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Review Article

Recent Advances in the Management of Infantile Colic

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ABSTRACT

The diagnosis and management of infantile colic has come a long way since the first "case series" published by Wessel et al in 1954. This paved the way for framing the diagnostic criteria for infantile colic i.e. Wessels criteria and to its current evolution of Rome IV criteria of Functional gastrointestinal disorders. The management of colic has evolved from the use of "gripe water" to its current use of probiotics. This review discusses the advances in the treatment of colic, the use of probiotics and the role of *Lactobacillus reuteri* DSM17938 in infantile colic. There is further emphasis on the other available options with their limitations and the side effects. *L reuteri* DSM 17938 since its discovery in the year 1962 by Professor Gerard Reuter has found its place in clinical research and multiple studies substantiate the efficacy of this naturally occurring probiotic which is not only limited to infantile colic but to multiple other indications and is recommended by the World Gastroenterology Organization (WGO) and the European Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN).

Keywords: Infantile colic; *L reuteri* DSM17938; Probiotics; FGID

INTRODUCTION

The first case series (as it is now known as) of colicky infants was first described by Dr. Wessel in the year 1954 [1]. He described the crying of newborns as “paroxysmal fussing” which is now being called as “infantile colic”. The initial crying was attributed to “family tension” and “allergy”. The symptoms of these babies were attributed to the somatic response to presence of tension in the environment.

Ever since the publication of this paper, there has been increased understanding of Functional Gastrointestinal Disorders (FGID) in infants and the various treatment options that have evolved in the past six decades. Scientific research and multiple studies have led to progress in safe treatment options in infants and young children with FGID’s.

Probiotics lead the path in the current treatment option with *Lactobacillus reuteri* DSM17938 emerging in the clinical forefront in the foray for treating infantile colic.

Oral sucrose appears to act as an analgesic and may therefore help to pacify a colicky baby, but it is only short lived, works in a dose-dependent fashion, repeated doses are more effective and hence it is not considered to be a healthy intervention.

A new pharmacological agent (Nepadutant) acting on intestinal motility and sensitivity is under investigation with multi-centre, multinational, randomised, double-blind, placebo controlled study at phase IIA.

Non-alcoholic gripe water consists of sodium bicarbonate (antacid) and herbs (anti-spasmodic) and is commonly used by parents and carers, but there is no evidence to recommend its use.

Homeopathic remedies have been associated with apparent life-threatening events (Gali-col), though possibly due to overdose of a product that contains potentially toxic components e.g., Vera album and Strychnos-vomica (Strychnine poisoning). The use of reflexology is another modality that has been used to treat colicky infants. Nonspecific reflexology did not target the areas of the feet considered to be therapeutic for colic, whereas colic-specific reflexology targeted the points related to the spine, digestion, colon, spleen, lungs, urinary tract, solar plexus, and endocrine system. But further evidence is needed to recommend this therapy.

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BACKGROUND

Ever since the publication of research on infantile colic in 1954 by Wessel et al., the diagnostic criteria for infantile colic remained as the "Wessels rule of 3". This simply translates to any infant crying for more than "three hours per day, three days per week and for three weeks" this remained as the gold standard and was the Rome 3 criteria for the diagnosis. The Rome 4 criteria defines infantile colic as "An infant who is less than five months of age when symptoms start and stop; recurrent and prolonged periods of infant crying, fussing or irritability reported by caregivers that occur without any obvious cause and cannot be prevented or resolved by care givers; no evidence of infant failure to thrive, fever or illness" [2].

Multiple hypothesis exists for the cause and origin of infantile colic of which the top four are given below:

1. Altered Gut Microbiota (Dysbiosis)

2. Altered gut motility

3. Hypersensitivity to normal light and sounds

4. Exacerbation of normal crying.

The crying pattern of infants seem to have a cultural variation, infants from different cultural backgrounds having different crying times and patterns (Figure 1). All studies done in relation to "normal crying" in infants seem to show a variable pattern as shown by Brazelton, Barr et al. and Kramer et al. [3-5].

