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INFANTILE COLIC

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Abstract. The lecture is devoted to the current problem of pediatrics — infant colic. They are in the light of the recommendations of the Rome criteria, reflecting the opinion of experts — pediatricians, gastroenterologists, allergists. The key to diagnosing infant colic is to exclude organic pathology ("red flags"), which accounts for no more than 5%. The article discusses modern ideas about the pathogenetic mechanisms of infant colic and modern principles of their correction based on these data. Correction of infant colic includes psychological support for the family, continued breastfeeding and the use of probiotics.

Key words: *infant colic; "red flags"; Rome IV criteria; probiotics.*

МЛАДЕНЧЕСКИЕ КОЛИКИ

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Резюме. Лекция посвящена актуальной проблеме педиатрии — младенческим коликам. Они рассматриваются в свете рекомендаций Римских критериев, отражающих мнение экспертов — педиатров, гастроэнтерологов, аллергологов. Ключевым моментом в постановке диагноза младенческих колик является исключение органической патологии («красные флаги»), которая составляет не более 5%. В статье рассмотрены современные представления о патогенетических механизмах младенческих колик и основанные на этих данных современные принципы их лечения. Терапия младенческих колик включает психологическую поддержку семьи, сохранение грудного вскармливания и применение пробиотиков.

Ключевые слова: *младенческие колики; «красные флаги»; Римские критерии IV; пробиотики.*

The term "colic" (colicos) means "pain in the large intestine". Colic is an attack-like pain in the abdomen accompanied by marked restlessness and crying of an infant in the first months of life [1].

A meta-analysis (2017) included 28 diary studies covering 8690 infants, showed that the average daily duration of crying in infants amounts from 117 to 133 minutes per day in the first 6 weeks of life, and to 68 minutes per day — from 10 to 12 weeks of life [2]. The WhyCry 2G crying analyzer identifies five reasons for infant crying: hunger, boredom, pain, sleep and stress. It is estimated that less than 5% of infants have identifiable medical explanations for their crying [3]. Unreasonable infants's cry began to attract the attention of the medical community since the

1890s. For the first time, an infantile colic (IC) was described by M. Wessell et al. in the 1960s [4]. The criteria proposed by M. Wessell et al. were used to diagnose colic for a long time. The criteria consists of the so-called rule of three: crying for 3 hours a day or more (usually not longer than 1 hour), at least 3 days a week, for 3 consecutive weeks; age from 6 weeks to 3–4 months; a good general condition: children have good weight gain, maintain a positive emotional attitude, good appetite, normal stools; possible infrequent regurgitation; absence of "anxiety symptoms". Clinical practice has shown that it was hard for parents to evaluate periods of crying and anxiety retrospectively, thus the Wessell criteria were considered inappropriate for practical use since they were associated with certain difficulties and diagnostic errors. According to the Rome IV criteria revision committee, the Wessell criteria are random, culturally independent, impractical, and do not reflect the impact of the child's symptoms on the family. For this reason, the new clinical criteria are based on symptoms that have been shown to cause more discomfort for parents. In addition, the Rome IV criteria extended the age of IC diagnosis to 5 months [5]. Thus, for clinical purposes, the diagnostic criteria should include following features: an infant under 5 months old at the beginning and end of symptoms; recurrent and prolonged periods of crying, restlessness, or irritability reported by caregivers, occurring for no apparent reason and that cannot be prevented or managed by caring adults; no evidence of developmental delay, fever, or illness with clinical signs, i.e., "red flags" or "anxiety symptoms" [5]. "Anxiety symptoms" indicate organic diseases manifesting itself in fever, persistent regurgitation including coughing fits, absence of weight gain, mucus and blood in stools, passive abdominal wall tension, refusal to eat, abdominal bloating, signs of atopic dermatitis and persistent constipation.

IC is defined as one of the most common complaints that parents adress to primary care physicians [6, 7]. A recently published systematic review (2020) reported colic incidence rates ranging from 2 to 73% [8]. Symptoms peak around the sixth week of life and cease naturally after 4–6 months of age [9], allowing it to be considered a benign, self-healing condition.

The need to treat this self-healing condition stems from the negative impact of excessive crying on an infant's family. Prolonged infant crying is harmful to sibling-parent relationships [10], is associated with maternal problems such as depression, anxiety, and loss of parental confidence [11, 12], is a frequent cause of early cessation of breastfeeding [13], and can lead to severe infant injury or death due to abuse [14]. A second important argument for the treatment of colic is the presence of its long-term consequences, such as migraine, sleep and behavioral disorders, hyperactivity, decreased intelligence and cognitive disorders, eating disorders, atopic diseases and functional gastrointestinal (GI) diseases [15–18]. Knowledge of IC pathogenesis is necessary for selecting an adequate therapy.

