NCPD 2.5 ANCC Contact Hours

THE GASTROINTESTINAL MICROBIOME IN INFANT COLIC: A SCOPING REVIEW

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Abstract

The significant crying of infantile colic adds stress to the infant and their family, yet it has no recognized etiology. Gastrointestinal health problems and dysfunction have been suspected in the etiology of colic. Disruptions to the microbiome colonization of the gastrointestinal system may lead to excess gas and inflammation that are associated with the crying of colic. Infants with colic have increased colonization with gas-producing bacteria, like *Escherichia coli* and *Klebsiella*, and they have lower colonization of anti-inflammatory bacteria, like *Bifidobacterium* and *Lactobacillus*. Colic is known to self-resolve around 3 months of age. However, few researchers have investigated how the microbiome may be changing at colic's natural resolution without the intervention of a probiotic. With a better understanding of what leads to colic's self-resolution, future researchers may be able to identify more effective therapies for colic prevention or treatment. This scoping review presents the collective evidence from 21 original, primary research articles on what is known about the gastrointestinal microbiome at colic onset and resolution.

Key words: Colic; Crying; Dysbiosis; Infant; Microbiota.

Colic causes significant stress to 10% to 25% of infants and their parents, yet it has no recognized etiology (Dubois & Gregory, 2016; García Marqués et al., 2017). The significant stress of colic is associated with recurrent periods of prolonged, inconsolable crying or fussiness that cannot be prevented in infants less than 5 months of age without signs of failure to thrive, fever, or illness (Benninga et al., 2016). Although colic self-resolves, parental stress over crying has been implicated in delayed bonding and in cases of child abuse and shaken baby syndrome (Dubois & Gregory, 2016; Liu et al., 2018).

The suspected etiology of colic is likely multifactorial, involving gastrointestinal (GI) system health, parenting style, and infant temperament (Banks & Chee, 2020; Mai et al., 2018; Savino et al., 2009). Specifically, an imbalance or dysbiosis within the GI microbial landscape has been implicated (Fatheree et al., 2017; Mai et al., 2018; Nation et al., 2017; Ong et al., 2019). Colic and increased crying time are associated with increased GI colonization of gas-producing coliforms like the Proteobacteria, *Escherichia coli*, and *Klebsiella* (Dubois & Gregory, 2016; Fatheree et al., 2017). Colic and crying time are also associated with lower GI colonization of Bacteroidetes, Actinobacteria, like *Bifidobacterium*, and Firmicutes, like *Lactobacilli* (Dubois & Gregory, 2016; Nocerino et al., 2020; Savino et al., 2004).

Colic typically self-resolves by 3 to 4 months of age, yet its resolution is as undefined as its etiology. Although evidence supports microbiome differences at colic onset, there is little evidence of microbiome changes at colic resolution. Existing studies have evaluated effectiveness of probiotics on colic resolution (Simonson et al., 2021), but there is limited evidence about how the microbiome changes at colic resolution without probiotics. The purpose of this scoping review is to evaluate the state of the evidence on what is known about the GI microbiome of infants at colic onset and resolution.

The Colic Experience

The impact of colic on the infant and their family has been explored to better understand the lived parental experience of colic. These qualitative studies identified themes of overwhelming parental emotions and feelings of survival, loss, shame, suffering, guilt, frustration, and hopelessness (Cirgin Ellet & Swenson, 2005; Landgren & Hallstrom, 2011). In both studies, the family was described as being in a state of crisis and everyone was crying, infants and parents, due to the stress of colic. Landgren and Hallstrom (2011) note that parents used a variety of strategies to stop the crying associated with colic. Cirgin Ellet and Swenson (2005) report parental frustration at the lack of remedies and ambiguous understanding of colic's origin. This frustration, desperation for relief, and the themes of stress highlight the importance of studies to identify colic's etiology and develop effective strategies for prevention and treatments.

The Role of Gastrointestinal Microbiome

Colic's emotional impact has been explored, yet the etiology of colic remains unclear. Colic most likely has a multifactorial origin, involving the interaction of the GI system, parenting style, infant temperament, and infant neurologic immaturity. Gastrointestinal system involvement is the subject of this review, but it is important to consider how other factors may influence colic.