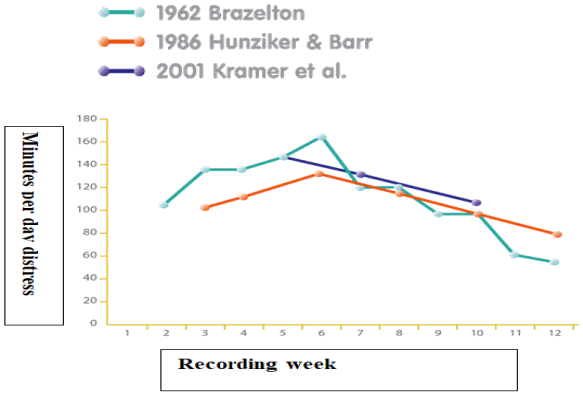

Figure 1: Showing the crying pattern of infants in studies (related to various causes).

Despite decades of research, the aetiology of infantile colic remains elusive. Increasing evidence states that food allergies like cow's milk proteins and lactose intolerance may play an important role in the pathogenesis of infantile colic [6]. Parental factors like maternal ingestion of eggs, chocolate, citrus fruits, and certain seafood while breastfeeding, and psychological factors in the parents, such as stressful pregnancies, postpartum depression, parental anxiety, dissatisfaction with the sexual relationship, and negative experiences during childbirth, as well as poor parental skills were associated with infantile colic [7]. The prevalence of colic is approximately doubled among infants of mothers who were exposed to cigarette smoking both during and after pregnancy [5,6]. Breastfed infants are less likely to have infantile colic [8]. Neurophysiologic response of immature infant (gastrointestinal immaturity), flatulence, alteration in faecal micro flora and colon inflammation were other factors associated with infantile colic [9,10].

PATHOPHYSIOLOGY OF COLIC

Nayak has explained the pathophysiology of colic which has been summarized below [11]. Lactose intolerance plays a major role in the etiopathogenesis of Infantile Colic [12,13].

Infants who may be intolerant to lactose in the food due to which significant amounts of lactose enters the colon where it acts as a substrate for *lactobacilli* and *bifidobacteria*. Due to fermentation of the sugar (lactose) by the bacteria, there is rapid production of hydrogen and lactic acid in the gut, both these gases have deleterious effects on the milieu. The lactic acid induces osmotic pressure, favouring the influx of water, which causes gut distension. The hydrogen gas also distends the colon and results in pain. Studies have shown elevated breath hydrogen levels in infants with colic, thus corroborating the hypothesis that the colicky infants have carbohydrate mal-absorption causing colic. There are several hormones that affect the gut functions and motility especially motilin, cholecystokinin, gastrin, vasoactive intestinal peptide and ghrelin. Motilin is a 22-amino acid hormone, which is produced in jejunal and duodenal mucosa and is present everywhere in the GI tract of humans. It enhances gastric emptying, increases small bowel peristalsis and decreases the transit time. It also stimulates inter-digestive migrating contractions. In infantile colic, higher basal motilin levels may be responsible for propulsive gut contractions that trigger the symptoms of colic [13]. Motilin has been found in breast milk and may trigger the endogenous release in breast fed infants stimulating gut contractions. Maternal smoking, which is a recognized risk factor for colic, is associated with elevated levels of motilin. Besides the direct effects on the intestinal smooth muscles, the vagal impulses also effect changes in motilin levels [14]. Ghrelin may promote abnormal hyper peristalsis and appetite, typically seen in colicky infants. The unopposed activity of serotonin in the initial months of life due to the absence of melatonin may be responsible for the occurrence of evening colic in infants.

There is also evidence for decreased contractility of the gallbladder in colicky infants due to a disturbance in cholecystokinin secretion. Intestinal permeability to macromolecules is increased in some infants with colic; this reflects an immature function of the gastrointestinal tract and accounts for acquired food allergy. The occurrence of colic has been attributed to personality disorders associated with an irritable and hypersensitive infant. Inexperienced and anxious parents create a situation for a severely colicky infant.

