch. Dis. Child.* **61**, 1232–1233 (1986).
235. Vandenplas, Y. et al. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American society for pediatric gastroenterology, hepatology, and nutrition (naspghan) and the European society for pediatric gastroenterology, hepatology, and nutrition. *J. Pediatr. Gastroenterol. Nutr.* **49**, 498–547 (2009).
236. Berkowitz, D. Naveh, Y. & Berant, M. "Infantile colic" as the sole manifestation of gastroesophageal reflux. *J. Pediatr. Gastroenterol. Nutr.* **24**, 231–233 (1997).
237. Heine, R. G., Jaquiery, A., Lubitz, L., Cameron, D. J. & Catto-Smith, A. G. Role of gastro-oesophageal reflux in infant irritability. *Arch. Dis. Child.* **73**, 121–125 (1995).
238. Jordan, B., Heine, R. G., Meehan, M., Catto-Smith, A. G. & Lubitz, L. Effect of antireflux medication, placebo and infant mental health intervention on persistent crying: a randomized clinical trial. *J. Paediatr. Child Health* **42**, 49–58 (2006).
239. Moore, D. J. et al. Double-blind placebo-controlled trial of omeprazole in irritable infants with gastroesophageal reflux. *J. Pediatr.* **143**, 219–223 (2003).
240. Heine, R. G., Jordan, B., Lubitz, L., Meehan, M. & Catto-Smith, A. G. Clinical predictors of pathological gastro-oesophageal reflux in infants with persistent distress. *J. Paediatr. Child Health* **42**, 134–139 (2006).
241. Sutphen, J. L. Is it colic or is it gastroesophageal reflux? *J. Pediatr. Gastroenterol. Nutr.* **33**, 110–111 (2001).
242. Putnam, P. E. GERD and crying: cause and effect or unhappy coexistence? *J. Pediatr.* **140**, 3–4 (2002).
243. Savino, F. et al. Ghrelin and motilin concentration in colicky infants. *Acta Paediatr.* **95**, 738–741 (2006).
244. Miller, A. R. & Barr, R. G. Infantile colic. *Is it a gut issue? Pediatr. Clin. North Am.* **38**, 1407–1423 (1991).
245. Kurtoglu, S., Uzüm, K., Hallac, I. K. & Coskum, A. 5-Hydroxy-3-indole acetic acid levels in infantile colic: is serotoninergic tonus responsible for this problem? *Acta Paediatr.* **86**, 764–765 (1997).
246. Stevens, B., Yamada, J. & Ohlsson, A. Sucrose for analgesia in newborn infants undergoing painful procedures. *Cochrane Database Syst. Rev.* **20**, CD001069 (2010).
247. Markestad, T. Use of sucrose as a treatment for infant colic. *Arch. Dis. Child.* **76**, 356–357; discussion 357–358 (1997).
248. Leung, A. K. C. & Lemay, J. F. Infantile colic: a review. *J. R. Soc. Promot. Health* **124**, 162–166 (2004).
249. Sethi, K. S. & Sethi, J. K. Simethicone in the management of infant colic. *Practitioner* **232**, 508 (1988).
250. Danielsson, B. & Hwang, C. P. Treatment of infantile colic with surface active substance (simethicone). *Acta Paediatr. Scand.* **74**, 446–450 (1985).

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251. Metcalf, T. J., Irons, T. G., Sher, L. D. & Young, P. C. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics* **94**, 29–34 (1994).
252. Savino, F., Cresi, F., Castagno, E., Silvestro, L. & Oggero, R. A randomized double-blind placebo-controlled trial of a standardized extract of Matricariae recutita, Foeniculum vulgare and Melissa officinalis (ColiMil) in the treatment of breastfed colicky infants. *Phytother. Res.* **19**, 335–340 (2005).
253. Alexandrovich, I., Rakovitskaya, O., Kolmo, E., Sidorova, T. & Shushunov, S. The effect of fennel (Foeniculum Vulgare) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *Altern. Ther. Health Med.* **9**, 58–61 (2003).
254. Weizman, Z., Alkrinawi, S., Goldfarb, D. & Bitran, C. Efficacy of herbal tea preparation in infantile colic. *J. Pediatr.* **122**, 650–652 (1993).
255. Newmaster, S. G., Grguric, M., Shanmughanandhan, D., Ramalingam, S. & Ragupathy, S. DNA barcoding detects contamination and substitution in North American herbal products. *BMC Med.* **11**, 222 (2013).
256. Rodriguez-Gonzalez, M. et al. Toxicity of remedies for infantile colic. *Arch. Dis. Child.* **99**, 1147–1148 (2014).
257. Cui, K. M. et al. Electro-acupuncture relieves chronic visceral hyperalgesia in rats. *Neurosci. Lett.* **376**, 20–23 (2005).
258. Liao, J. M. et al. Electroacupuncture at Hoku elicits dual effect on autonomic nervous system in anesthetized rats. *Neurosci. Res.* **42**, 15–20 (2002).
259. Skjeie, H., Skonnord, T., Fetveit, A. & Brekke, M. Acupuncture for infantile colic: a blinding-validated, randomized controlled multicentre trial in general practice. *Scand. J. Prim. Health Care* **31**, 190–196 (2013).
260. Adams, D. et al. The safety of pediatric acupuncture: a systematic review. *Pediatrics* **128**, e1575–e1587 (2011).

Author contributions

J.Z., P.D.B., M.L.H., C.d.W. and M.A.B. researched data for this article and drafted the initial manuscript. All authors contributed equally to substantial discussions of content and reviewing and/or editing the manuscript before submission.

Competing interests

M.A.B. was a member of the Pediatric Working Committee of the Rome Foundation that developed the Rome IV criteria for infants and toddlers discussed in this Review. M.A.B. is a scientific consultant for Shire, Sucampo, AstraZeneca, Norgine, Zeria, Coloplast, Danone, Friesland Campina, Sensus and Novalac. P.D.B. is a scientific consultant for CR2O and participated as a speaker for Winclove Probiotics. J.Z., M.P.L. and C.d.W. declare no competing interests.

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