Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: September 30, 2023

Citation: Kesavelu D, 2023. Alleviating Gasto-Intestinal Discomfort in Infants: Quest for Effective Interventions, Medical Research Archives, [online] 11(9). https://doi.org/10.18103/mra.v11i9.4459

DOI
https://doi.org/10.18103/mra.v11i9.4459

ISSN: 2375-1924

RESEARCH ARTICLE

Alleviating Gasto-Intestinal Discomfort in Infants: Quest for Effective Interventions

Dhanasekhar Kesavelu

Email: drdskgastro@gmail.com

ABSTRACT

Functional gastrointestinal disorders (FGIDs) are common among infants, yet precise diagnosis and optimal management strategies remain a challenge. Understanding the prevalence and impact of these conditions is essential for improving infant health. We present a comprehensive review of the evolution of treatment strategies for FGIDs tracing the identification of the first case to the recent advancements in disease management. The article explores the journey of the Rome criteria, which is the most widely used diagnostic parameter for FGIDs, as it transformed from consensus-based recommendations culminating in the present-day evidence-based guidelines, setting the stage for the upcoming Rome V criteria. FGIDs were initially hypothesized solely as a GI entity; however, thorough etio-pathologic research has elucidated the complex bio-psychosocial basis of FGIDs. In infants, these conditions can be particularly challenging to identify and manage due to their limited ability to communicate discomfort and distress. The article briefly refers to pathophysiology and diagnostic challenges as an exploratory background for effective management. An overview of existing research can shed light on the various treatment approaches for FGIDs in infants. We examined pharmacotherapy in FGID management in terms of its indications and limitations, which would allow its judicious use in clinical practice. The article underscores the efficacy and safety of a dietary approach in FGID management in infants, especially in the absence of red flags. We highlight key research details that led to newer advancements in nutritional interventions such as probiotics. L reuteri DSM 17938 is the most extensively studied probiotic with proven benefits and manifold indications. We highly recommend large prospective studies to identify the ideal therapeutic agent that can provide a potential opportunity to prevent FGIDs.

Keywords: Functional gastrointestinal disorders (FGIDs), Rome criteria, infant nutrition, probiotics, L reuteri DSM 17938.

Introduction

Functional gastrointestinal disorders (FGIDs) in infancy constitute a diverse combination of persistent chronic or recurrent gastrointestinal (GI) signs and symptoms without any discernible structural or biochemical alterations.[1,2] Certain functional disorders tend to occur concurrent with the physiological development of the infant, such as regurgitation, while other FGIDs, like constipation, may be triggered by an age-specific but maladaptive response.[3] Such symptoms are frequently encountered in almost 50% of infants during the first year of life.[1] Infants with FGIDs display reduced quality of life with considerable impact on the caregivers. Frequent medical consultations impose significant psychological and financial burdens on the infants' families.[1,4]

Infantile FGIDs broadly encompass the presentations of regurgitation, rumination, vomiting, diarrhea, constipation, colic, and dyschezia (**Table 1**[1,5–11]).

Muhardi L et al. (2021) collated the global data on FGIDs and identified regurgitation as the most frequently encountered gastrointestinal (GI) discomfort in infants aged 0-6 months, followed by colic.[5]

Table 1: Age of presentation and prevalence of FGIDs:

FGIDs	Age of presentation	Prevalence in infants aged 0–6 months
Infant regurgitation	3 wk to 12 mo, peak age around 2-4 months Physiological Gastroesophageal reflux (GER) peaks at 3 months, Gastroesophageal reflux disease (GERD) at 1 month	33.9%
Infant rumination syndrome	3-8 mo	1%
Cyclic vomiting syndrome	Wide range, infancy to adulthood	0.6%
Infant colic	Early infancy to 5mo, a behavioral phenomenon in infants aged 1 to 4 months Termed as a "noisy phenomenon" which is usually self-limiting by 4months of age	10–15%
Functional diarrhea	6 to 60 mo	0-2.2%
Infant dyschezia	Birth to 9 mo	0.9-3.6%
Functional constipation	Birth to adulthood	1.5%

Regurgitation is the most commonly presenting FGID in infants aged 0-6 months followed by colic and constipation. Diarrhea, dyschezia, and rumination syndrome are seen less frequently seen while cyclic vomiting is rarely encountered in pediatric practice.

Despite the extensive body of published literature, the conundrum surrounding the prevalence and manifestations of FGIDs remains unresolved. It is noteworthy that low- and middle-income countries, despite harboring a significant portion of the global population, are underrepresented in scientific investigations. The limited evidence from these regions is primarily attributed to the dearth of robust healthcare infrastructure and large-scale studies within these regions. Furthermore, a significant challenge arises from the fact that the documentation of FGID symptoms relies heavily on subjective metrics, often collected through parent-reported questionnaires. These assessments are susceptible to significant influence from cultural norms, societal practices, and individual perception leading to high variability in retrieved data.

The objective of this article is to explore the evolution of treatment strategies for FGIDs tracing the identification of the first case to the recent advancements in disease management. FGIDs are not a single clinical entity, but a conglomeration of GI symptoms with similar pathophysiology identified on a case-to-case basis. Recorded history through published literature set the stage for a better understanding of functional GI symptoms.

History of Identifying Functional Gastrointestinal (GI) symptoms in infants

Cyclic Vomiting Syndrome (CVS), a relatively underdiagnosed syndrome of episodic, acute and recurrent intense nausea and incoercible vomiting,

was first described by Heberden in 1806. But it was only till 1882 that the most accurate contemporary description of CVS was published by Samuel Gee in the St. Bartholomew's Hospital Reports.[12,13]

The rumination disorder of infancy, a fairly uncommon syndrome, was first described in 1907 by Maas H. Considered as the eating disorder of infancy, it had potentially fatal implications due to unexplainable weight loss or inability to gain weight.[14]

Reports of constipation were first presented by Arthur Hertz in 1908 in a communication to the Medical Section. He divided the cases into intestinal constipation and dyschezia. The former was defined as the delayed passage of feces through the intestines with normal defecation while dyschezia referred to the inadequate expulsion of feces without any colonic delay.[15] Later on in 1912, Hertz comprehensively summarized the literature on congenital dyschezia.[15] A detailed report on long-standing drug-resistant chronic constipation was presented by Clayden and Lawson in 1976.[16]

The classic picture of infantile colic was described by Joe Brennemann in 1943 and a year later by Benjamin Spock as that of a thriving baby who in the early evening, for no apparent reason, develops paroxysms, followed by high pitched screaming within a few seconds that ended suddenly in a few minutes, immediately ensued by another paroxysm.[17] This paroxysmal fussing was described as an environmental somatic response to tension by Morris Wessel in 1954,[18] who concurrently presented the most widely used criteria for infant colic.[19]

In 1979, Lloyd-Still published a report on chronic diarrhea of childhood and the misuse of elimination diets, which formed the basis of defining functional diarrhea characterized by frequent loose stools.[20] (**Figure 1**)

It has been over a century since the documentation of FGIDs was established through published reports. Nevertheless, the progress in comprehending this pathological dilemma has been relatively gradual. In the words of Professor Illingsworth, "This controversy, spanning several decades and marked by the scarcity of comprehensive clinical studies and reliance on anecdotal accounts, will persist as a testament to the ineffectiveness of anecdotal reports."