Infantile colic has a multifactorial pathogenesis. Physiologic imbalance in the development of the central nervous system explains the time of IC manifestation. At the age of 2 months, brain systems tolerate changes, as a result reflex mechanisms supervising behavioral responses are replaced by a system of control proceeded by the cerebral cortex. Many authors believe that inconsolable crying, which is noted in infantile colics, is a consequence of transient behavioral response deficits in the first 2 months of life [19, 20]. Complex interactions between behavioral factors (psychological and social) such as postpartum depression, parental anxiety, stressful pregnancy, adverse experiences during delivery, poor parenting skills [24–26], alterations from the endogenous opioid system and neuropeptide regulation [27–31], as well as nutritional factors (hypersensitivity or food allergy, especially allergy to cow's milk proteins) [28, 30], immaturity of gastrointestinal tract (GIT) [21, 24, 32], excessive intestinal gases [21, 24], imbalance of intestinal hormones and impaired intestinal motility [31, 32], changes in the intestinal microbiota [33, 34], disruption of the microbiota-brain axis [35], impaired intestinal permeability and low intensity inflammation [22, 36, 37] are among numerous mechanisms that play a role in the pathogenesis of colic.

The role of the gut microbiota has the greatest evidence base in the colic pathogenesis. Table 1 summarizes studies examining the quantitative and qualitative composition of the microbiota in children with and without IC.

Despite the diversity of results, most researchers indicate a low qualitative diversity of intestinal microbiota in children with colic compared to the microbiota of children without colic during the first 2 weeks of life [39]. Other studies suggest the presence of certain microorganisms in the gut microbiota associated with increased

Table 1. Studies of microbiota composition in children with colic and healthy infants

Таблица 1. Исследования состава микробиоты у детей с коликами и здоровых младенцев

Автор / Author	Метод / Method	Результаты / Results
Savino et al., 2004 [38]	Культуральный / Cultural	Младенцы с коликами имеют более высокие показатели и плотность кишечной палочки и других газообразующих кишечных палочек и более низкие уровни *Lactobacillus* spp. по сравнению со здоровыми младенцами / Colicky infants have higher counts and densities of *E. coli* and other gas-forming coliforms and lower levels of *Lactobacillus* spp. compared to healthy babies
Savino et al., 2009 [39]	Культуральный + ПЦР / Culture + PCR	*Escherichia coli*, *Klebsiella pneumoniae*, *K. oxytoca*, *Enterobacter cloacae*, *E. aerogenes* и *Enterococcus faecalis* были преобладающими видами у младенцев с коликами / *Escherichia coli, Klebsiella pneumoniae, K. oxytoca, Enterobacter cloacae, E. aerogenes* and *Enterococcus faecalis* were the predominant species in colicky infants
Mentula S., 2009 [40]	Культуральный + анализ клеточных жирных кислот, КЦЖК и производства газов / Culture + analysis of cellular fatty acids, SCFAs and gas production	Распространенность индолпродуцирующих колиформ была значительно выше у младенцев с коликами по сравнению с контрольной группой, в то время как многие аэробные роды, присутствующие в контрольной группе, не были обнаружены у младенцев с коликами / The prevalence of indole-producing coliforms was significantly higher in colicky infants compared with controls, while many aerobic labors present in controls were not found in colicky infants
de Weerth C., 2013 [41]	Молекулярные методы / Molecular methods	Colic phenotype was positively correlated with *Serratia, Vibrio* and *Pseudomonas* content / Фенотип колик положительно коррелировал с содержанием *Serratia*, *Vibrio* и *Pseudomonas*
Rhoads J.M., 2018 [42]	Секвенирование ДНК / DNA sequencing	Таксоны, которые в значительной степени связаны с коликами: *Acinetobacter*, *Lactobacillus iners*. Снижение относительного содержания бифидобактерий в среднем в 30 раз / Taxa significantly associated with colic: *Acinetobacter, Lactobacillus iners*. Reduction in the relative content of bifidobacteria by an average of 30 times
Loughman A, et al., 2021 [43]	Секвенирование 16S рРНК / 16S rRNA sequencing	Альфа-разнообразие фекальной микробиоты не имело существенной связи с плачем. Несколько таксонов микробиоты (включая *Bifidobacterium*, *Clostridium*, *Lactobacillus* и *Klebsiella*) связаны с тяжестью колик / Alpha diversity of fecal microbiota was not significantly associated with crying. Several microbiota taxa (including *Bifidobacterium, Clostridium, Lactobacillus*, and *Klebsiella*) are associated with colic severity
Kozhakhmetov S., 2023 [44]	Полное метагеномное секвенирование образцов кала / Whole metagenomic sequencing of stool samples	В группе колик обнаружено относительное изобилие *Bifidobacterium* и обогащение *Bacteroides Clostridiales*, в то время как микробное биоразнообразие в этой группе было обогащено /The colic group revealed a relative abundance of *Bifidobacterium* and an enrichment of *Bacteroides Clostridiales*, while microbial biodiversity was enriched in this group
Новикова В.П., 2023 [37] / Novikova V.P., 2023 [37]	Метод газовой хроматографии-масс-спектрометрии по Г.А. Осипову образцов кала / Method of gas chromatography-mass spectrometry of fecal samples according to G.A. Osipov	В группе колик значимо выше уровень *Acinetobacter* spp, *Nocardia* spp. и *Micromycetes* spp. по сравнению со здоровыми / In the colic group, the level of *Acinetobacter* spp., *Nocardia* spp. and *Micromycetes* spp. was significantly higher compared to healthy people

Note: SCFAs — short-chain fatty acids; PCR — polymerase chain reaction.

