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THE ROLE OF THE GUT MICROBIOME IN THE DEVELOPMENT OF INFANTILE COLIC: A MODERN PERSPECTIVE ON ETIOPATHOGENESIS

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Abstract. Traditionally, infantile colic has been regarded as a physiological phenomenon associated with gastrointestinal immaturity and excessive gas formation. Modern pediatrics has shifted toward a neuroimmunobiological model centered on disruption of the gut–microbiome–brain axis and pathological microbial colonization during the first weeks of life. The aim of the study was to analyze the current understanding of the etiopathogenesis of infantile colic from the perspective of microbiome disturbances and to review the evidence supporting the clinical efficacy of Limosilactobacillus reuteri strains. The review included publications from PubMed, Google Scholar, and CyberLeninka, with randomized controlled trials, meta-analyses, and clinical guidelines published mainly between 2014 and 2024. Source selection focused on strict strain specificity and the reliability of diagnostic criteria (Rome IV and Wessel criteria). The "hyperergic" microbiota is characterized by reduced species diversity and predominance of Gram-negative opportunistic bacteria, especially Enterobacteriaceae such as Klebsiella and Escherichia. Their lipopolysaccharides trigger a pronounced inflammatory response, and a sharp rise in fecal calprotectin serves as a clinical marker. The resulting inflammation contributes to visceral hypersensitivity, in which normal intestinal peristalsis may be perceived as severe pain. Limosilactobacillus reuteri DSM 17938 acts through three principal mechanisms: suppression of competing microorganisms via reuterin secretion, attenuation of inflammation through regulatory T-cell activation and reduced calprotectin, and direct modulation of the enteric nervous system through inhibition of TRPV1 nociceptors. Probiotic therapy appears most effective in breastfed infants, reducing daily crying duration by 49–74 minutes with an NNT of 3. In formula-fed infants, probiotic strains have not shown statistically significant superiority over placebo.

Keywords: infantile colic, intestinal microbiome, Limosilactobacillus reuteri, probiotics, gut–microbiota–brain axis.

INTRODUCTION

Infantile colic remains a major challenge for parents and affects up to one quarter of infants. The diagnosis has traditionally been based on the "rule of threes": crying for more than 3 hours per day, episodes occurring at least 3 times per week, and persistence for 3 weeks.

For decades, the pathogenesis of colic was interpreted mechanistically. Proposed causes included enzymatic immaturity, transient lactase deficiency, flatulence, and intestinal smooth-muscle spasms. Medical treatment therefore commonly relied on

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carminative agents such as simethicone and antispasmodics, although their therapeutic benefit often did not exceed the placebo effect [18].

Genomic sequencing of the intestinal microbiota has substantially changed this view, and the condition can no longer be reduced to simple "dysbiosis." Infantile colic is now recognized as a multifactorial functional gastrointestinal disorder in which impaired communication within the gut–microbiota–brain axis plays a central role [7,12].

The pathogenetic cascade begins with abnormal colonization of the gastrointestinal tract. The direction of syndrome development is strongly determined by microbiota status, and this observation provided the rationale for targeted probiotic therapy. At present, Limosilactobacillus reuteri DSM 17938 occupies a leading position among strains used for directed correction of dysbiosis [12].

Aim of the study. To analyze the current understanding of the etiopathogenesis of infantile colic from the perspective of microbiome disturbances and to review the evidence supporting the effectiveness of Limosilactobacillus reuteri strains in clinical practice.

Materials and methods. The review was based on publications from international databases including PubMed, Google Scholar, and CyberLeninka. The final sample included randomized controlled trials, meta-analyses, and clinical guidelines published mainly between 2014 and 2024. Sources were selected according to strict strain specificity and the reliability of diagnostic criteria (Rome IV criteria and Wessel criteria).

