The Role of Probiotics in Common Paediatric Gastrointestinal Diseases

Dekanić Baraba, Kristina

Source / Izvornik: **The Central European Journal of Paediatrics, 2019, 15, 30 - 36**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.5457/p2005-114.227

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:406836

Rights / Prava: Attribution-NonCommercial 4.0 International/Imenovanje-Nekomercijalno 4.0 međunarodna

Download date / Datum preuzimanja: **2024-07-10**

Repository / Repozitorij:

Repository of the University of Rijeka, Faculty of Medicine - FMRI Repository

UNIRI DIGITALNA KNJIŽNICA

dabar
DIGITALNI AKADEMSKI ARHIVI I REPOZITORIJI

Narrative Review
Central Eur J Paed 2019;15(1):30-36
DOI 10.5457/p2005-114.227

The Role of Probiotics in Common Pediatric Gastrointestinal Diseases

Kristina Baraba Dekanić

Department of Pediatrics, Clinical Hospital Centre Rijeka, Rijeka, Croatia

Correspondence:
k.baraba.dekanic@gmail.com
Tel.: ++ 385 51 659 157
Fax.: + 385 51 623 126

Received: October 25, 2018
Accepted: January 12, 2019

Key Words: Probiotics ▪ Antibiotic Associated Diarrhea ▪ Acute Gastroenteritis ▪ Functional Gastrointestinal Disorders ▪ Children.

The aim of this paper is to specify the use of clinically proven probiotics in common pediatric gastrointestinal disorders. The PubMed and Cochrane Library databases were searched in May and June 2018, using the following key words: „probiotics", „children", „antibiotic associated diarrhea", „acute gastroenteritis", and „functional gastrointestinal disorders". Only studies published in English and published data were considered. The search included clinical trials, systematic reviews, guidelines and recommendations for clinical practice, and only relevant, high-quality and recent data were taken into account. Probiotics in general are nowadays used for numerous clinical indications and there is also a very large and still growing number of papers addressing this issue. **Conclusion –** According to current knowledge, two probiotic strains are recommended for antibiotic associated diarrhea prevention and treatment of acute gastroenteritis, LGG and *S. boulardii*. For the strain *L. reuteri DSM 17938* there is a weak recommendation for treatment of acute gastroenteritis. There are still not enough data to recommend the use of probiotics in pediatric functional gastrointestinal disorders, with the exception of *L. reuteri DSM 17938* for treatment of infantile colic in breastfed infants.

Introduction

In recent decades, numerous papers have been written trying to explain the role of probiotics in a large number and variety of diagnoses. Within this large amount and variety of information, it is most important to clarify which probiotics have sufficient recommendations for use with which diagnoses.

The World Health Organization (WHO) and the International Scientific Association for Probiotics and Prebiotics stated in 2014 that probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (1). Probiotics can be added to foods or can be registered as food supplements or drugs packed into pills, capsules, powder sachets and drops; they may contain only one microorganism, or may contain a mixture of several different microorganisms (2, 3). Since they are not registered as drugs or medicinal products, their production follows less strict criteria. This is why The European Society for Paediatric Gastroenterology, Hepatology and Nutrition's (ESPGHAN) Working Group for Probiotics and Prebiotics reviewed the literature and gave their recommendations (4). Their work provided evidence of the inadequate quality of commercial probiotic products. Many products have strains that are misidentified and misclassified, many of them contain significantly lower amounts of viable bacteria, sometimes to an extent that precludes the possibility of any health ef-

Copyright © 2019 by the University Clinical Centre Tuzla, Tuzla, Bosnia and Herzegovina.

fect. The products may also be contaminated with facultative or obligatory pathogens. Moreover, the regulatory status of probiotics products has not been established on an international basis, and there is no label control or periodic screening of the products' quality or safety (4). They emphasized the need for more stringent quality control for all commercially available probiotic products, especially for those prescribed for specific clinical indications and for those used in vulnerable populations, such as infants and children (4). The effect of any probiotic microorganism is strain specific and the recommendations are to use strains with clinically proven efficacy (3, 4, 5).

The aim of this paper is to provide current information on the use of probiotics in common gastrointestinal diseases.

Methods

The PubMed and Cochrane Library databases were searched in May and June 2018, using the following keywords: „probiotics", „children", „antibiotic associated diarrhea", „acute gastroenteritis", and „functional gastrointestinal disorders". Only studies published in English and published data were considered. The search included clinical trials, systematic reviews, guidelines and recommendations for clinical practice, and only relevant, high-quality and recent data were taken into count.