The journey to Rome

The Rome criteria is the most widely accepted recommendation for the diagnosis of FGIDs. In the earlier stages, the criteria were fairly complex and could only moderately differentiate between functional and organic symptoms. Evolving iterations were made culminating in the present-day evidence-based guidelines.

The working committee of the Rome Foundation introduced the first set of comprehensive parameters for all FGIDs in 1990 which was predominantly symptom-based and was only applicable to adults.[21] In 1994, the articles were compiled into a book: "The Functional Gastrointestinal Disorders: Diagnosis, Pathophysiology, and Treatment" and in retrospect is considered Rome I.[22] The Rome working group updated the criteria in 1999 as Rome II, and introduced specific standardized criteria for FGIDs in children as suggested by pediatric gastroenterology experts.[1] The diagnostic criteria for infant (<8 months) rumination syndrome were described for the first time in Rome II criteria.[3] At that time, there was a paucity of literature regarding FGIDs in children, and for some diagnoses, the criteria mimicked the standards assembled by adult gastroenterologists. These were revised in 2006, with the launch of the Rome III criteria,[21] and a consensus-based criteria for diagnosing FGIDs in infants and toddlers was described. A distinction was made between FGIDs in the younger (neonate/ toddler) and older children (child/adolescent).[1,6] The definition of FGIDs changed from the prior absence of structural disease to a more appropriate disorder of GI functioning.[23] Nonetheless, robust evidence regarding epidemiology, pathophysiology, diagnostic workup, treatment strategies, and follow-up was limited.[1,6]

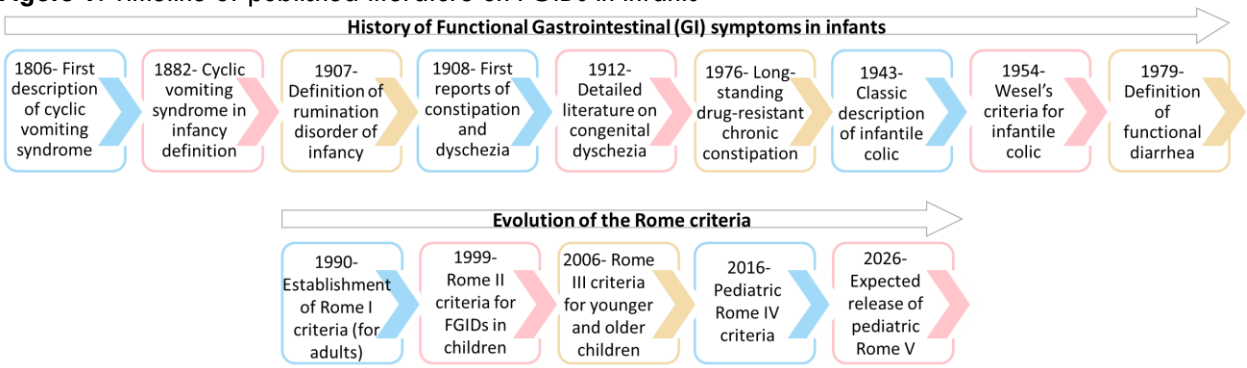
With time more comprehensive and precise scientific data became available which led to better appreciation of FGIDs.

The revised pediatric Rome IV criteria were publis hed in 2016.[21] Notable revisions observed were: the Wessel rule of threes (requirement for a certain duration of crying) for infantile colic was omitted,[19,21] and the focus was shifted on factors that have been shown to cause distress in parents, such as prolonged, unexplained and hard-to-soothe crying,[6,24] a differentiation was made between toilet-trained and non-toilet-trained children in the diagnosis of functional constipation.[25] The wording of the criteria for the diagnoses of regurgitation, rumination syndrome, and CVS, were changed to address the difficulty in assessing complex symptoms in young children, like the inability to adequately report nausea or pain. The defecation frequency required for the diagnosis of functional diarrhea was changed from 3 to 4 stools per day and stool passage during sleep was removed. For

infant dyschezia, straining and crying are no longer required to precede a successful passage of stools but may also be associated with an unsuccessful passage of stools.[6] The relevance of the Rome IV criteria for the pediatric population lies in the more profound understanding of the role of internal and external factors in the pathogenesis of FGIDs in acknowledging these disorders, developing prevention strategies, and encouraging early identification and treatment to improve personal and family quality of life.[2]

The Rome V Pediatric Committees are already working diligently on updating the science and recommendations and will be releasing this new information in the Spring of 2026.[23] (**Figure 1**)

Figure 1: Timeline of published literature on FGIDs in infants



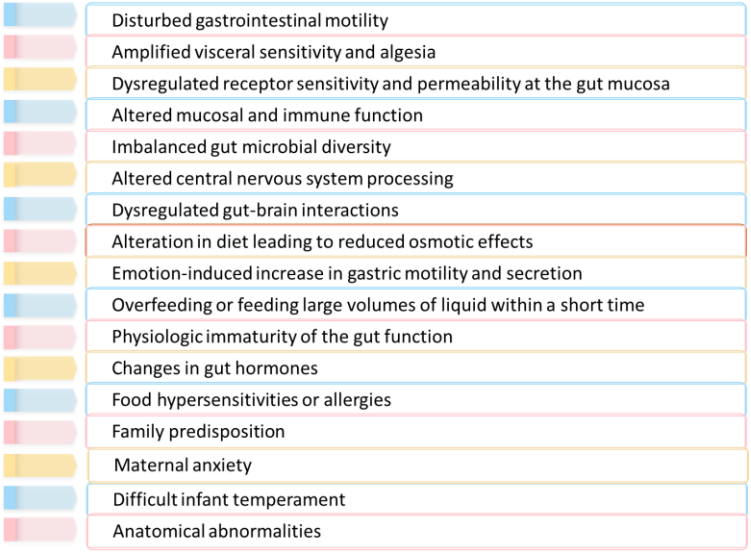
The diagnostic criteria for infantile FGIDs have undergone several revisions over the years from consensus driven recommendations to evidence-based guidelines.

Pathophysiology of FGIDs

Despite extensive research, FGIDs remain a clinical enigma and the underlying physiopathology remains elusive. Knowing the causative factors may help in management of FGIDs. Several efforts have been made over the years to accurately identify the etiologic basis of this multifactorial entity. Initially considered to have only a gastro-intestinal background, it is now established that FGIDs result from complex interactions between various biological, psychological, and social factors.[26]

While the majority of FGIDs share common biological etiologies, specific factors are directed towards individual conditions. For example, overfeeding is linked to regurgitation, and the formation of calcium soaps can induce constipation. With scientific advancements, various other influencing factors have been identified, such as gut-brain interactions, emotion-induced dysmotility, and inadequate infant-caretaker interactions. (**Figure 2**) [22,26–28]

Figure 2: Proposed etiologies of infantile FGIDs



Earlier considered to be only GI based entity, FGIDs are proven to have a complex bio-psycho-social etiologic basis

Barriers to Diagnosis

Adequate diagnoses improve clinical care in infants with FGIDs. Nevertheless, the heterogenous presentation and subjective evaluation are critical interferences in diagnostic accuracy. Functional diseases are symptom-based clinical entity unlike organic diseases, and lack distinct methods of detection.[29] It is even more crucial to accurately categorize the gastrointestinal symptoms as a positive diagnosis, as the first visit is associated with an increased propensity for resolution of symptoms.[30]