RESULTS AND DISCUSSION

The first three months of life are particularly important for formation of the intestinal microbiome. Modern studies show that in infants with colic its composition changes markedly: lactobacilli and bifidobacteria decrease, whereas opportunistic Proteobacteria increase rapidly [2]. According to Huttenhower et al. (2014), predominance of Escherichia coli and Klebsiella may serve as a marker of profound dysbiosis [4].

Intestinal epithelial cells directly recognize bacterial lipopolysaccharides (LPS) through Toll-like receptor 4 (TLR4). Ligand binding initiates the primary inflammatory response and rapidly activates an intracellular signaling cascade in which the nuclear transcription factor NF-κB acts as a key regulator. Cellular stress stimulates local synthesis of inflammatory mediators, including IL-8, IL-1β, and TNF-α. The molecular cascade results in excretion of biomarkers, with fecal calprotectin accumulating in the intestinal lumen. According to Karabayır et al. (2018) and Lee et al. (2017), its concentration in severe colic may reach approximately 650 μg/g compared with about 354 μg/g in controls [6,9].

Sensory nerve endings of the gastrointestinal tract acquire pathological reactivity, producing a state of visceral hyperalgesia. As a result, normal intestinal peristalsis or gas formation may be interpreted by the central nervous system as a painful stimulus, clinically manifesting as persistent crying in the infant [10].

Limosilactobacillus reuteri DSM 17938 is the most extensively studied representative of this profile. Before the taxonomic reclassification of lactobacilli in 2020, the strain was known as Lactobacillus reuteri. Its therapeutic potential is not limited to competitive antagonism against pathogens; the probiotic acts systemically by initiating a cascade of neuroimmune interactions with the host (Table 1) [17].

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Table 1. Key mechanisms of action of L. reuteri DSM 17938 in the pathogenesis of infantile colic.

Mechanism of action	Pathogenetic target	Physiological and clinical effect
Antimicrobial (metabolic)	Overgrowth of Proteobacteria (Klebsiella, E. coli).	Fermentation of glycerol into reuterin, a broad-spectrum antimicrobial compound that selectively suppresses pathobionts without damaging commensal flora [16].
Immunomodulatory (molecular)	TLR4/NF-κB signaling pathway and pro-inflammatory cytokines.	Inhibition of IL-8, IL-1β, and TNF-α expression in the intestinal mucosa, resulting in a systemic reduction in fecal calprotectin levels [11].
Cell-regulatory	Imbalance between pro-inflammatory Th17 cells and regulatory T cells (Treg).	Induction of IL-10 and the transcription factor FOXP3, with reduction of the RORγ/FOXP3 ratio and restoration of immune tolerance [7,11].
Neurogastroenterological	TRPV1 receptors (mediators of visceral pain) on afferent neurons.	Dose-dependent blockade of TRPV1 ion currents and reduction of intracellular calcium (Ca2+) influx in dorsal root ganglia, thereby inhibiting transmission of pain signals [5].
Intercellular signaling	Epithelial barrier and local immunity.	Secretion of extracellular vesicles containing 5′-nucleotidase, which catalyzes adenosine formation and contributes to reduced hypersensitivity [1,13].

Visceral nociception is regulated by transient receptor potential vanilloid type 1 (TRPV1). In a study by Kamiya et al. (2006), interaction of L. reuteri DSM 17938 with TRPV1 effectively blocked pain impulses, and the authors demonstrated a clear dose-dependent inhibitory effect. Live bacteria and their metabolites significantly reduced impulses in spinal pathways that are normally activated by mechanical distension of the intestine or chemical irritants [5].

According to Rhoads et al. (2018), dysbiosis and elevated fecal calprotectin in infants with colic occur regardless of whether they receive breast milk, formula, or mixed feeding [10]. However, the meta-analysis by Sung et al. (2018) showed that the efficacy of the strain depends critically on feeding type. Randomized controlled trials and meta-analyses demonstrate a therapeutic paradox: L. reuteri DSM 17938 is effective mainly in breastfed infants. With daily administration of 10^8 CFU, a clinical response is observed by day 21. Total crying time decreases by 49–74 minutes compared with placebo. The number needed

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to treat (NNT) is 3, which is a favorable indicator for functional disorders, and the risk of persistent infantile colic decreases by 39% [14].