Early descriptions of colic include excessive crying, gassy tendencies, and abdominal distension that point to GI involvement (Wessel et al., 1954). The GI microbiome, consisting of all microorganisms living within the human GI system, plays an important role in processing nutrients, preventing colonization by potentially pathogenic organisms, and developing the intestinal immune system and inflammatory responses (Human Microbiome Project Consortium, 2012; Pärtty et al., 2017; Savino et al., 2009). As sequencing technology has advanced, the understanding of how humans relate to their microbial flora has grown. Having a commensal, or healthy, microbiome results in a eubiotic state.

Dysbiotic microbes communicate with the host through inflammatory markers thus promoting GI inflammation (Dubois & Gregory, 2016; Pärtty et al., 2017; Rhoads et al., 2018). The microbes primarily colonizing the infant with colic's microbiome tend to be coliforms, gas producers (Dubois & Gregory, 2016; Ong et al., 2019; Savino et al., 2009). Coliforms link to the crying, gas, and distension often identified with colic (Mai et al., 2018).

Methods

The objectives for this scoping literature review were to identify what is known about the microbiome at colic onset and resolution. In July 2021, searches of SCOUT, PubMed, and CINAHL returned 935 articles using the search terms "infant colic" AND "microbiome" NOT "equine." After removing duplicates, a total of 637 articles were reviewed by title and abstract (Figure 1). Reference lists of the final literature were reviewed. Two sources were extracted and included in the scoping review. Articles were selected if they included infants less than 5 months of age with colic and sequenced the GI microbiome at either colic onset or resolution. This review includes interventional studies with probiotics if they also sequenced the microbiome and assessed for colic onset or resolution. Articles were not excluded based on infant feeding method. Some studies included only breastfed infants, whereas others were inclusive of all feeding methods. Savino et al. (2017) is the only study of exclusively formula-fed infants in this review, and Pärtty and Isolauri (2012) did not address feeding methods in their report. Articles were excluded if they did not study humans, if they did not study infants less than 5 months of age with colic, and if they did not sequence the GI microbiome. Thus, studies of skin, oral, vaginal, and maternal microbiome studies were excluded. Articles that focused on other outcomes of colic such as reduced

crying time or focused on etiological theories of colic without also including the GI microbiome were excluded. Reviews and clinical guidelines were excluded from the scoping review to focus on original, primary evidence. Thirty-eight articles met criteria for full-text review.