Due to their varied presentation and limited literature, the classification and diagnosis of FGIDs are quite challenging. Beser OF et al evaluated 2383 infants aged 1–12 months at nine tertiary care hospitals on the same day. They observed that only 31% of the infants diagnosed with an FGID had distinct symptoms indicative of an FGID, rather 69% presented to hospital with other symptoms, but were later diagnosed with FGIDs by a pediatrician.[31] Similar variability in the clinical presentation and challenges in diagnoses were also reported by another non-interventional, cross-sectional, and multicenter study. [32]

To date, specific laboratory marker have not been identified to confirm the presence of FGIDs, as a result, clinical examination forms the basis for establishing diagnosis.[2] The clinical expression displays varied presentations with age and stage of development in terms of physiologic, autonomic, affective, and intellectual parameters. During the first year of life, infants have underdeveloped verbal skills to accurately report symptoms such as nausea or pain nor can they discriminate between emotional and physical distress. Therefore, clinicians depend on the reports and interpretations of the parents, considered to know their child best.[6] Infant regurgitation and rumination often occur in secret without parents being aware,[33] while colic is still a mysterious disorder of the gut microbiota and brain axis.[19]

The subjective presentation of FGIDs is perplexing. Diagnostic guidelines have evolved with the profound pathophysiologic understanding and are invaluable adjuncts, yet they have certain limitations. The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) introduced “bothersome symptoms” as one criterion to differentiate infant regurgitation from gastroesophageal reflux disease (GERD). The challenging part here is that quantitative methods to define “troublesome” are missing. Variations in interpretations of troublesome have resulted in unnecessary evaluation and treatment of many infants with regurgitation, not GERD.[6]

There is a lack of assessment tools, and the existing ones have limitations to be used as appraisement and diagnostic. Most tools predominantly focus on the key variables of crying, irritability, and fussiness among the vast symptomatology of FGIDs overlooking the variety of etiological hypotheses.[34]

Pragmatic Management of Infantile FGIDs

Infantile FGIDs are not dangerous when the symptoms and caregiver’s concerns are addressed and contained. Conversely, failed diagnosis and inappropriate treatments of functional symptoms may be the cause of needless physical and emotional suffering.[6] Numerous interventions have been studied over the years owing to the multifactorial and varied presentation of FGIDs. As with any functional disorder, parental and caregiver reassurance, counseling, support, and education are integral aspects of the management of infantile FGIDs.[35] Treatment approaches can be broadly categorized into pharmacological therapies and dietary interventions.

In most cases pharmacotherapy is rarely needed as the gastrointestinal symptoms are transient and resolve spontaneously with dietary changes. Certain cases of marked distress and failed non-pharmacological interventions may respond to medications. However, the literature elucidating the benefits of GI comforting drugs is insubstantial.[36]

PHARMACOLOGICAL THERAPIES

Infantile FGID pharmacotherapy can be traced back to 1955 when Illingsworth conducted a controlled investigation for the efficacy of methylscopolamine nitrate, a new antispasmodic anticholinergic drug during those times. It was concluded that the atropine derivative was ineffective in treating three months’ colic in infants.[37] Illingworth's observations were further explored by O’Donovan and Bradstock by comparing 3 groups: homatropine with phenobarbitone and alcohol, phenobarbitone and alcohol, alcohol alone, with placebo in providing symptomatic relief. Although the conditions of colic in the vast majority of the 97 infants aged 2-6 weeks old improved in two weeks, 14% cried longer after they began taking medications. Of the drugs studied, none was more efficacious than a placebo, therefore, the authors concluded that neither alcohol, phénobarbital, nor homatropine are of value in the therapy of colic.[38]

Gripe water is a non-prescription over-the-counter product frequently used to relieve colic and other gastrointestinal ailments and discomforts in infants. It was introduced by Woodward who borrowed the formulation that physicians used to treat "fen fever," a form of malarial illness in infants in the 1840s. Earlier gripe water was a combination of dill seed oil, sodium bicarbonate and alcohol, among other substances. The alcohol content, which was found to be as high as 9% in some commercial products, was purported to provide the soothing effect. Not surprisingly, reports surfaced of adults getting addicted to gripe water. In the present scenario there is no justification for including alcohol or cariogenic sugars in gripe water.[39] A Puducherry-based study observed that 64.18% of Indian mothers used gripe water for the relief of indigestion and abdominal pain in infant aged 1-6 months. Infantile colic and constipation were significantly more common in infants administered gripe water than the ones who did not receive gripe water (p-values of 0.0001 and 0.0007 respectively).[40] Present day gripe water are alcohol free but lack any proven health benefits and are no more recommended. Furthermore, the World Health Organization (WHO) recommends against the use of any pre lacteal feed in infants less than 6 months old.[41]

Simethicone, a silicone latex of dimethicone and SiO2(Silicon di oxide), is a defoaming agent that acts as a detergent to reduce the surface tension of bubbles in the intestinal tract, thus reducing abdominal bloating.[42] A double-blind cross-over study demonstrated no beneficial effects of simethicone in reducing the symptoms of infantile colic. A striking finding was that 67% of the infants improved regardless of the treatment, compared with the pre-treatment period, which could be ascribed to a high-grade placebo-effect.[43] Similar results were obtained by Metcalf CJ et al in infants between 2 and 8 weeks of age with infant colic.[44] It was concluded that simethicone had no role in decreasing the symptoms of colic in infants.

Dicyclomine hydrochloride is an anticholinergic-antispasmodic drug. It relaxes muscles in the gut wall and is commonly used to relieve spams.[42] Illingworth reviewed published reports and treatment synopses concluding that dicyclomine hydrochloride syrup was the only drug which had proven to be of value in infant colic.[17] Likewise a double-blind crossover trial in 25 infants with colic reported superior symptoms relief ($p < 0.025$) and reduction in sleep disturbance ($p < 0.05$) with dicyclomine hydrochloride (5 mg 4-times daily) than placebo. Side-effects with both therapies were minimal.[45] Though dicyclomine is effective in treating infantile colic, 5% of the treated infants had side effects like breathing difficulties, seizures, syncope, asphyxia, muscular hypotonia, and coma. Although rare, these side effects can have a significant impact on infants. Therefore, dicyclomine hydrochloride use in treating FGIDs in infants <6 months is best avoided.[46]

Cimetropium bromide is an antimuscarinic compound derivative of belladonna with competitive, surmountable antagonism of muscarine receptors of visceral smooth muscle and direct myolytic activity.[42] The only reported RCT was conducted by Savino F et al. to evaluate the role of cimetropium bromide (1.2 mg/kg) in infants with colic crisis. Infants in the treatment arm showed 74% response rate compared to 33% in the placebo group which was statistically significant ($p<0.05$).[47] Cimetropium bromide was well tolerated and increased sleepiness was the only registered side-effects. Biagioli E et al concluded in their Cochrane analysis that owing to low-quality evidence, cimetropium bromide cannot be recommended for infants with colic.[42]

To summarize, there are numerous medicines touted for the relief of excessive infantile crying, but none is uniformly successful in ameliorating the child's symptoms.[38] In their systematic review of randomized controlled trials (RCTs), Salvatore S et al. observed a lack of evidence-based guidelines on the utility of pharmacological therapy in functional regurgitation, infant colic and functional diarrhea. Limited evidence suggests a short trial with alginate in a stepped-care approach in complicated cases of regurgitation. Drug therapy is not recommended for constipation, dyschezia and cyclic vomiting in infants less than 6 months. If at all needed, then lactulose can be used in severe cases of constipation. Whilst polyethylene glycol (PEG) represents the first-line therapy for fecal disimpaction and maintenance in older infants. Retrospective studies have shown some benefit with cyproheptadine, propanolol and pizotifen in vomiting.[36] Gastric acid inhibitors or prokinetic drugs are associated with an increased rate of infection, and are mostly ineffective for these conditions.[27]

Considering the non-utility of pharmacotherapy in alleviating GI symptoms in infants, a dietary approach is the safer and preferrable approach especially in the absence of red flags.