Примечание: КЦЖК — короткоцепочечные жирные кислоты; ПЦР — полимеразная цепная реакция.

crying duration in infants up to 3–4 months of age. These microorganisms include the family of gram-negative bacteria (Proteobacteria phylum), among which Escherichia, Klebsiella, and Proteobacteria species were predominant in stool samples of infants with colic [39, 42, 45]. Along with these microorganisms, Serratia, Yersinia, and Vibrio species were found in children with colic at the age of 2–4 weeks of life [42]. Two studies revealed significant differences in the content of *Acinetobacter* spp. [37, 42]. The first pathogenetic mechanism in IC connected with the increased content of Gram-negative opportunistic bacteria is excessive gas production as a result of fermentation of lactose, other carbohydrates and proteins. The second possible mechanism is an inflammatory response in the gut, which is triggered by the lipopolysaccharide complex of the outer envelope of Gram-negative bacteria resulting in increased production of pro-inflammatory cytokines and chemokines. High levels of fecal calprotectin and biomarkers of neutrophil infiltration in infants with colic evidence the above mentioned[22, 36]. Intestinal mucosa is more permeable due to inflammation which result in visceral hypersensitivity with clinical manifestation of IC symptoms. At the same time, Bifidobacterium and Lactobacillus microorganisms have an inverse association with colic symptoms in children during the first 3 months of life [34, 36, 45]. The pathogenetic mechanisms explaining the association of these microorganisms with the reduction of colic symptoms are the positive effects of Lactobacilli and lactic acid bacteria on the epithelial function of the intestinal mucosa, its barrier function and intestinal kinetics. Additionally, specific strains of Bifidobacterium and Lactobacillus have an anti-inflammatory response as they have antagonistic effects against gas-producing bacteria including Escherichia, Klebsiella and Enterobacter strains [46].

Each factor influencing on the formation of the intestinal microbiome (maternal microbiome and health status, mother's use of medications, type of delivery, condition of a child after birth, type of infant feeding, use of antibacterial drugs in a neanatal period) separately has no reliable significance in IC genesis [40, 47–49]. At the same time, it was proven that bacterial colonization was associated with malabsorption of fats and other nutrients due to immaturity of enterohepatic circulation of bile acids and salts [15, 24]. Microbiota produces local gut neurotransmitters (serotonin, gamma-aminobutyric acid, melatonin, histamine, acetylcholine) and coordinates local adaptive responses to stressors through the system of neuroimmunoendocrine hierarchy. In addition, the microbiota can alter brain physiology through the production of a wide range of cytokines, short-chain fatty acids, and increased afferent nerve activity. This the way the microbiota-brain axis works, and correspondingly plays a role in the genesis of IC [35].

Lactose tolerance disorder is a physiologic transient state in 3–4 months old infants, it often causes infantile colic. The literature describes the relationship between the severity of pain in infantile colic and the amount of carbohydrate excretion with feces in both breastfed and formula-fed infants. Data show that 25% of infants develop moderate to severe symptoms of colic dependent on cow's milk protein [50–53].

Mothers' conditions also contribute to predisposition of infantile colic, among them: unfavorable obstetric and gynecological history of the mother, gestosis, hypodynamia during pregnancy; nutritional disorders of the nursing mother (consumption of fatty foods, foods that increase flatulence, excessive amounts of cow's milk and its products); bad habits (smoking, alcohol, drugs); emotional stress in the family. Infants' contributions are prematurity; symptoms of post-hypoxic damage to the central nervous system; infant temperament. Incorrect feeding technique (swallowing air during feeding); force feeding; overfeeding; feeding from two breasts, improper preparation of nutritional formula (excessive or insufficient dilution), lack of proper mother-child interaction in the feeding situation also predispose to the development of infant colic [1].

The classic picture of colic is a dyad — extremelly anxious parents and an infant with a persistent, piercing cry that is audiologically distinct from other infant cries [54]. Cry episodes are associated with hypertension, facial redness, pulling the legs up to an abdomen, and flatulence. Assessment of the infant during an episode of colic may indicate that the infant is in moderate to severe pain according to the FLACC scale (Face, Legs, Activity, Cry, Consolability scale, a measurement used to assess pain for children). [55]. The crying starts and stops abruptly on its own, i.e., the nature of the episodes is paroxysmal [55]. It is very difficult to calm the baby. Typical crying of a baby with colic is presented under the QR code.

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XA circadian rhythm of crying (or "crying curve") with maximum intensity of crying and restlessness in the afternoon is specific for IC. An important characteristic of crying is its age-dependent appearance and dynamics: it appears from the 2nd week of life, peaks at 2–3 months of age with6 then gradually decrease and disappears by 4–5 months of age.

The presence of multifactorial pathogenesis leads to difficulties in therapeutic approaches. There are no international consensus documents, and national guidelines compiled by experts from the standpoint of evidence-based medicine are available only in three countries: the UK, the USA, and Ireland [56, 57]. An analysis of the recommendations of these guidelines is presented in Table 2.

In Russia, infantile colic is described in the National Guidelines for Pediatric Gastroenterology [58] and in the 2022 recommendations of the Society of Pediatric Gastroenterologists, Hepatologists, and Nutritionists on Functional Gastrointestinal Tract Diseases [1, 59].