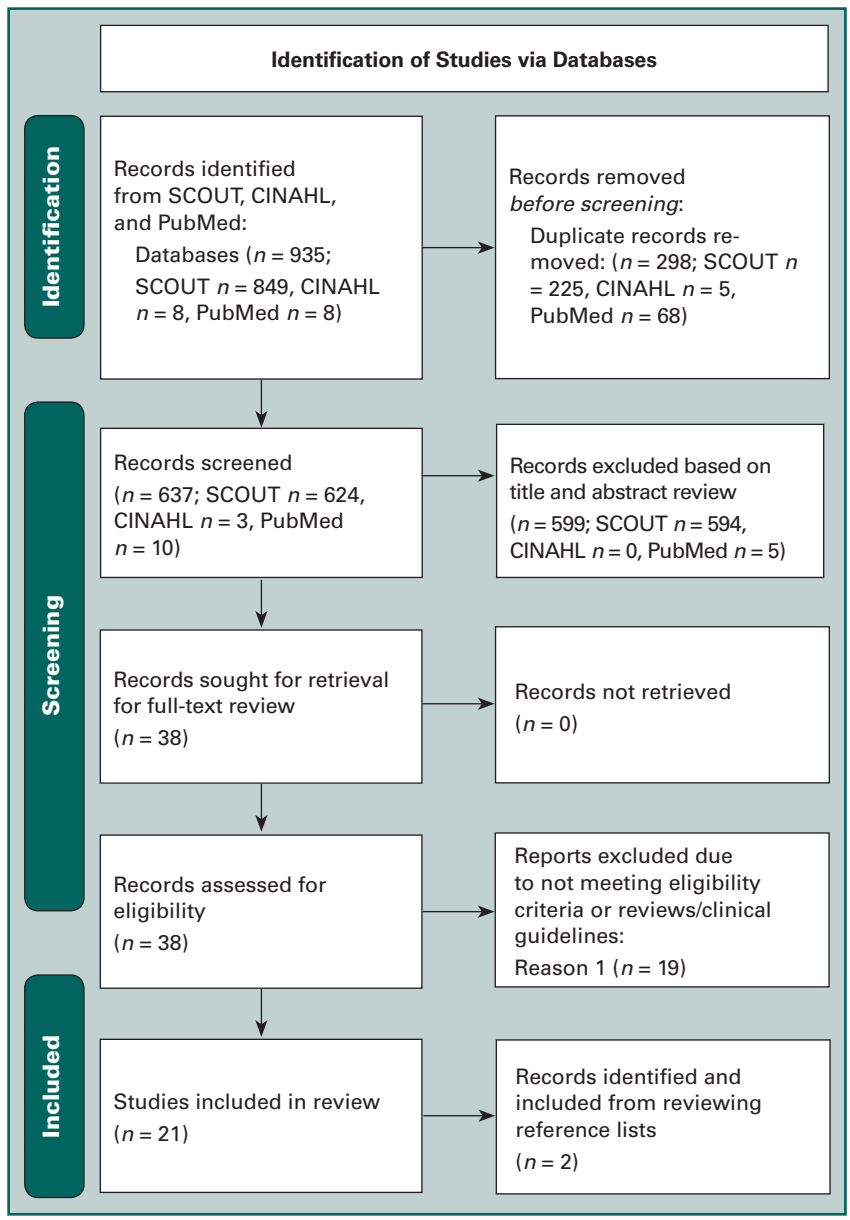
Results

After full-text review, 21 meeting inclusion criteria comprise this scoping review, including 2 articles identified from the references. See Table 1. The primary evidence in this review includes randomized control trials (n = 12), prospective cohort studies (n = 4), case-control studies (n = 4), and cross-sectional studies (n = 1). Dates of publication were not limited, to cover the evolution of knowledge relating to the infant GI microbiome in colic. Articles' publication dates ranged from 2004 to 2021.

Methods of Microbiome Detection

Microbiome technologies have advanced in specificity over the 18 years of literature from this scoping review. Earlier studies with less advanced technologies, such as fluorescence in situ hybridization and stool cultures, were included to show the evolution and scope of knowledge about the GI microbiome and colic (Mentula et al., 2008; Pärtty et al., 2012; Savino et al., 2004). The more recent studies in this review used 16s rRNA sequencing and real-time quantitative polymerase chain reaction (Korpela et al., 2020; Nocerino et al., 2020; Savino et al., 2020). Level of bacterial taxa reported varied from phylum to species level, which may relate to the specificity capabilities of the technology used in each study. The genus *Bifidobacterium* is known for anti-inflammatory effects, but some studies indicate the species *B. breve* to increase crying and inflammation (Pärtty & Isolauri, 2012; Pärtty et al., 2012; Pärtty et al., 2017). This example demonstrates how greater taxonomic specificity may explain discrepancies between study findings and may lead to better evidence for identifying the etiology and treatment of colic.

FIGURE 1. PRISMA DIAGRAM



Note. Adapted from Page et al. (2021).

Gastrointestinal Microbiome Composition at Colic Onset

The GI microbiome of infants at colic onset must be compared with infants without colic to understand the relationship between the microbiome and colic. Many studies identified higher colonization of Proteobacteria, like *Klebsiella* and *Escherichia*, beginning as early as 2 weeks of age and continuing through colic diagnosis in infants with colic when compared with their counterparts (de Weerth, Fuentes, Puylaert, et al., 2013; Nocerino et al., 2020; Savino et al., 2018). First-pass meconium in infants who later developed colic was found to have lower abundance of the phylum Firmicutes and the genus *Lactobacillus* demonstrating that colonization patterns leading to colic may be present at birth (Korpela et al., 2020). Reductions in crying and fuss time have been associated with increased colonization of Bacteroidetes, Actinobacteria, like *Bifidobacterium*, and Firmicutes, like *Lactobacillus* (de Weerth, Fuentes, Puylaert, et al., 2013; Nocerino et al., 2020; Pärtty & Isolauri, 2012; Rhoads et al., 2018; Roos et al., 2013). *B. breve* has been