NUTRITIONAL INTERVENTIONS

Dietary modifications are the most widely accepted approach for managing vulnerable groups such as infants. It offers the benefit of a simple yet effective

drug free therapeutic opportunity. Frequency of infantile FGIDs tends to increase with mistakes made in feeding like early introduction of complementary feeding (<6 months). When FGIDs are diagnosed in infants, nutritional support should be the first-line treatment.[31]

Honey is a frequently used prelacteal for soothing infants. Honey contains clostridium botulinum spores which can grow and release toxins in an infant's intestines, causing infant botulism. Therefore, the American Academy of Pediatrics (AAP) advises against putting honey in food, water or formula that is fed to infants under age 12 months. Processed foods containing honey also should not be given to infants.[48]

The apparent pain-relieving effect of sucrose is attributed to its sweet taste. Sucrose decreased crying in neonates subjected to heel prick blood sampling. However, the effects diminished after 2 weeks of age probably due to the slower rate of opiate metabolism in newborns compared to older infants. Markestad examined the analgesic effects of sucrose in a small cohort of 19 infants with colic. The results were recorded as subjective scores by the parents. 12% sucrose given orally when the infant was crying had an ameliorating effect than placebo.[49] Similar effects on daily crying time and colic improvement scores were observed in 40 healthy Korean term infants aged 4 to 12 weeks.[50] Due to the poor quality of these studies and variable extent of the benefit, a Cochrane review reported insufficient evidence for sucrose recommendation.[42]

Lactase enzyme deficiency is prevalent worldwide primarily due to lactase non-persistence characterized by decreased lactase activity during infancy. Lactose intolerance (LI) can be managed with either lactase supplementation or low lactose diet. A double-blind RCT in Karachi, Pakistan reported significant ($p<0.05$) improvement in the duration of crying in 0-6 months infants with colic who received lactase supplements for 2 weeks compared to placebo.[51] On the other hand, a UK-based study observed significant relief in cry time and/or breath hydrogen in only a subset of infants. In context to the difference between responders and non-responders, the authors pointed out the heterogenous patho-aetiologies of FGIDs. Based on different authors' observations, lactase drops can be logically recommended for a week in infants with LI. While, in infants who do not benefit, a negative result with lactase indicates a different aetiology.[52]

Cow's milk is widely used for feeding infants. Distinct differences exist between cow's milk and human milk. Human milk contains 9 g protein/l compared with 34 g/l in cow's milk. The fat content is similar while lactose is higher in human milk (70 g/l) than cow's (48 g/l) milk.[53] Cow milk is a poor source of key micronutrients like zinc, iron, and vitamin C, on the other hand saturated fatty acid content is high. Also, cow milk protein allergy (CMPA), an exaggerated immune response to one or more proteins milk proteins, can have long-term health consequences.[54] Diet is one factor that contributes majorly to infant distress in the colic syndrome. Cow milk as a major etiology inducing infantile colic in formula-fed infants was established as early as in 1982 by Lothe L et al. A challenge with cow's milk-based formula produced epidermal and gastrointestinal symptoms in 36% of infants after one month (nearly age 3 months) and 11% of infants by age 6 months.[55] Lucassen PLBJ et al compiled data from 5 trials in their systematic review to evaluate the effect of eliminating cow's milk protein on excessive crying. The pooled effect size was 0.22 (95% confidence interval 0.10 to 0.34) for eliminating cows' milk.[46]

Elimination of cows' milk protein is effective not only in highly selected subgroups of infants but also in primary care settings. It is probable, yet not proved, that infants with one or more atopic features would benefit more from the elimination of cows' milk protein than those without atopy.[46]

ADAPTED FORMULAS

Modern infant formulas use human milk composition as reference and cow's milk as protein source.[53] Elimination of cow's milk protein raises the question of which adapted formula to use. The options available are hydrolysate proteins based formula or soy-based or amino acid- based formulas.[46]

David JH et al studied the effect of changing formulas from standard preparations to adapted formulas in 38 bottle-fed colicky infants between the ages of 4 and 16 weeks in a randomized, placebo-controlled trial. Infants on the active diet of hypoallergenic casein hydrolysate preparation had distress reduced by 39% compared with 16% for those on the control diet of modified cow's milk preparation ($p = 0.012$).[56] In another study colicky infants alternately received three changes of four 4-day periods of a casein hydrolysate formula and a formula containing cow milk with a washout period. There were significantly ($p<0.01$) less crying and colic symptoms than cow's milk with the first formula change. By the second change there was less colic ($p<0.05$) but not significantly less crying. By the third change there were no significant

differences between formulas. The study had a dropout rate of 47%, and an intention-to-treat analysis was not performed. These results demonstrated that colic improvement with casein hydrolysate tends to diminish with time, and only infrequently is the effect reproducible.[57] Another study found that two casein hydrolysate formulas varying in composition were equally effective in managing colicky symptoms associated with protein sensitivity. Interestingly, crying was rated as more intense during whey and milk protein challenges.[58] Substitution of cow milk protein based formula with a hypoallergenic casein-based formula was reported to be effective in infantile colic by a highly sensitive methodological quality review of RCTs.[46]

Bovine milk protein is dominated by the casein fraction, which constitutes 80% of total protein, while the whey protein fraction constitutes 20%. The corresponding figures for human milk are 40 and 60%. Also, within the casein fraction the relative proportion of the various subclasses differ between bovine and human milk.[53] This led to the advent of whey-based hydrolysates. A Netherlands based study showed around 63 minutes per day difference in crying duration reduction [95% confidence interval: 1-127 minutes per day] in favor of the whey hydrolysate formula in 23 infants <6 months old compared to 20 infants fed standard formula.[59] An advantage of whey protein hydrolysates over casein hydrolysates is their better taste and favourable cost.[46] It was concluded that partially hydrolyzed whey proteins are effective in reducing colic in bottle-fed infants.[60] Limited data suggest infants with hard and infrequent stools could benefit from a formula with a partial whey hydrolysate. Routine use of hydrolysate formulas is not recommended.[27]