All domestic and foreign guidelines emphasize the need for an individualized approach to the treatment of IC in close cooperation with patient's parents. It is necessary to reassure parents about the transient and benign nature of infantile colic and favorable outcome, to inspire them with confidence in the absence of severe disease in the child. Changing family habits has positive effects, it might be proposed to create a regime of "feeding — activity — sleep"; maintain a positive relationship "child — mother / family". Timely detection of maternal depression, cruel attitude to the child, counseling parents about psychological problems will avoid unwarranted diagnostic intervention in children, as well as anxiety and insecurity in parents [1, 56–59].

Dietary correction measures are considered to be effective as well6 omong them breastfeeding support, assessment of breastfeeding technique and suckling efficiency. Most experts recommend preserving natural feeding [1, 56–59]. A. Cohen Engler (2012) indicated that exclusively breastfed infants had significantly lower rates of colic episodes and tended to have longer nighttime sleep in comparison with formula-fed infants [60]. The authors of the study measured melatonin levels in breast milk every 2 h during the day and found its significant increase during the night hours. It is now known that the circadian rhythm of melatonin in infants is established by 3–5 months of life, and regression of infantile colic is also noted around this age [30]. It was also found that infants with infantile colic had a statistically significant decrease in the level of melatonin in the blood in the morning hours and later establishment of the circadian rhythm of melatonin compared to the control group. It is possible that infantile colic may be associated with desynchronization of the normal circadian rhythm of melatonin, and breast milk, which contains the highest melatonin levels at night, may compensate a transient circadian rhythm deficiency in infants [23]. In addition, night breast milk probably exerts antispasmodic, antioxidant, anti-inflammatory, and immunoregulatory effects on intestinal wall permeability membrane and infant microbiome development [23, 28, 61].

Currently, there are no united nutritional recommendations for breastfeeding women. According to recommendations of the Rome IV criteria, elimination of cow's milk-based products from the diet of breastfeeding women is recognized as effective only in the presence of allergy to cow's milk protein [62]. In all other cases, a causal relationship between maternal diet and colic has not been proven. A number of studies recommend the use of a hypoallergenic diet (exclusion of cow's milk, eggs, peanuts and other nuts, wheat, soy and fish) and associate it with a reduction of colic symptoms in children [63]. A 2012 systematic review identified 1 randomized controlled trial in infants whose mothers followed a diet with low big eight allergens during one week. Questionnaires noted a reduction in crying by 60 minutes over 48 h, however, mothers did not report a subjective decrease of colic. In addition, only 60% of mothers in this study were able to fully comply with the elimination diet, emphasizing the difficulty in implementing dietary restrictions [29, 63]. Based on the above mentioned, most researchers believe that elimination diets are not recommended for breastfeeding mothers as a cure for infantile colic [1, 56–59].

Table 2. Methods of treating colic from the point of view of evidence-based medicine

Таблица 2. Методы лечения колик с точки зрения доказательной медицины

Рекомендация/предложение / Recommendation/proposal	UK, 2013, 2017 [56] / Великобритания, 2013, 2017 [56]	USA, 2015 [56] / США, 2015 [56]	Ireland, 2014 [57] / Ирландия, 2014 [57]
Клиническая оценка отношений матери и ребенка / Clinical assessment of the mother-child relationship	✓	✓	✓
Информация для родителей, советы, поддержка и уверенность / Parenting information, advice, support and reassurance	✓	✓	✓
Продолжение грудного вскармливания / Continued breastfeeding	✓	✓	
Модификация рациона матери / Modification of the mother's diet	✗	✓	
Смена смеси, если ребенок вскармливается смесью (+), если не выявлена аллергия на молоко) / Changing the formula if the baby is formula-fed (+ if an allergy to milk is not detected)	✗	✓	
Пробиотические добавки (++) младенцам, находящимся только на грудном вскармливании) / Probiotic supplements (++ breastfed-only infants)	✗	✓+	✓
Симетикон / Simethicone	✗	✗	
Травяные добавки (например, фенхель) / Herbal supplements (such as fennel)	✗	✗	
Ингибиторы протонной помпы (например, омепразол, Лосек) / Proton pump inhibitors (eg, omeprazole, Losec)		✗	
Лактаза (например, капли Co-lief) / Lactase (eg Co-lief drops)	✗		
Антихолинергические препараты (включая дицикломин) / Anticholinergic drugs (including dicyclomine)		✗	
Детский массаж / Baby massage			✓
Мануальная терапия (включая манипуляции на позвоночнике и краниальную остеопатию) / Manual therapy (including spinal manipulation and cranial osteopathy)	✗	✗	
Физический контакт (например, удержание, раскачивание) / Physical contact (eg, holding, rocking)	✓		✓
«Белый шум» / «White noise»	✓		
Купание / Bathing	✓		
Обмотка (пеленание) / Winding	✓		
Пеленание / Swaddling		✗	
Акупунктура / Acupuncture		✗	
Режим сна / Sleeping mode			

Note: ✓ — recommended; ✓+ — high level of evidence; ✗ — not recommended; blank — not analyzed.