Table 1. Studies Included in the Review

First Author and Date	Infant Sample, Feeding Method, and Intervention (if applicable)	Characteristics and Geography
Korpela et al. (2020)	*N* = 212 (19 developed colic) Breastfed and formula-fed	Design: Prospective, population-based study Microbiome Detection:16s rRNA sequencing Location: Jyväskylä, Finland
Rhoads et al. (2018)	*N* = 65 (37 colic, 28 noncolic) Formula, breastfed, and both	Design: Nested case-control (part of 3 other studies) Microbiome Detection: 16s rRNA sequencing Location: Houston, TX, USA
Pärtty et al. (2017)	*N* = 40 (28 colic, 12 controls) Reference population comprised 12 healthy controls matched by mode of birth and feeding type from an ongoing prospective follow-up study that records infant behavior patterns (e.g., crying, sleeping, feeding). Formula and breastfed	Design: Part of an ongoing, double-blind, placebo-controlled RCT involving probiotic *Lactobacillus rhamnosus* GG (ATCC 53103) intervention Microbiome Detection: quantitative polymerase chain reaction (qPCR) Location: Finland *Note:* All samples were taken before any infants received probiotic intervention.
Savino et al. (2017)	*N* = 77 (38 colic, 39 noncolic) Formula-fed	Design: Cross-sectional study using Microbiome Detection: FISH assays Location: Turin, Italy
De Weerth et al. (2013) *Intestinal Microbiota of Infants with Colic*	*N* = 24 (12 colic, 12 controls) Collected 9 stool samples over first 100 days of life Formula and breastfed	Design: Part of a prospective longitudinal project Microbiome Detection: 16s rRNA sequencing Location: Major metropolitan areas in the Netherlands *Note:* Selected 12 colicky and 12 controls based on having the lowest and highest scores from *n* = 106 samples completing the study
De Weerth et al. (2013) *Crying in Infants*	*An addendum to the earlier publication*	
Savino et al. (2009)	*N* = 80 (41 colic, 39 control) Exclusively breastfed	Design: Case-control study Microbiome Detection: Real-time PCR Location: Turin, Italy
Savino et al. (2004)	*N* = 71 (42 colic, 29 control) Breastfed	Design: Case-control study Microbiome Detection: Stool cultures Location: Turin, Italy
Nocerino et al. (2020)	*N* = 80 colic (40 probiotic, 40 control) Exclusively breastfed Intervention: probiotic *Bifidobacterium animalis* subsp. *lactis* BB-12®	Design: RCT Microbiome Detection: 16s rRNA sequencing Location: Naples, Italy

	Johns Hopkins Nursing EBP: Levels of Evidence	Bacterial Findings in Colic	Clinical Implications
	Level 3	Lower relative abundance of *Lactobacillus* and Firmicutes than those without colic on the first-pass meconium	Microbial dysbiosis related to colic may trace back to first-pass meconium
	Level 2	Lower amounts of Actinobacteria including *Bifidobacterium* in colic Increased proportion of Proteobacteria (marginal/not statistically significant) in colic	*Bifidobacterium* may have anti-inflammatory effects and may inhibit the proliferation of proinflammatory Proteobacteria
	Level 1	*Clostridium leptum* and *Clostridium coccoides* colonization associated with lower levels of proinflammatory biomarkers *Bifidobacterium breve* colonization associated with increased inflammatory markers.	Facilitating *C. leptum* and *C. coccoides* colonization may reduce gastrointestinal inflammation and associated colic crying. Researchers and providers should consider dysbiosis and low-grade inflammation when choosing specific strains of probiotics for colic.
	Level 3	Lower total numbers of bacteria in colic Increased abundance of coliforms, esp. *Enterobacteriaceae*, in colic	Increased presence of coliforms may relate to gassy symptoms in colic
	Level 3	Proteobacteria were more abundant in colicky infants than controls by twofold. Specific proteobacteria associated with colic include *Escherichia*, *Klebsiella*, *Serratia*, *Vibrio*, *Yersinia*, and *Pseudomonas*. Bacteroidetes, *Bifidobacteria* and Firmicutes phyla, including *Lactobacilli* were lower in colicky infants.	Increased abundance of proinflammatory Proteobacteria may relate to colic symptoms. Phylum Bacteroidetes and Firmicutes colonization may have protective effect against colic. Lower *Lactobacilli* and *Bifidobacteria* colonization may allow proliferation of Proteobacteria.
		Increased Proteobacteria in colicky infants Decreased *Lactobacilli* and *Bifidobacteria*	Reinforces the previously published findings above and links inflammation
	Level 3	Increased coliform (gas-producing) bacteria, especially *E. coli*, in colic	Increased presence of coliforms may relate to gassy symptoms in colic and may impact ability of commensal bacteria to colonize
	Level 3	Detected microflora difference Reduced *Lactobacilli* and increased anaerobic gram-negative bacteria in colicky infants	Sentinel study Key early study into colic microbiome
	Level 1	Increased *Bifidobacterium* correlated with reduced crying Reduced inflammatory markers in probiotic group Both groups saw a reduction in crying, but statistically significant difference in probiotic with greater reduction in probiotic group Increase in Proteobacteria in colicky, placebo infants	*Bifidobacterium* colonization may reduce crying time and *Bifidobacterium* probiotics may influence their colonization.