THE ROLE OF MICROBIOTA IN COLIC

The term 'microbiota' has now replaced the old denomination "microflora".

The microbiota is an ecosystem formed by a variety of ecological niches, composed by several different bacterial species. The microbiota is in close contact with the intestinal mucosa or epithelial interface which is, after the respiratory area, the largest surface of the body, occupying approximately 250-400 m^2.The 100 trillion bacteria in the gut is called as the "gut microbiota".

The colonization of the gastrointestinal mucosa starts from the birth.

It's fascinating to see the microbiota evolve in the first few weeks of life and show a remarkable variation between breast and formula fed infants as shown in several studies.

Jeurink et al. one of the earlier papers which suggested the presence of "milk microbiome" which revealed the presence of pre and probiotics and how this can have implications on infant and maternal health [15]. Johnson proposed that the gut microbiota holds the key to the future to both maternal and child health and how the gut microbiota is diverse, depending on the feeds and how "dysbiosis" can set in with a single dose of oral antibiotic [16].

Harmsen et al. showed in their study the diversity of gut microbiome by molecular studies (FISH studies) in breast and formula fed infants [17].

At birth the gut is colonized by commensal bacteria derived from the maternal vagina, faecal and skin as well as the external environment, but the type of delivery can influence the bacterial population. The quality of the maternal vaginal and intestinal microbiota will therefore play a major role in the initial phase of colonization and perhaps even have long term consequences for infant development and health. Women suffering from unbalances or (subclinical) infections in their vaginal or intestinal microbiota will most probably transmit these to their infants, constituting a non-optimal basis for the further development of the intestinal microbiota [18]. In infants delivered by caesarean section, the natural colonization process is disrupted, and these neonates will acquire their intestinal microbiota from the environment (e.g., ward staff, other infants and children, and family and friends) and from the maternal skin which are characterized by low bacterial richness and diversity. Other factors like infants being formula-fed rather than breast-feeding, maternal peripartum psychological state, hygienic properties of the early environment, use of pacifier, the structure of the family an infant is born into were likely to influence the colonization of the intestinal tract.

Abnormalities in any of these factors, together with fortuitous encounters with pathogens may result in the colic phenotype [19]. It was observed that infants with colic have a different micro biota's composition. In particular, the infants with colic are most often colonized by anaerobic bacteria Gram-negative and less frequently by *bifidobacteria* and *lactobacilli*, with differences in the patterns of the same intestinal *lactobacilli*, *L. lactis* and *L. brevis*, producers of ethyl alcohol and carbon dioxide, while *L. acidophilus* has been shown only in healthy infants.

This diversity of strains may be involved in increasing the meteorism typical of infantile colic. The alteration of the microbial environment in infants with colic could lead to a deregulation of intestinal motor function and an increase in gas production, with the consequent onset of the typical symptoms of the disorder. Moreover infants with colic, a condition previously believed to be non-organic in nature, have evidence of intestinal Neutrophillic infiltration.

THE ROLE AND EFFICIENCY OF *L REUTERI* DSM17938

The use of probiotics in infantile colic is based upon the hypothesis that aberrant intestinal microflora could cause gut dysfunction and gas production, contributing to symptoms.

L. reuteri (strains-American Type Culture Collection Strain 55730 and DSM 17938) significantly decreased the rate (minutes/day) of crying. *L.reuteri* DSM 17938 is the only probiotic strain with highest level of evidence in prevention and treatment of infantile colic.

Supplementation with the probiotic *L. reuteri* administered at a dose of 10^8 CFUs once daily to breastfed infants less than six months of age resulted in significantly greater improvement in colic symptoms at the end of treatment (21 or 28 days) with no incidence of side effects [20] (Figure 2).