Примечание: ✓ — рекомендовано; ✓+ — высокий уровень доказательности, ✗ — не рекомендовано; пустая графа — не анализировалось.

According to systematic reviews, formula-fed infants of the first 3 months of life suffering from colic symptoms, are recommended to use partially hydrolyzed whey formulas with added prebiotics (oligosaccharides), formulas with reduced lactose content and fat component [1, 56–59].

Probiotic therapy has the highest level of evident efficacy among other therapeutic strategies in colic treatment [64–67]. Currently, the US Food and Drug Administration (FDA) has given probiotics a GRAS (Generally Recognized As Safe) status, which means: recognized as safe by leading FDA experts [48]. Taking into account the above mentioned pathogenetic mechanisms of the relashionship between intestinal microflora and IC, the correction of intestinal microbiome seems promising in the point of reducing colic symptoms. The efficacy of different strains of Lactobacillus reuteri has been demonstrated in naturally fed infants [23, 24, 66–68]. The factors behind the effects of *L. reuteri* are studied well. These are the ability to form biofilms; the resistance of *L. reuteri* colonies to low pH and bile salts; the ability of *L. reuteri* attach to mucin, intestinal epithelium and intestinal epithelial cells; production of metabolites with antimicrobial and immunomodulatory effects, the most studied of which is reuterin, which inhibits a wide range of microorganisms, mainly Gram-negative bacteria, while the strains of *L. reuteri* show marked resistance to reuterin. Some strains of *L. reuteri*, in addition to reuterin, produce other antimicrobial substances: lactic acid, acetic acid, ethanol, reutericycline. Therefore *L. reuteri* is effective against various bacterial infections of the gastrointestinal tract: *Helicobacter pylori*, *E. coli, Clostridium difficile* and salmonellae. Moreover, *L. reuteri* produces metabolites with antiviral properties which are effective against pneumoviruses, circoviruses, rotaviruses, coxsackie viruses and papillomaviruses. In addition, there are reports that L. reuteri also stops the growth and kills various Candida species; some strains of *L. reuteri* inhibit the production of few pro-inflammatory cytokines, affect immune cells, produce folate and gamma-aminobutyric acid (GABA), which determine its effect on visceral sensitization [69].

It should be noted that the effects of different *L. reuteri* strains are strain specific. The proven effects of some *L. reuteri* strains are summarized in Table 3.

Placebo-controlled and comparative studies demonstrate different results of colic treatment with L. reuteri probiotics, both positive and negative [75]. The data are summarized in Table 4.

In recent years, there has been increased interest in the use of other probiotic strains for the treatment of colic. The data are presented in Table 5.

Table 5 shows that Lactobacillus rhamnosus GG (ATCC 53103), Bifidobacterium animalis subsp. lactis, BB-12 and B. breve CECT7263 strains demonstrated a good therapeutic effect in colic in breastfed and formula-fed children. At the same time, multistrain probiotics have been shown to have synergistic effects that individual strains cannot achieve independently. It is suggested that multistrain probiotics may be effective in the treatment of colic due to their synergistic effects [88]. The data are summarized in Table 6.

Other pharmacologic agents that have been traditionally recommended for the relief of colic symptoms include simethicone, chamomile or fennel-based phytosupplements, other carminative and homeopathic preparations [4, 25, 92]. Most randomized clinical trials indicate low efficacy of these treatments. Concurrently, there is a lack of standardization of some homeopathic remedies consumption, as well as potential risks of undesirable effects. Thus, these remedies do not allow recommending most of them for the correction of infantile colic [21, 25, 56, 57, 93]. In some cases prescribed antispasmodics, proton pump inhibitors, and analgesics [3, 24, 66] have not proven effectiveness as well [56, 57]. Data published on lactase preparations for the treatment of colic is conflicting. There is evidence based on the results of randomized controlled trials (RCTs) showing a decrease in crying time in infants with proven lactose intolerance disorder when using lactase preparations compared to placebo [64]. At the same time, there are other RCTs indicating insufficient or weak effect of lactase preparations for relief of colic symptoms in infants on different types of feeding [65, 81]. It seems reasonable to recommend the use of lactase preparations only in case of proven lactase deficiency for 2 weeks. If there is no effect during this period of time, lactase therapy must be canceled.

It should be noted that a number of manipulations, such as infant massage, physical contact (e.g., holding, rocking an infant), bathing, swaddling and listening to the "white noise" have an evidence base for effectiveness agains colic [56, 57] . The "white noise" is a background sound that contains frequencies of the entire sound range, from 20 to 20,000 Hz, it is similar with the sounds