(Continues)

Table 1. Studies Included in the Review *(Continued)*

First Author and Date	Infant Sample, Feeding Method, and Intervention (if applicable)	Characteristics and Geography	
Savino et al. (2020)	*N* = 47 colic (26 intervention, 21 placebo) Exclusively breastfed Intervention: probiotic, *L. rhamnosus* ATCC 53103	Design: RCT Microbiome Detection: Real-time PCR Turin, Italy *Note:* They do note that a double-blind, placebo-controlled study with a larger population is needed to validate these results.	
Baldassarre et al. (2018)	*N* = 53 colic (27 probiotic, 26 placebo) Exclusively breastfed Intervention: probiotic mixture of 4 different strains of lactobacilli (*L. paracasei* DSM 24733, *L. plantarum* DSM 24730, *L. acidophilus* DSM 24735, and *L. delbrueckii* subsp. bulgaricus DSM 24734), 3 strains of *bifidobacteria (B. longum* DSM 24736, *B. breve* DSM 24732, and *B. infantis* DSM 24737), and 1 strain of *Streptococcus thermophilus* DSM 24731. Brand names: Vivomixx® (Europe), Visbiome® (USA), and DeSimone Formulation (Korea)	Design: Double-blind, placebo-controlled RCT Microbiome Detection: real-time PCR sequencing Location: Bari, Italy	
Savino et al. (2018)	*N* = 87 (60 colic, 27 healthy control) *N* = 60 colic (32 probiotic, 28 placebo) Breastfed and formula-fed Intervention: probiotic, *Lactobacillus reuteri* DSM 17938.	Design: Double-blind, placebo-controlled RCT Microbiome Detection: 16s rRNA sequencing for microbiome detection Location: Turin, Italy *Note:* The control group (*n* = 27) was recruited among those hospitalized for episodes of apnea, apparent life-threatening event, congenital hypothyroidism, and mild infections of the high respiratory tract.	
Fatheree et al. (2017)	*N* = 18 colic (11 probiotic, 7 placebo) Exclusively breastfed Intervention: probiotic *L. reuteri* (DSM) 17938	Design: Double-blind, placebo-controlled RCT Microbiome Detection: 16s rRNA sequencing Location: Houston, TX, USA *Limitation:* Small sample size and diversity of the stool samples made comparison across groups difficult. Target sample size was *n* = 45.	
Nation et al. (2017)	*N* = 65 colic (31 probiotic, 34 placebo) Breastfed and formula-fed Intervention: probiotic *L. reuteri*	Design: Part of a larger double-blind, randomized, placebo-controlled trial Microbiome Detection: 16s rRNA sequencing Location: Melbourne, Australia	

	Johns Hopkins Nursing EBP: Levels of Evidence	Bacterial Findings in Colic	Clinical Implications
	Level 1	Intervention group saw a significant reduction in crying and fecal calprotectin, and an increase in total bacteria and *Lactobacillus*. These effects were not observed in controls.	Probiotic *L. rhamnosus* can improve gastrointestinal inflammation and reduce crying time.
	Level 1	Probiotic intervention did not modify microbiome composition of Lactobacilli or *Bifidobacteria* There was a higher rate of colic reduction (reduction of symptoms by 50%) in probiotic group	Probiotic effects may be due to microbial metabolomics
	Level 1	Infants with colic had higher percentages of *E. coli* *L. reuteri* increased *Lactobacillus* abundance and correlated with decreased crying time, therefore increased *Lactobacillus* abundance correlated with decreased crying time. Additionally, inflammatory markers were elevated in colicky infants and reduced with the *L. reuteri* treatment.	Probiotic *L. reuteri* DSM 17938 may decrease crying time and reduce gastrointestinal inflammation
	Level 1	Higher fecal calprotectin on enrollment in all (colicky) infants. Proteobacteria *Escheria* most commonly found organism and increased in 5 of 6 infants at colic resolution Reduced *Bacteroides* abundance as colic resolved	GI inflammation was present, but not systemic. Breastfeeding increases fecal calprotectin, but it did not explain the increase in this study.
	Level 1	Increased *L. reuteri* colonization associated with increased crying time Negative correlation with *E. coli* and microbial diversity	Clinical findings differ from other studies and these authors suggest that geography and feeding method may have influenced results Their findings did not replicate Savino (2010) that found that *L. reuteri* administration and subsequent colonization had a negative correlation with *E. coli* colonization.