The key to this effect is component synergy. According to Skonieczna-Zydecka et al. (2020), exogenous bacteria interact with human milk oligosaccharides (HMOs, including lacto-N-hexaose), creating an optimal intestinal biotope and supporting mucosal colonization. In formula-fed or mixed-fed infants, the situation differs substantially. As shown by Sung et al. (2018), in these cohorts L. reuteri DSM 17938 does not outperform placebo, and total crying duration remains unchanged [12,14].

Based on their observations, the Happy Tummy Consortium et al. (2023) identified three possible reasons. First, the necessary prebiotic substrate is absent because conventional formulas lack specific carbohydrate chains. Second, the baseline microbiome of formula-fed infants differs in structure and has a higher pH, which may suppress lactobacilli. Third, the composition of the formula itself influences microbial metabolism and may reduce bacterial adhesion. Nevertheless, inclusion of the strain in milk substitutes may still be justified because overall gastrointestinal tolerance improves, regurgitation frequency decreases, and stool consistency normalizes [3].

In 2023, ESPGHAN issued a revised position paper that clearly defined the principles of probiotic use in children. International clinical recommendations now incorporate evidence on L. reuteri, with strain specificity as the central principle: the effect of one strain cannot be extrapolated to other representatives of the same species or genus [15].

Management of infantile colic is therefore guided by specific criteria (Table 2).

Table 2. Current ESPGHAN recommendations on probiotic use in infantile colic.

Population	Probiotic strain and dosing regimen	Recommendation level
Breastfed infants with colic	Limosilactobacillus reuteri DSM 17938 (at least 10^8 CFU/day for 21–28 days).	May be recommended (weak recommendation, moderate certainty of evidence).
Breastfed infants with colic	Bifidobacterium lactis BB-12 (at least 10^8 CFU/day for 21–28 days).	May be recommended (weak recommendation, moderate certainty of evidence).
Formula-fed infants	L. reuteri DSM 17938 or other strains.	No recommendation for or against use because of insufficient evidence.
Prevention of colic in healthy newborns	Any studied strains.	No recommendation for or against use because of insufficient evidence.

According to ESPGHAN (2023), only two probiotics currently have an evidence base for breastfed infants. Bifidobacterium lactis BB-12 has been included in the pediatric therapeutic arsenal and has been shown to significantly reduce crying periods through targeted correction of bifidogenic gastrointestinal flora [15]. Other strains are also being

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investigated. Local clinical trials suggest that L. reuteri LR92 and L. reuteri UBLRu-87 may reduce pain intensity and the risk of food intolerance [8].

According to a number of authors, Limosilactobacillus reuteri DSM 17938 addresses a key pathogenetic mechanism of colic in breastfed infants. Symptomatic treatment is increasingly being replaced by targeted therapy aimed at reducing visceral intestinal hypersensitivity. Clinical benefit is attributed to three mechanisms: first, reuterin has potent antimicrobial properties; second, the TLR4/NF-κB inflammatory cascade is inhibited; and third, TRPV1 nociceptors are directly blocked [5,7,8,11].

It should also be emphasized that many authors agree that this probiotic is not a universal solution for formula-fed infants. Microbiome therapy in this group requires a comprehensive approach. A basic step is structural modification of infant formula by adding specific carbohydrate chains (prebiotics), followed by selection of targeted synbiotic combinations. The altered biochemistry of the gastrointestinal tract may hinder colonization, whereas appropriately selected synbiotics may help interrupt this cycle [1,3,9,11,15].

CONCLUSIONS

The gut–microbiota–brain axis has transformed the traditional view of infantile colic. Colic is now considered not a physiological developmental norm, but a functional gastrointestinal disorder. Clinicians are increasingly using targeted restoration of the intestinal microbiota, while the range of probiotic approaches continues to expand.

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