Soy-based formulas are non-protein options for reducing colic symptoms in infants with allergy to cow milk proteins. A double-blind clinical study compared a soya milk formula with a standard modified cow's milk formula in 19 infants with colic. The duration of colic symptoms was significantly reduced in infants on soya milk ($p<0.01$), with 11 out of 19 babies fulfilling the diagnostic criteria for cow's milk intolerance. 4 infants whose symptoms failed to improve either spontaneously or with soya milk were given a hydrolysed protein milk with a positive response in two, confirmed by challenge testing.[61] Accordingly, soy-based formula is considered a probable treatment for infants with allergy to cows' milk mediated by IgE.[46] However, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) stated that there is insufficient evidence to support the use of soy formulas for colic.[27] Additionally, soy based formulas are not recommended for infants less than 6 months.[41] The argument against soy formula milks is that infants with allergies to cows' milk are more prone to developing allergy to soya. Therefore, protein hydrolysate is the preferred treatment for colicky infants with allergic features.[46] Soy-based formulas can be used for infants with galactosemia or those who cannot consume dairy-based products for cultural or religious reasons.[62]

Amino acid-based formulas are another non-protein option for infants with cow milk protein allergy. A preliminary comparative study reported a 45% reduction in total time spent crying and fussing corresponding to a decrease of 1-5.2 hours daily with an amino-acid based formula in 3-7 weeks old infants with colic.[63] Confirming the results, all infants displayed increased colic behaviour when challenged with bovine immunoglobulin G.[62]

Despite years of research into the development, adapted formulas have limited indications and ambiguous recommendations. This gap can be filled by a nutritional intervention with a safe and durable profile catering to multiple GI symptoms (**Figure 3**).

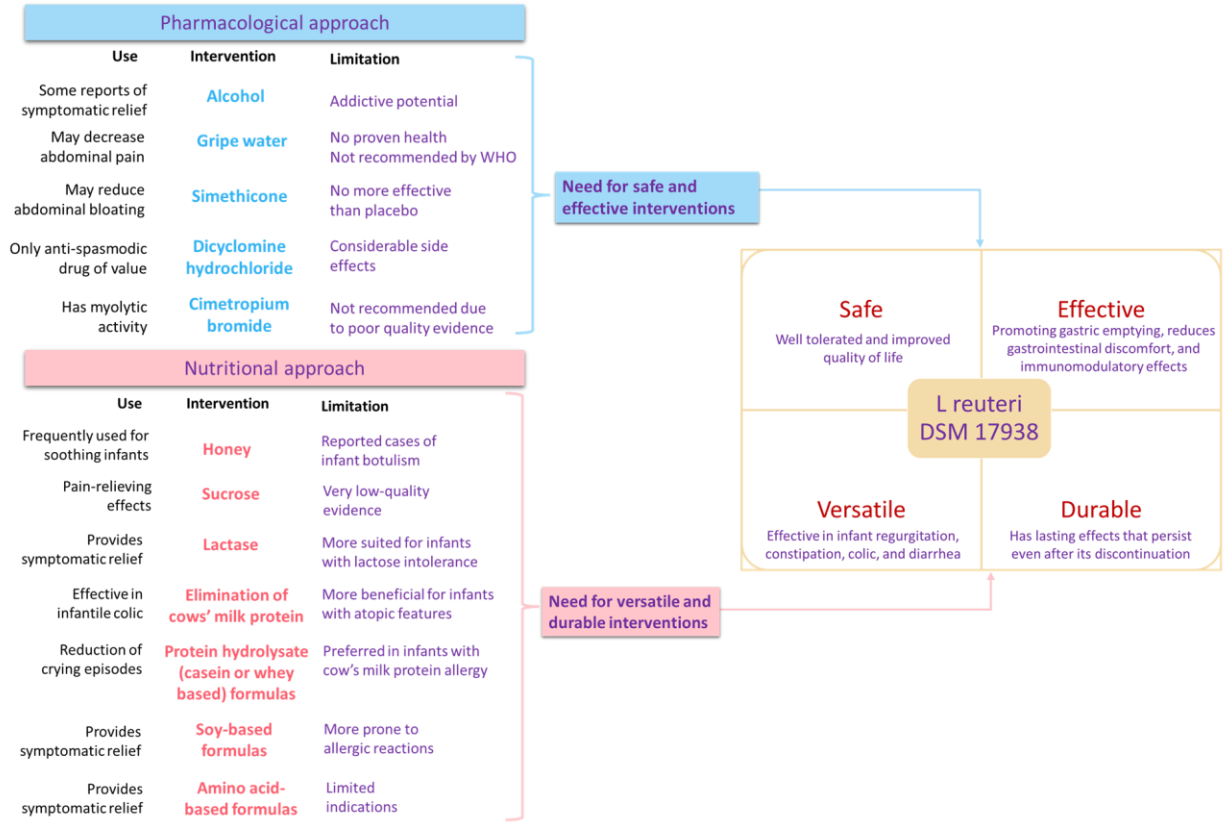
QUEST FOR THE IDEAL AGENT

Pharmacological agents used in managing infantile FGIDs are predominantly analgesic in nature which may provide symptomatic relief but do not treat the root cause. Furthermore, the adverse effects and side effects of medications in this vulnerable group are highly significant. In this regard, probiotics are the most promising advancement in managing infantile FGIDs. The use of probiotics is based upon the hypothesis that aberrant intestinal microflora could cause gut dysfunction and gas production, contributing to symptoms which is counteracted by the anti-inflammatory actions of probiotics.[60,64] The most researched bacteria is Lactobacillus or Limosilactobacillus reuteri named so after the German microbiologist Gerhard Reuter who discovered it. Among a number of strains, L.reuteri DSM 17938, a strain of plasmid-cured ATCC 55730 obtained from a Peruvian mother's milk, is probably the best studied and most effective strain.[49]

L. reuteri can improve functional symptoms of esophagus and stomach by promoting gastric emptying and reducing the number of episodes of regurgitations per day. It is significantly correlated with reduction of colic symptoms, increase of Bacteroidetes, and improved family quality of life,[65] reduction in diarrheal duration and duration of hospitalization, reduced methane production and improved gut transit time. Apart from GI functions

L. reuteri also has immunological properties. It can reduce the production of pro-inflammatory cytokines and stimulate regulatory T-cell development and function.[66] The administration of L. reuteri might have a lasting effect, as demonstrated by the relief in abdominal pain intensity that persisted even after its discontinuation.[65] L reuteri 17938 strain has also been shown to act as a visceral anti-nociceptive agent.[67] Other notable features include secretion of antimicrobial reuterin, production of short-chain fatty acids, down-regulation of inflammatory immune response, and direct influence on enteric nervous system among the others, which render them good candidates for prevention and treatment of various FGIDs.[68]

Figure 3: Quest for the suitable agent



Pharmacological agents may provide symptomatic relief but do not treat the root cause of FGIDs. The adverse effects tend to have profound implications in this vulnerable group. Adapted formulas have proven efficacy but have limited indications. In this regard, probiotics are the most promising advancement in managing infantile FGIDs.