(Continues)

Table 1. Studies Included in the Review *(Continued)*

First Author and Date	Infant Sample, Feeding Method, and Intervention (if applicable)	Characteristics and Geography
Sung et al. (2014)	*N* = 167 colic (85 probiotic, 82 placebo) Breastfed and formula-fed Intervention: probiotic *L. reuteri* *Subset for microbial diversity: N* = 55 who had microbial diversity analysis, *n* = 65 who had *E. coli*, *n* = 102 with fecal calprotectin analysis	Design: Double-blind, placebo-controlled RCT (Subset of larger *L. reuteri* probiotic study) Microbiome Detection: 16s rRNA and qPCR detection of *E. coli* Location: Melbourne, Australia *Note:* They were largest RCT at time and first to include formula-fed infants.
Roos et al. (2013)	*N* = 29 colic (15 probiotic, 15 placebo) Exclusively breastfed Intervention: probiotic *L. reuteri*	Design: Double-blind, placebo-controlled RCT Microbiome Detection: 16s rRNA sequencing Location: Turin, Italy
Pärtty et al. (2012) *Compositional Development*	*N* = 89 Formula and breastfed 47% probiotic intervention, *L. rhamnosus GG.*	Design: Double-blind, placebo-controlled RCT Microbiome Detection: FISH assays Location: Turku, Finland *Note:* This study explored full spectrum of crying rather than colic specifically through parental diary
Pärtty & Isolauri (2012)	*N* = 88 Feeding method not addressed	Design: Prospective cohort study Microbiome Detection: qPCR and FISH assays Location: Turku, Finland *Note:* This study explored full spectrum of crying rather than colic specifically through parental diary. Part of ongoing study from Pärtty et al. (2012) above.
Savino et al. (2010)	*N* = 46 colic (25 probiotic, 21 control) Exclusively breastfed Intervention: probiotic *L. reuteri* DSM 17938	Design: Double-blind, placebo-controlled RCT Microbiome Detection: FISH assay Location: Turin, Italy
Mentula et al. (2008)	*N* = 18 (9 colic, 9 noncolic) *N* = 9 colic (5 probiotic, 4 placebo) Exclusively breastfed Intervention: probiotic mixture (*L. rhamnosus GG, L. rhamnosus LC705, B. breve Bbi99,* and *Propionibacterium freudenreichii ssp. shermanii JS*)	Design: Double-blind RCT Microbiome Detection: Stool culture Location: Helsinki, Finland

associated with increased crying and fussiness in colic, and elevated proinflammatory marker levels (Pärtty & Isolauri, 2012; Pärtty et al., 2012; Pärtty et al., 2017).

This dysbiosis may lead to increased GI inflammation and affect future immune system function (Dubois & Gregory, 2016; Pärtty et al., 2017; Rhoads et al., 2018; Savino et al., 2020). More research is needed with higher taxonomic specificity to better define the microbiome of infants with and without colic and better understand its influence on colic development and symptoms.

Gastrointestinal Microbiome Composition at Colic Resolution

Infants with colic have a different microbiome at onset than infants without colic. To better describe the evolu-

	Johns Hopkins Nursing EBP: Levels of Evidence	Bacterial Findings in Colic	Clinical Implications
	Level 1	Found no difference in intervention and placebo group in fecal microbial diversity, *E. coli* colonization or fecal calprotectin levels There was no significant difference in the treatment and probiotic group as far as symptom reduction. Infants with 50% reduction in crying at 1 month had significantly lower calprotectin levels with comparable *E. coli* and microbial diversity when compared with nonresponders.	These findings differ from previous smaller trials of selected populations and do not support a general recommendation for the use of probiotics to treat colic in infants. Geography and feeding method may influence results.
	Level 1	*L. reuteri* did not significantly change the microbiome, however, responders (defined as a 50% decrease in crying) had an increased relative abundance of *Bacteroidetes* at 21 days compared with the first day	Probiotic *L. reuteri* did not produce a statistically significant reduction in crying in a 21-day trial
	Level 1	Increased proportion of *Bifidobacteria* and Lactobacilli correlated with reduced crying over the first 3 months of life. *B. breve,* however, was positively associated with infant crying.	Facilitating Lactobacilli and *Bifidobacteria* colonization may reduce crying time or even protect against onset of colic crying *B. breve*'s association with crying highlights the need for increased specificity in microbiome research and targeting probiotic strains in future studies.
	Level 3	Proportion of *Bifidobacterium* inversely associated with crying time in first 3 months of life. *B. breve* behaved conversely to the rest of the *Bifidobacterium* class. *Lactobacillus* colonization at 3 weeks of age inversely associated with crying time at 7 weeks.	Facilitating lactobacilli and *bifidobacteria* colonization may reduce crying time or even protect against onset of colic crying
	Level 1	*L. reuteri* group had higher responders (50% reduction in crying time from baseline) on days 7, 14, and 21. *L. reuteri* group had an increase in fecal Lactobacilli and a reduction in *E. coli* and ammonia.	Probiotic *L. reuteri* may improve crying time
	Level 1	Increased coliforms in colic (*E. coli* and *Klebsiella oxytoca*)	Increased presence of coliforms may relate to gassy symptoms in colic