Table 3. Proven effects of different strains of *L. reuteri*

Таблица 3. Доказанные эффекты различных штаммов *L. reuteri*

Автор / Author	Штамм / Strain	Эффекты / Effects
Garcia Rodenas C.L., 2016 [70]	*L. reuteri* DSM 17938	Снижение количества энтеробактерий и повышение числа бифидобактерий у детей, рожденных путем кесарева сечения, т.е. модулировало развитие кишечной микробиоты / A decrease in the number of enterobacteria and an increase in the number of bifidobacteria in children born by cesarean section, i.e. modulated the development of intestinal microbiota
Savino et al., 2015 [53]	*L. reuteri* DSM 17938	Снижение количества анаэробных грамотрицательных и увеличение количества грамположительных бактерий в кишечной микробиоте, тогда как содержание энтеробактерий и энтерококков в значительной степени снижено / A decrease in the number of anaerobic gram-negative and an increase in the number of gram-positive bacteria in the intestinal microbiota, while the content of enterobacteria and enterococci decreased significantly
Martoni C.J., 2015 [71]	*L. reuteri* NCIMB 30242	Увеличивает соотношение *Firmicutes* и *Bacteroidetes* / Increases the ratio of *Firmicutes* to *Bacteroidetes*
Savino F., 2009 [39]	*L. reuteri* DSM 17938	Увеличение количества лактобацилл и уменьшение *E. coli* в фекальной микробиоте / Increase in the number of lactobacilli and decrease in *E. coli* in the fecal microbiota
Savino et al., 2019 [72]	*L. reuteri* DSM 17938	Снижает восприятие боли двумя путями: через переходный рецепторный потенциал — ваниллоидный канал 1, влияя на калийзависимую активность кальциевых каналов и снижение вызванных капсаицином и растяжением потенциалов действия спинномозговых нервов / Reduces pain perception in two ways: through transient receptor potential — vanilloid channel 1, influencing potassium-dependent calcium channel activity and reducing capsaicin- and stretch-induced action potentials of spinal nerves
Hojsak I., 2019 [73]	*L. reuteri* DSM 17938	Снижение уровня фекального кальпротектина / Decrease in fecal calprotectin levels
Pourmirzaiee M.A., 2020 [74]	*L. reuteri* LR92 (DSM 26866)	Выделяет уксусную кислоту, которая снижает pH *in vivo* и оказывает выраженное антибактериальное действие на многие патогены и реутерин, способный вызвать окислительный стресс у патогенов и эффективно предупреждать развитие воспалительной реакции / Produces acetic acid, which lowers pH *in vivo* and has a pronounced antibacterial effect on many pathogens and reuterin, which can cause oxidative stress in pathogens and effectively prevent the development of an inflammatory response
Новикова В.П., 2023 [37] / Novikova V.P., 2023 [37] /	*L. reuteri* DSM 17938	В группе детей, получавших *L. reuteri*, значимо снижался уровень *Bacillus megaterium*, *Bacteroides fragilis* и *Prevotella ruminicola*. Снижение уровня зонулина / In the group of children receiving *L. reuteri*, the level of *Bacillus megaterium, Bacteroides fragilis and Prevotella ruminicola* decreased significantly. Decreased zonulin levels

Table 4. Results of placebo-controlled and comparative studies of treatment of colic with *L. reuteri* **probiotics**

Таблица 4. Результаты плацебоконтролируемых и сравнительных исследований лечения колик пробиотиками *L. reuteri*

Автор / Author	Штамм / Strain	Эффекты / Effects
Лечение эффективно / Treatment is effective		
Savino F., 2007 [76]	*L. reuteri* ATCC 55730	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Szajewska H. et al., 2013 [77]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика в сравнении с плацебо / Reduction in anxiety and cry duration compared to placebo

Ending of the table 4 / Окончание табл. 4

Автор / Author	Штамм / Strain	Эффекты / Effects
Chau K. et al., 2015 [78]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Mi G.L. et al., 2015 [79]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Tatari M. et al., 2017 [80]	*L. reuteri* DSM 17938	Снижение беспокойства и продолжительности крика / Reduced anxiety and cry duration
Dryl R., 2018 [81]	*L. reuteri* DSM 17938	Положительный лечебный и профилактический эффект исключительно у детей на грудном вскармливании (21–28 дней) / Positive therapeutic and preventive effect exclusively in breastfed children (21–28 days)
Novikova V.P., 2023 [37] / Новикова В.П., 2023 [37]	*L. reuteri* DSM 17938	Положительный лечебный и профилактический эффект в виде снижения плача менее 1 часа к 10-му дню лечения у детей, независимо от вида вскармливания / Positive therapeutic and preventive effect in the form of reduced crying for less than 1 hour by the 10th day of treatment in children, regardless of the type of feeding
Лечение неэффективно / Treatment is ineffective		
Sung V. et al., 2014 [82]	*L. reuteri* DSM 17938	Нет различий с группой плацебо / No difference with placebo group
Fatheree N.Y. et al., 2017 [83]	*L. reuteri* DSM 17938	При искусственном вскармливании не было получено положительного результата / No positive results were obtained with artificial feeding
Dryl R., 2018 [81]	*L. reuteri* DSM 17938	При искусственном вскармливании не было получено положительного результата / No positive results were obtained with artificial feeding

Table 5. Results of placebo-controlled studies of the treatment of colic with different single-strain probiotics

Таблица 5. Результаты плацебоконтролируемых исследований лечения колик разными моноштаммовыми пробиотиками