A recent (2023) real world study conducted across 6 countries reported significantly lower scores of the validated Infant Gastrointestinal Symptom Questionnaire (IGSQ) in formula-fed 6-16 weeks old infants receiving either *L. reuteri*-containing formula than those fed standard formula and comparable to breastfed infants.[69] Based on the evidences, the guidelines recommend that if the use of probiotic is considered, *L. reuteri* DSM 17938 is the only strain shown to be effective in the treatment of infantile colic in breastfed infants. The use of probiotics in children seems to be safe in general, even when provided in high doses.[70]

GUIDELINES-BASED FGID MANAGEMENT

Guidelines underscore parental education and awareness with adequate nutritional counselling as the first-line management. Nutritional advice should support continued breastfeeding, while adapted infant formulas may be considered for non-breastfed and mixed-fed infants with common FGIDs.[27] A non-interventional, cross-sectional, and multicenter study in 1722 infants aged 1-12 months reported that physicians frequently (77-82%) recommended an adapted infant formula and prescribed a specific (51-66%) treatment such as probiotics (in 35-64% of the cases).[32]

Pharmacotherapy is not recommended for the management of FGIDs such as infant regurgitation and colic due to a lack of evidence and the potential risk of adverse events.[35] Drug therapy can be considered for functional constipation.[27] Scientific and medical experts have developed and

discussed practical recommendations and algorithms to manage FGIDs (**Table 2**).[1,35,41,71–74]

Table 2: Treatments per Recommendations/ Guidelines

Interventions=>	Nutritional	Pharmacological
Infant regurgitation	Thickened feedings, anti-regurgitation formulas, partially hydrolysed whey based formulas Avoid "home thickening" of a regular formula as it increases the osmolarity Probiotics Lreuteri DSM 17938 offers a better gastric emptying rate	Antisecretory drugs or prokinetic agents are of no benefit
Rumination syndrome	Improve the infant's nutritional status	Medical management is usually not needed
Cyclic vomiting syndrome	Multifaceted treatment based on the phase of illness. Recovery phase is managed with supportive care and nutritional rehabilitation	IV fluids, antiemetics, analgesics, and sedative s can be used to manage the vomiting phase
Infant colic	L reuteri DSM 17938 is safe and effective, and can be considered as first-line treatment Elimination of CMP and the use of an extensively hydrolyzed protein formula with high beta-palmitate, and a specific prebiotics mixture with GOS/FOS	Pharmacological interventions have failed to show benefits.
Functional diarrhea	Evaluate fruit juice and fructose intake	No medical interventions are needed
Infant dyschezia	Resolves spontaneously	Medical interventions are not necessary
Functional constipation	Infant formulas containing partially or extensively hydrolyzed proteins, fortified with prebiotics (GOS/FOS) and/or probiotic strains such as L reuteri DSM 17938 and Bifidobacterium longum, and without palm oil as the main source of fat in the oil blend In the absence of alarm signs, trial of a formula with L reuteri DSM 17938 might be considered for 2–4 weeks	Macrogol (polyethylene glycol, PEG) is not approved for use in infants less than 6 months of age

L reuteri= Limsilolactobacillus; GOS/ FOS= galacto-oligosaccharides / fructo-oligosaccharides; CMP= cow milk protein; IV= intravenous

Pharmacotherapy has limited application and nutritional modifications remain the first-line management of infantile FGIDs.

Conclusion

In the endeavor to present a contemporary perspective on FGIDs in infants, this article seeks to establish a foundation for an improved comprehension of these conditions and the enhancement of patient diagnosis and care. The Rome IV criteria, a dynamic one, was the culmination of immense knowledge and intense efforts by several internationally recognized investigators and clinicians. The seven years following the publication of Rome IV have witnessed significant advancements, particularly in our understanding of the etiopathogenesis, diagnostic symptoms and therapeutics. Our examination of the role of pharmacotherapy in FGID management focuses on delineating its specific indications and limitations, thereby facilitating its prudent utilization in clinical contexts. It is worth noting that pharmacotherapy finds limited utility in addressing gastrointestinal discomfort in infants, making dietary approaches more favorable, especially in the absence of red flags. In retrospect, the knowledge acquired thus far is comprehensive, yet a great deal of information remains unexplored in this dynamic field. Going forward, large- scale, well-designed, and diversified epidemiological studies would enable comparison of FGIDs prevalence between various geographical regions and ethnicities. Community education, awareness, and diet modification are the pillars of management. Future research in identifying the ideal therapeutic agent can provide a potential opportunity for evidence-based prevention of infantile FGIDs.

References

1. Zeevenhooven J, Koppen IJN, Benninga MA. The New Rome IV Criteria for Functional Gastrointestinal Disorders in Infants and Toddlers. *Pediatr Gastroenterol Hepatol Nutr*. 2017;20(1):1-13. doi:10.5223/pghn.2017.20.1.1
2. Velasco-Benítez CA, Collazos-Saa LI, García-Perdomo HA. Functional Gastrointestinal Disorders in Neonates and Toddlers According to the Rome IV Criteria: A Systematic Review and Meta-Analysis. *Pediatr Gastroenterol Hepatol Nutr*. 2022;25(5):376. doi:10.5223/pghn.2022.25.5.376
3. Rasquin-Weber A, Hyman PE, Cucchiara S, et al. Childhood functional gastrointestinal disorders. *Gut*. 1999;45(Supplement 2):ii60-ii68. doi:10.1136/gut.45.2008.ii60
4. Mahon J, Lifschitz C, Ludwig T, et al. The costs of functional gastrointestinal disorders and related signs and symptoms in infants: a systematic literature review and cost calculation for England. *BMJ Open*. 2017;7(11):e015594. doi:10.1136/bmjopen-2016-015594
5. Muhardi L, Aw MM, Hasosah M, et al. A Narrative Review on the Update in the Prevalence of Infantile Colic, Regurgitation, and Constipation in Young Children: Implications of the ROME IV Criteria. *Front Pediatr*. 2022;9. Accessed May 14, 2023. https://www.frontiersin.org/articles/10.3389/fped.2021.778747
6. Benninga MA, Nurko S, Faure C, Hyman PE, Roberts ISJ, Schechter NL. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. *Gastroenterology*. 2016;150(6):1443-1455.e2. doi:10.1053/j.gastro.2016.02.016
7. Curien-Chotard M, Jantchou P. Natural history of gastroesophageal reflux in infancy: new data from a prospective cohort. *BMC Pediatr*. 2020;20:152. doi:10.1186/s12887-020-02047-3
8. Vernon-Roberts A, Alexander I, Day AS. Systematic Review of Pediatric Functional Gastrointestinal Disorders (Rome IV Criteria). *J Clin Med*. 2021;10(21):5087. doi:10.3390/jcm10215087
9. Rogovik AL, Goldman RD. Treating infants' colic. *Can Fam Physician*. 2005;51(9):1209-1211.
10. Huang Y, Tan SY, Parikh P, Buthmanaban V, Rajindrajith S, Benninga MA. Prevalence of functional gastrointestinal disorders in infants and young children in China. *BMC Pediatr*. 2021;21:131. doi:10.1186/s12887-021-02610-6
11. Chia LW, Nguyen TVH, Phan VN, et al. Prevalence and risk factors of functional gastrointestinal disorders in Vietnamese infants and young children. *BMC Pediatr*. 2022;22(1):1-7. doi:10.1186/s12887-022-03378-z
12. Raucci U, Borrelli O, Di Nardo G, et al. Cyclic Vomiting Syndrome in Children. *Front Neurol*. 2020;11:583425. doi:10.3389/fneur.2020.583425
13. Sunku B. Cyclic Vomiting Syndrome. *Gastroenterol Hepatol*. 2009;5(7):507-515.
14. Franco K, Campbell N, Tamburrino M, Evans C. Rumination: The Eating disorder of infancy. *Child Psychiatry Hum Dev*. 1993;24(2):91-97. doi:10.1007/BF02367262
15. 15. Hertz AF. Congenital Dyschezia. *Proc R Soc Med*. 1912;5(Sect Study Dis Child):169-174.
16. Clayden GS, Lawson JO. Investigation and management of long-standing chronic constipation in childhood. *Arch Dis Child*. 1976;51(12):918-923. doi:10.1136/adc.51.12.918
17. Illingworth RS. Infantile colic revisited. *Arch Dis Child*. 1985;60(10):981-985.
18. WESSEL MA, COBB JC, JACKSON EB, HARRIS GS JR, DETWILER AC. PAROXYSMAL FUSSING IN INFANCY, SOMETIMES CALLED "COLIC." *Pediatrics*. 1954;14(5):421-435. doi:10.1542/peds.14.5.421
19. Pärtty A, Kalliomäki M. Infant colic is still a mysterious disorder of the microbiota–gut–brain axis. *Acta Paediatr*. 2017;106(4):528-529. doi:10.1111/apa.13754
20. Lloyd-Still JD. Chronic diarrhea of childhood and the misuse of elimination diets. *J Pediatr*. 1979;95(1):10-13. doi:10.1016/s0022-3476(79)80074-8
21. Koppen IJN, Nurko S, Saps M, Di Lorenzo C, Benninga MA. The pediatric Rome IV criteria: what's new? *Expert Rev Gastroenterol Hepatol*. 2017;11(3):193-201. doi:10.1080/17474124.2017.1282820
22. Drossman DA. Functional Gastrointestinal Disorders: History, Pathophysiology, Clinical Features, and Rome IV. *Gastroenterology*. 2016;150(6):1262-1279.e2. doi:10.1053/j.gastro.2016.02.032
23. Rome Pediatrics. Rome Foundation. Accessed May 14, 2023. https://theromefoundation.org/rome-pediatrics/
24. Banks JB, Rouster AS, Chee J. Colic. In: *StatPearls*. StatPearls Publishing; 2023.