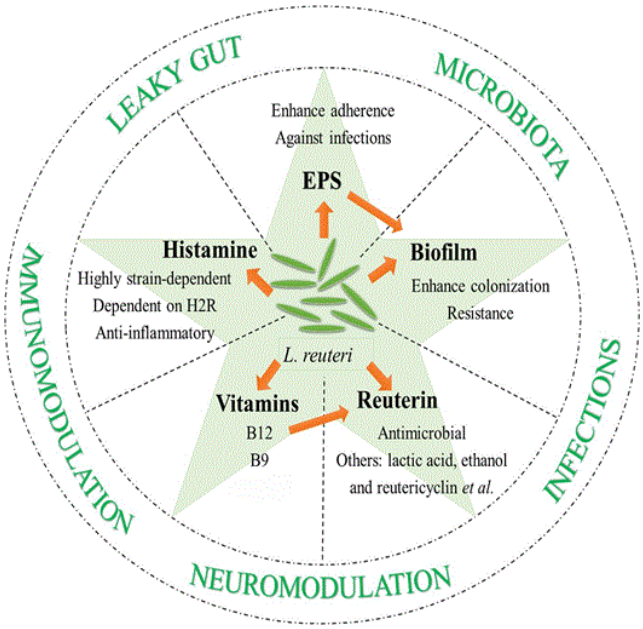

Figure 2: The mechanizations of *L reuteri* are depicted in the picture above Used with permission from © 2018 Mu, Tavella and Luo [21].

MECHANISM OF ACTION OF *L REUTERI* DSM17938

Qinghui Mu et al. in their paper have explained the multi-faceted and multi-dimensional role of *L reuteri* and the predominant role played by it in the human gut microbiota with focus on the elimination of infections and attenuating infections [22].

STUDIES SUPPORTING THE USE OF *L REUTERI* DSM17938

The efficacy of *L reuteri* has been clearly demonstrated in many clinical trials and the below table tries to summarize the results of all the studies (Table 1).

Condition	L reuteri strain	Weeks	Feeding	Outcome	Study
Infant colic	DSM17938	3	Breast fed	Significant reduction	Mi et al. 2015

				in crying time	
Infant colic	DSM17938	3	Breast fed infants	Reduction in crying and fussing time	Chau et al. 2015
Infant colic	DSM17938	12	Newborns	Effective preventive and protective action	Savino et al. 2015a
Infant colic	DSM17938	21 days	Breast fed	Improved symptoms : increase of Lactobacilli-Increase and decrease of E. coli in the fecal microbiota.	Savino et al. 2010
Infant colic	DSM17938	21 days	Colicky infants	No effect on global microbiota composition	Roos et al. 2013
Infant colic	DSM17938	21 days	Breast fed infants	Higher rate of responders and reduced median crying time	Sjazewska et al. 2013
Infant colic	DSM17938	1 month	Infants	No effect on crying time	Sung et al. 2014
Infant colic	DSM17938	90 days	Infants	Significant reduction of mean crying time	Indrio et al. 2014

Table 1: showing studies and their outcomes on *L reuteri* DSM17938.

Overall, all studies have shown the efficacy, clinical response and response time of *L reuteri* DSM17938 in infantile colic much superior to Simethicone or placebo. It finds a place in the recommendations for pre and probiotics in the World Gastroenterology organization guidelines both in the prevention and treatment of infantile colic [23]. The use of *L reuteri* DSM17938 doesn't limit itself only to infantile colic (prevention and treatment) but its uses expand to acute viral diarrhoea, preventing infections acquired at day care centres, antibiotic associated diarrhoea, functional abdominal pain and various FGID's [23,24].

CONCLUSION

The use of probiotics in infantile colic is based upon the hypothesis that aberrant intestinal microflora could cause gut dysfunction and gas production, contributing to symptoms.

L. reuteri (strains-American Type Culture Collection Strain 55730 and DSM 17938) significantly decreased the rate (minutes/day) of crying.

L.reuteri DSM 17938 is the only probiotic strain with highest level of evidence in prevention and treatment of infantile colic. Supplementation with the probiotic *L reuteri* administered at a dose of 10^8 CFUs once daily to breastfed infants less than six months of age resulted in significantly greater improvement in colic symptoms at the end of treatment (21 or 28 days) with no incidence of side effects.

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