Автор / Author	Штамм / Strain	Клинический эффект / Clinical effect	Патогенетический механизм / Pathogenetic mechanism
Savino F. et al., 2020 [45]	*Lactobacillus rhamnosus GG (ATCC 53103)*	Значительное снижение плача / Significant reduction in crying	Наблюдалось значительное увеличение общего количества бактерий в образцах кала (*Lactobacillus* spp.) и значительное снижение уровня кальпротектина / There was a significant increase in total bacterial counts in stool samples (*Lactobacillus* spp.) and a significant decrease in calprotectin levels
Xinias I. et al., 2017 [84]	*Bifidobacterium animalis subsp. lactis, BB-12*	Значительное снижение времени плача, повышение качества жизни семьи / Significant reduction in crying time, improved family quality of life	Не изучался / Not studied
Nocerino R. et al., 2020 [85]	*Bifidobacterium animalis subsp. lactis, BB-12*	Значительное снижение времени плача / Significant reduction in crying time	Достоверное увеличение HBD-2, LL-37, sIgA и бутирата и снижение кальпротектина / Significant increase in HBD-2, LL-37, sIgA and butyrate and decrease in calprotectin

Ending of the table 5 / Окончание табл. 5

Автор / Author	Штамм / Strain	Клинический эффект / Clinical effect	Патогенетический механизм / Pathogenetic mechanism
Chen K. et al., 2021 [86]	*Bifidobacterium animalis subsp. lactis, BB-12*	Значительное снижение времени плача / Significant reduction in crying time	Увеличение sIgA, бутирата в конце 21-дневного вмешательства, увеличение кальпротектина β-дефензина-2 и кателицидина / Increase in sIgA, butyrate at the end of the 21-day intervention, increase in calprotectin β-defensin-2 and cathelicidin
Suanes-Cabello S., 2020 [87]	*B. breve CECT7263*	Большая эффективность в сокращении ежедневного времени плача у детей на грудном и искусственном вскармливании, чем в контроле / Greater effectiveness in reducing daily crying time in breastfed and bottle-fed children than in controls	Ингибирование роста *Enterobacteriaceae* spp., противовоспалительное действие / Inhibition of the growth of *Enterobacteriaceae* spp., anti-inflammatory effect

Table 6. Results of placebo-controlled and comparative studies of the treatment of colic with different multi-strain probiotics

Таблица 6. Результаты плацебоконтролируемых и сравнительных исследований лечения колик разными мультиштаммовыми пробиотиками

Авторы / Authors	Состав пробиотиков / Composition of probiotics	Клиническая эффективность / Clinical effectiveness
Gerasimov et al., 2018 [89]	*L. rhamnosus 19070-2* + *L. reuteri 12246* + фруктоолигосахарид и витамин D_3	Значительная разница в среднем времени плача между пробиотиком и контрольной группой / Significant difference in mean crying time between probiotic and control group
Baldassarre et al., 2018 [90]	*L. paracasei DSM 24733, L. plantarum DSM 24730, L. acidophilus DSM 24735 L. delbrueckii subsp. bulgaricus DSM 24734), B. longum DSM 24736, B. breve DSM 24732 B. infantis DSM 24737) Streptococcus thermophilus DSM 24731*	Статистически значимое снижение количества минут плача в день. Незначительная разница в общем количестве пробиотических бактерий, лактобацилл и бифидобактерий была обнаружена между группами вмешательства и плацебо / A non-significant difference in the total counts of probiotic bacteria, lactobacilli and bifidobacteria was found between the intervention and placebo groups
Chen et al., 2021 [86]	*Bifidobacterium longum CECT7894* + *Pediococcus pentosaceus CECT8330*	Значительное сокращение времени плача в группе вмешательства и улучшение консистенции стула / Significant reduction in crying time in the intervention group and improvement in stool consistency
Astó E. et al., 2022 [91]	*B. longum KABP042* + *P. pentosaceus KABP041*	Уменьшение тяжести симптомов у младенцев, страдающих коликами и/или запором на грудном и искусственном вскармливании / Reducing the severity of symptoms in breastfed and formula-fed infants with colic and/or constipation
Novikova V. P. 2023 [37] / Новикова В.П., 2023 [37] /	*Lactobacillus casei PXN 37, Lactobacillus rhamnosus PXN 54, Streptococcus thermophilus PXN 66, Lactobacillus acidophilus PXN 35, Bifidobacterium breve PXN 25, Bifido bacterium infantis PXN 27, Bifidobacterium longum PXN 30*; и пребиотик: ФОС (фруктоолигосахариды)	Купирование колик к 6-му дню, что раньше, чем при использовании *L. reuteri DSM 17938* (10-й день) и симптоматической терапии (12-й день). Увеличение уровня фекального зонулина на 44%, что больше, чем при использовании *L. reuteri DSM 17938* (40%) и симптоматической терапии (10%). Увеличение количества таких доминирующих представителей микробиоты, как эубактерии и пропионобактерии / Relief of colic by day 6, which is earlier than when using *L. reuteri DSM 17938* (day 10) and symptomatic therapy (day 12). Increase in fecal zonulin levels by 44%, which is greater than with the use of *L. reuteri DSM 17938* (40%) and symptomatic therapy (10%). An increase in the number of such dominant representatives of the microbiota as eubacteria and propionobacteria