Accessed May 14, 2023. http://www.ncbi.nlm.nih.gov/books/NBK518962/

25. Baaleman DF, Di Lorenzo C, Benninga MA, Saps M. The Effects of the Rome IV Criteria on Pediatric Gastrointestinal Practice. *Curr Gastroenterol Rep*. 2020;22(5):21. doi:10.1007/s11894-020-00760-8
26. novalac-symposium-2019-pr-salvatore-presentation.pdf. Accessed May 17, 2023. https://novamil.com/sites/default/files/2020-06/novalac-symposium-2019-pr-salvatore-presentation.pdf
27. Salvatore S, Abkari A, Cai W, et al. Review shows that parental reassurance and nutritional advice help to optimise the management of functional gastrointestinal disorders in infants. *Acta Paediatr*. 2018;107(9):1512-1520. doi:10.1111/apa.14378
28. Jakobsson I, Lindberg T. Cow's milk proteins cause infantile colic in breast-fed infants: a double-blind crossover study. *Pediatrics*. 1983;71(2):268-271.
29. Sood R, Ford AC. Rome IV criteria for FGIDs — an improvement or more of the same? *Nat Rev Gastroenterol Hepatol*. 2016;13(9):501-502. doi:10.1038/nrgastro.2016.110
30. Trivić I, Hojsak I. Initial Diagnosis of Functional Gastrointestinal Disorders in Children Increases a Chance for Resolution of Symptoms. *Pediatr Gastroenterol Hepatol Nutr*. 2018;21(4):264-270. doi:10.5223/pghn.2018.21.4.264
31. Beser O, Cokugras F, Doğan G, et al. The frequency of and factors affecting functional gastrointestinal disorders in infants that presented to tertiary care hospitals. *Eur J Pediatr*. 2021;180. doi:10.1007/s00431-021-04059-2
32. Campeotto F, Barbaza MO, Hospital V. Functional Gastrointestinal Disorders in Outpatients Aged up to 12 Months: A French Non-Interventional Study. *Int J Environ Res Public Health*. 2020;17(11):4031. doi:10.3390/ijerph17114031
33. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, Van Tilburg M. Childhood Functional Gastrointestinal Disorders: Child/Adolescent. *Gastroenterology*. 2016;150(6):1456-1468.e2. doi:10.1053/j.gastro.2016.02.015
34. García Marqués S, Chillón Martínez R, González Zapata S, Rebollo Salas M, Jiménez Rejano JJ. Tools assessment and diagnosis to infant colic: a systematic review. *Child Care Health Dev*. 2017;43(4):481-488. doi:10.1111/cch.12454
35. Indrio F, Enninger A, Aldekhail W, et al. Management of the Most Common Functional Gastrointestinal Disorders in Infancy: The Middle East Expert Consensus. *Pediatr Gastroenterol Hepatol Nutr*. 2021;24(4):325-336. doi:10.5223/pghn.2021.24.4.325
36. Salvatore S, Barberi S, Borrelli O, et al. Pharmacological interventions on early functional gastrointestinal disorders. *Ital J Pediatr*. 2016;42:68. doi:10.1186/s13052-016-0272-5
37. Illingworth RS. Three month's colic; treatment by methylscopolamine nitrate (skopyl). *Acta Paediatr*. 1955;44(3):203-208. doi:10.1111/j.1651-2227.1955.tb04133.x
38. O'Donovan JC, Bradstock AS Jr. The Failure of Conventional Drug Therapy in the Management of Infantile Colic. *Am J Dis Child*. 1979;133(10):999-1001. doi:10.1001/archpedi.1979.02130100023003
39. Blumenthal I. The gripe water story. *J R Soc Med*. 2000;93(4):172-174. doi:10.1177/014107680009300404
40. Jain K, Gunasekaran D, Venkatesh C, Soundararajan P. Gripe Water Administration in Infants 1-6 months of Age-A Cross-sectional Study. *J Clin Diagn Res JCDR*. 2015;9(11):SC06-SC08. doi:10.7860/JCDR/2015/13727.6738
41. Sarasu JM, Narang M, Shah D. Infantile Colic: An Update. *Indian Pediatr*. 2018;55(11):979-987. doi:10.1007/s13312-018-1423-0
42. Biagioli E, Tarasco V, Lingua C, Moja L, Savino F. Pain-relieving agents for infantile colic. *Cochrane Database Syst Rev*. 2016;2016(9):CD009999. doi:10.1002/14651858.CD009999.pub2
43. Danielsson B, Hwang CP. Treatment of Infantile Colic with Surface Active Substance (Simethicone). *Acta Paediatr*. 1985;74(3):446-450. doi:10.1111/j.1651-2227.1985.tb11001.x
44. Metcalf TJ, Irons TG, Sher LD, Young PC. Simethicone in the treatment of infant colic: a randomized, placebo-controlled, multicenter trial. *Pediatrics*. 1994;94(1):29-34.
45. Grunseit F. Evaluation of the efficacy of dicyclomine hydrochloride ('Merbentyl') syrup in the treatment of infant colic. *Curr Med Res Opin*. 1977;5(3):258-261. doi:10.1185/03007997709110175
46. Lucassen PLBJ, Assendelft WJJ, Gubbels JW, van Eijk JTM, van Geldrop WJ, Neven AK. Effectiveness of treatments for infantile colic: systematic review. *BMJ*. 1998;316(7144):1563-1569.
47. Savino F, Brondello C, Cresi F, Oggero R, Silvestro L. Cimetropium bromide in the treatment of crisis in infantile colic. *J Pediatr*