tion of colic, it is important to understand the microbiome as colic resolves. De Weerth, Fuentes, Puylaert, et al. (2013) investigated the microbiome at colic resolution without probiotic intervention during the first 100 days of life and found that Proteobacteria were significantly increased, and *Bifidobacterium* and *Lactobacillus* were significantly decreased in infants with colic compared with noncolic infants. These differences were no longer detectable at age of colic resolution. However, these researchers do not state whether the change in microbiome composition correlated with the reduced crying of colic resolution.

Studies using probiotic interventions used different probiotic strains and mixtures, including species from *Lactobacilli*, *Bifidobacteria, Streptococcus,* and *Propionibacterium* (Baldassarre et al., 2018; Fatheree et al.,

CLINICAL IMPLICATIONS

- Pediatricians and nurse practitioners may be able to choose a targeted probiotic approach to preventing or treating colic by understanding the connection between the microbiome and inflammatory biomarkers.
- The relationship between the GI microbiome and GI inflammatory markers needs further investigation and may provide a way for pediatricians and nurse practitioners to identify colic development.
- Increasing *Lactobacillus* or *Bifidobacterium* colonization through probiotics may have anti-inflammatory effects that reduce colic crying.
- Increased presence of coliforms, gas-producing bacteria, may relate to the gassy symptoms in colic.

2017; Mentula et al., 2008; Nation et al., 2017; Nocerino et al., 2020; Pärtty & Isolauri, 2012; Pärtty et al., 2012; Roos et al., 2013; Savino et al., 2010; Savino et al., 2018; Savino et al., 2020). Safety, effects on colic symptoms, and the microbiome were assessed. Although adding bacteria to the GI system through probiotics may have affected microbiome colonization, the crying and colic symptom reductions associated with these microbiome changes may be important to understand how the microbiome affects colic onset and resolution.

Probiotic studies found that reductions in crying with colic were associated with an increase in *Lactobacillus* and *Bifidobacterium* (Nocerino et al., 2020; Savino et al., 2018; Savino et al., 2020). Baldassarre et al. (2018) found that though *Lactobacillus* and *Bifidobacterium* remained relatively the same in the probiotic and placebo groups of breastfed babies with colic, there was a higher rate of crying reduction in the probiotic group. Pärtty et al. (2012) investigated crying and fuss time rather than colic specifically but noted that over the first 3 months of life, as *Bifidobacterium* increased, crying and fuss time decreased. Approximately half of the participants received the probiotic intervention during the study, but the researchers noted no difference in total crying in these infants (Pärtty et al., 2012). Bacteroidetes produced conflicting results; Roos et al. (2013) found that increased relative abundance correlated with a reduction in crying, whereas Fatheree et al. (2017) found that *Bacteroides* decreased as colic resolved. These different results may be due to sample size, as Fatheree et al. noted their small sample size may have affected results but may derive from the differences between the phylum and genus taxa. Savino et al. (2010) also found a reduction in *E. coli* that correlated with reduced crying time in the probiotic arm of their study of breastfed infants with colic. Overall, these findings suggest the microbiome at colic resolution resembles the noncolic microbiome by increased *Bifidobacterium* and *Lactobacillus* and decreased *E. coli*. However, more research is needed to understand the microbiome at colic self-resolution and the involvement of Proteobacteria at resolution.

Probiotic studies demonstrated safety of use; however, only a few revealed an improvement in clinical symptoms. If the probiotic did not demonstrate an effect, the researchers often noted that crying reduced in all groups throughout the study (Fatheree et al., 2017; Mentula et al., 2008; Nation et al., 2017).