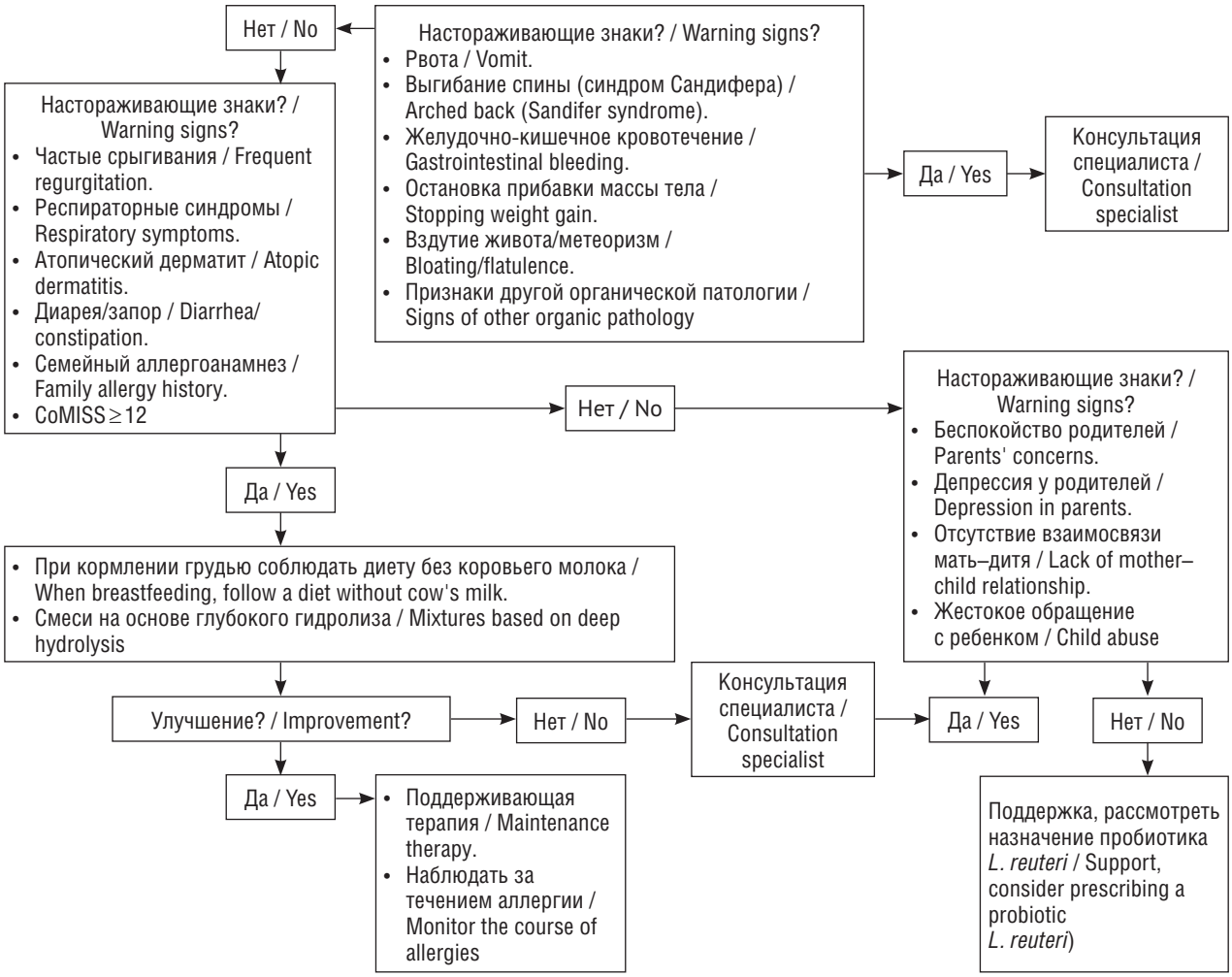

Fig. 1. Algorithm for diagnosing and treating colic (Vandenplas Y., 2016)
Рис. 1. Алгоритм диагностики и лечения колик (Vandenplas Y., 2016)

that the fetus hear in the womb hence it has a positive effect on the duration of crying and sleep in infants. However, there are limited studies that compare different treatments [37, 93].

Currently, the algorithm for diagnosis and treatment of colic proposed by ESPHAN (The European Society for Paediatric Gastroenterology Hepatology and Nutrition) experts in 2016 is generally accepted (Figure 1) [94].

Thus, infantile colic is a transient functional condition in children of the first 4–5 months of life that resolves on its own. However, it should always be remembered that serious pathologic conditions (gastrointestinal manifestations of food allergy, metabolic disorders, infectious processes, etc.) may hide under the mask of infantile colic, which requires differential diagnosis. Correction of IC symptoms is primarily based on psychological support of a family. With regard to breast-fed infants, breastfeeding support is mandatory, as well as the use of probiotics with proven anti-colic properties (Lactobacillus reuteri DSM 17938). Mothers are recommened to correct diet if food intolerance is suspected. In case an infant under 3 months old suffers from infantile colic, when breastfeeding is not feasible, it is preferable to use partially hydrolyzed whey formula with reduced lactose content and enriched with prebiotics. Additional, well-organized studies comparing different therapeutic strategies for colic are needed to develop optimal therapeutic approaches.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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