Gastroenterol Nutr. 2002;34(4):417-419. doi:10.1097/00005176-200204000-00020

48. Korioth T, Writer S. Remind families: honey can cause infant botulism. Published online November 19, 2018. Accessed May 17, 2023. https://publications.aap.org/aapnews/news/13225/Remind-families-honey-can-cause-infant-botulism
49. Markestad T, BELL R. Use of sucrose as a treatment for infant colic. *Arch Dis Child*. 1997;76(4):356-358.
50. Kim JS, Kwon KH, Lee YA, Kim HJ, Lee KW. Analgesic Effect of Sugar Solution in Infantile Colic. *J Korean Pediatr Soc*. 2002;45(6):712-718.
51. Ahmed M, Billoo AG, Iqbal K, Memon A. Clinical Efficacy Of Lactase Enzyme Supplement In Infant Colic: A Randomised Controlled Trial. *JPMA J Pak Med Assoc*. 2018;68(12):1744-1747.
52. Kanabar D, Randhawa M, Clayton P. Improvement of symptoms in infant colic following reduction of lactose load with lactase. *J Hum Nutr Diet Off J Br Diet Assoc*. 2001;14:359-363. doi:10.1046/j.1365-277X.2001.00304.x
53. Hernell O. Human Milk vs. Cow's Milk and the Evolution of Infant Formulas. Published online February 15, 2011. doi:10.1159/000325572
54. Kesavelu D, Sethi G, Bangale N, Anwar F, Rao S. Common gastrointestinal distress among infants: Role of optimal nutritional interventions. *Clin Epidemiol Glob Health*. 2018;6(1):5-9. doi:10.1016/j.cegh.2017.07.003
55. Lothe L, Lindberg T, Jakobsson I. Cow's milk formula as a cause of infantile colic: a double-blind study. *Pediatrics*. 1982;70(1):7-10.
56. Hill DJ, Hudson IL, Sheffield LJ, Shelton MJ, Menahem S, Hosking CS. A low allergen diet is a significant intervention in infantile colic: results of a community-based study. *J Allergy Clin Immunol*. 1995;96(6 Pt 1):886-892. doi:10.1016/s0091-6749(95)70224-5
57. Forsyth BW. Colic and the effect of changing formulas: a double-blind, multiple-crossover study. *J Pediatr*. 1989;115(4):521-526. doi:10.1016/s0022-3476(89)80274-4
58. Jakobsson I, Lothe L, Ley D, Borschel MW. Effectiveness of casein hydrolysate feedings in infants with colic. *Acta Paediatr Oslo Nor 1992*. 2000;89(1):18-21. doi:10.1080/080352500750028997
59. Lucassen PL, Assendelft WJ, Gubbels JW, van Eijk JT, Douwes AC. Infantile colic: crying time reduction with a whey hydrolysate: A double-blind, randomized, placebo-controlled trial. *Pediatrics*. 2000;106(6):1349-1354. doi:10.1542/peds.106.6.1349
60. Savino F, Ceratto S, De Marco A, Cordero di Montezemolo L. Looking for new treatments of Infantile Colic. *Ital J Pediatr*. 2014;40:53. doi:10.1186/1824-7288-40-53
61. Campbell JP. Dietary treatment of infant colic: a double-blind study. *J R Coll Gen Pract*. 1989;39(318):11-14.
62. Critch J. Infantile colic: Is there a role for dietary interventions? *Paediatr Child Health*. 2011;16(1):47-49.
63. Estep DC, Kulczycki A. Treatment of infant colic with amino acid-based infant formula: a preliminary study. *Acta Paediatr Oslo Nor 1992*. 2000;89(1):22-27. doi:10.1080/080352500750029004
64. Shirazinia R, Golabchifar AA, Fazeli MR. Efficacy of probiotics for managing infantile colic due to their anti-inflammatory properties: a meta-analysis and systematic review. *Clin Exp Pediatr*. 2021;64(12):642-651. doi:10.3345/cep.2020.01676
65. Capozza M, Laforgia N, Rizzo V, Salvatore S, Guandalini S, Baldassarre M. Probiotics and Functional Gastrointestinal Disorders in Pediatric Age: A Narrative Review. *Front Pediatr*. 2022;10. Accessed May 18, 2023. https://www.frontiersin.org/articles/10.3389/fped.2022.805466
66. Alam MDJ, Islam MMD, Tayab MDA, et al. Role of Probiotic Lactobacillus reuteri in Improving Gut Health and Immunity in Infants and Toddlers: A Review. *Int J Nutr Sci*. 2022;7(2). doi:10.30476/ijns.2022.94849.1182
67. Srinivasan R, Kesavelu D, Veligandla KC, Muni SK, Mehta SC. Lactobacillus reuteri DSM 17938: Review of Evidence in Functional Gastrointestinal Disorders. *Pediatr Ther*. 2018;08(03). doi:10.4172/2161-0665.1000350
68. Orel R. Effectiveness of Lactobacillus reuteri for prevention and treatment of functional gastrointestinal disorders in infants, children and adolescents (Review). *Zdr Vestn*. 2013;82:183-193.
69. Happy Tummy Consortium, Lavalle L, Sauvageot N, et al. Limosilactobacillus reuteri DSM 17938-Containing Infant Formulas and the Associations with Gastrointestinal Tolerance: A Cross-Sectional Observational Study. *Nutrients*. 2023;15(3):530. doi:10.3390/nu15030530
70. Hojsak I, Fabiano V, Pop TL, et al. Guidance on the use of probiotics in clinical practice in children with selected clinical conditions and in specific vulnerable groups. *Acta Paediatr*. 2018;107(6):927-937. doi:10.1111/apa.14270

71. Vandenplas Y, Gutierrez-Castrellon P, Velasco-Benitez C, et al. Practical algorithms for managing common gastrointestinal symptoms in infants. *Nutr Burbank Los Angel Cty Calif*. 2013;29(1):184-194. doi:10.1016/j.nut.2012.08.008
72. Vandenplas Y, Alturaiki MA, Al-Qabandi W, et al. Middle East Consensus Statement on the Diagnosis and Management of Functional Gastrointestinal Disorders in <12 Months Old Infants. *Pediatr Gastroenterol Hepatol Nutr*. 2016;19(3):153-161. doi:10.5223/pghn.2016.19.3.153
73. Vandenplas Y, Hauser B, Salvatore S. Functional Gastrointestinal Disorders in Infancy: Impact on the Health of the Infant and Family. *Pediatr Gastroenterol Hepatol Nutr*. 2019;22(3):207-216. doi:10.5223/pghn.2019.22.3.207
74. Li BUK. Managing cyclic vomiting syndrome in children: beyond the guidelines. *Eur J Pediatr*. 2018;177(10):1435-1442. doi:10.1007/s00431-018-3218-7