Geography and feeding methods likely influence microbiome colonization. Nation et al. (2017), in a study conducted in Australia, confirmed this notion and noted different results from multiple studies in other countries, including Savino et al. (2010). Savino et al. (2018) conducted another Italian probiotic study that further supported their earlier (Savino et al., 2010) findings. Variations in feeding type and method are associated with variations in GI microbiome colonization (Dubois & Gregory, 2016). Breastfed infants receive bacteria through the breastmilk microbiome and human milk oligosaccharides that nourish the bacteria in the human gut (de Weerth, Fuentes, & de Vos, 2013). Formula-fed infants have different GI microbiomes than their exclusively breastfed peers (Forbes et al., 2018; Mueller et al., 2015). Geography and feeding methods may explain the discrepancies between studies of different probiotics in infants with colic.

Discussion and Future Implications

Colic is associated with microbiome changes. The dysbiosis associated with colic may lead to increased GI inflammatory biomarkers and GI inflammation. The connection between the microbiome, inflammatory biomarkers, and GI inflammation may help to explain GI system involvement in the etiology of colic. Fecal calprotectin and proinflammatory chemokines have been used to investigate the presence and role of GI inflammation in colic (Nocerino et al., 2020; Pärtty et al., 2017; Savino et al., 2020). Researchers are investigating connections between microbial colonization and the presence of inflammatory biomarkers. *Lactobacillus* and *Bifidobacterium* colonization has been associated with decreases in fecal calprotectin, indicating a protective effect against GI inflammation (Nocerino et al., 2020; Savino et al., 2020). Increased colonization with Proteobacteria may increase gas production due to fermentation of carbohydrates and proteins by the Proteobacteria. Increases in *Bifidobacteria* or *Lactobacilli* inhibit the growth of Proteobacteria that would inhibit the fermentation, gas production, and proinflammatory biomarker production associated with Proteobacteria colonization in colic (Nocerino et al., 2020; Rhoads et al., 2018). These studies highlight that the microbiome composition of infants with colic may affect GI inflammatory markers and GI inflammation. Possible connection between how the microbiome and GI inflammatory markers relate needs further investigation, but in the future, may provide a way to identify colic development. By understanding the connection between the microbiome and inflammatory biomarkers, pediatricians and nurse practitioners may be able to choose a targeted probiotic approach to preventing or treating colic.

Population Differences

Nutrition is known to affect the GI microbiome, and early infant feeding affects this early colonization. Colic dysbiosis was supported both in breastfed and formula-fed infants. In the nonintervention studies including breastfeeding and formula-feeding, infants with colic were found to have differing microbiomes than their noncolic counterparts regardless of feeding method (de Weerth, Fuentes, Puylaert, et al., 2013; Korpela et al., 2020; Rhoads et al., 2018; Savino et al., 2017). Australian probiotic studies of breastfed and formula-fed infants did not find a difference in microbiome colonization or improvement in crying time between intervention and control groups (Nation et al., 2017; Sung et al., 2014). The difference in findings may be due to geography or feeding methods when compared with the probiotic benefits seen in Italian probiotic studies of exclusively breastfed infants (Savino et al., 2010; Savino et al., 2018). These examples demonstrate how population differences involving feeding methods and geography may influence the choice of probiotic therapies.

Conclusions

The difference between the microbiome composition of infants with colic compared with their noncolic counterparts has been well established. The dysbiosis associated with colic is marked by increased colonization of proinflammatory Proteobacteria and decreased colonization of anti-inflammatory Firmicutes, especially *Lactobacillus*, and Actinobacteria, *Bifidobacterium*. Newer studies are beginning to associate proinflammatory Proteobacteria and anti-inflammatory Firmicutes and Actinobacteria with inflammatory biomarkers. These findings provide insights into how GI microbiome dysbiosis may manifest as symptoms of colic. More research into colic dysbiosis and GI inflammation may improve the understanding of colic's etiology and guide treatment development.

Data are limited on the microbiome composition at colic resolution. There is some indication that the infant microbiome at colic resolution resembles infants without colic, however, many of these studies used a probiotic intervention that likely influenced results. There is a gap in the literature concerning microbiome composition at colic self-resolution, especially without the influence of probiotic treatments. It is important to better understand how the microbiome contributes to colic resolution. Future research is needed to fill this gap without the influence of probiotic treatments. By better understanding how the microbiome affects colic onset and resolution, future researchers and clinicians can intervene to better prevent and treat colic. By preventing and treating colic, the stress caused by colic on the infant and their family can be reduced. ✣

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