Prevention of Antibiotic Associated Diarrhea

Antibiotic-associated diarrhea (AAD) is defined as diarrhea that occurs in association with the administration of antibiotics, with the exclusion of other etiologies (6). The spectrum of its presentation ranges from mild diarrhea to fulminant pseudomembranous colitis caused by *Clostridium difficile (C. difficile)*. Almost any oral or parenteral antibiotic can cause AAD, but clindamycin, cephalosporines and penicillins are the most frequently associated with *C. difficile* colitis, and can also cause other types of diarrhea (6, 7). The reduction of AAD is connected with the reduction of antibiotic use, the choice of the antibiotic and the use of probiotics (5, 7). It is believed that AAD is caused by dysbiosis triggered by the use of antibiotics, and since probiotics modulate the intestinal microbiota, they can be used for AAD prevention (7).

Recently, the ESPGHAN Working Group for Probiotics/Prebiotics undertook a systematic review with meta-analysis in order to define the strains that may be used for AAD prevention (7). Only two strains were proven to have the desired effect.

Lactobacillus rhamnosus GG (LGG) was investigated in 5 randomized controlled trials (RCT) with a total of 445 participants. Compared with a placebo or no treatment, LGG can reduce the risk of AAD from 23% to 9.6% (RR 0.48, 95% CI 0.26-0.89) (7). The effect was dose-dependent, with the best effect from the highest dose ($1\text{-}2\times10^{10}$ colony-forming units, CFU) (7). There was only one study that examined the effect of LGG on the risk of *C. difficile* colitis, and it found no effect (RR 0.95, 95% CI 0.06-14.85) (8).

The other strain with proven efficacy was *Saccharomyces boulardii (S. boulardii)* (7). The strain was investigated in 6 RCTs with 1653 participants. Compared with a placebo or no treatment, *S. boulardii* reduced the risk of AAD from 20.9% to 8.8% (RR 0.43, 95% CI 0.3-0.6) (7). Two RCTs with a total of 579 participants proved that *S. boulardii* also reduced the risk of *C. difficile* diarrhea (RR 0.25, 95% CI 0.08-0.73). The daily dose for children should be 250-500 mg. (7). For all other probiotic strains there is still no evidence to support their use in AAD prevention (7).

There are still no clear instructions about when to administer probiotics in order to

prevent them being killed by antibiotics. *S. boulardii* and some other strains are resistant to antibiotics used for bacterial infections, and LGG, although sensitive to antibiotics, was effective in RCTs, so it should be used as in those trials (5).

Treatment of Acute Gastroenteritis

Acute gastroenteritis (AGE) is a worldwide problem and is responsible for 15% of child mortality; among children younger than 5 years there are more than 1.3 million deaths annually (9). It is defined as a decrease in the consistency of stools (loose or liquid) and/or an increase in the frequency (typically 3 in 24 hours), with or without fever or vomiting (10). Acute diarrhea lasts no longer than 14 days (19). In European countries the incidence of diarrhea ranges from 0.5 to 2 episodes/child/year, with Rotavirus as the main cause, although norovirus is becoming the leading cause in countries with high rotavirus vaccine coverage (10). The cornerstone of the therapy is rehydration which can in most cases be provided orally using oral rehydration solutions, and in certain cases parenterally (10). It has been shown that the addition of probiotics may diminish the duration of the disease and the severity of symptoms (2).

The ESPGHAN Working Group on Probiotics and Prebiotics summarized all the evidence found in the literature and issued guidelines for the use of probiotics (11). Overall, probiotics as a group reduces the duration of diarrhea by approximately 1 day (mean difference, MD -25 hours, 95% CI 16-34) and the risk of diarrhea lasting ≥4 days (RR 0.41, 95% CI 0.32-0.53). However, only 2 probiotic strains can be strongly recommended on the basis of evidence from at least two RCTs, LGG and *S. boulardii* (11).

The Cochrane review collected the data from 11 RCTs with a total of 2072 participants, and showed that LGG reduces the duration of diarrhea (MD -27 hours, 95% CI -41 to -13), mean stool frequency (MD-0.8, 95% CI -1.3 to -0.2) and the risk of diarrhea lasting ≥4 days (RR 0.6, 95% CI 0.4-0.9) (12). The systematic review by Szajewska, et al. found 15 RCTs with 2963 participants and showed that LGG significantly reduced the duration of diarrhea compared with a placebo or no treatment (MD -1.05 days, 95% CI -1.7 to -0.4); LGG was more effective in higher doses, that is $\geq 10^{10}$ CFU daily (MD -1.1 days, 95% CI -1.9 to – 0.3) (13).

Compared with a placebo or no intervention, *S. boulardii* significantly reduced the duration of diarrhea (11 RCTs, N=1306, MD -0.99 days, 95% CI -1.4 to -0.6) and the risk of diarrhea on day 3 (9 RCTs, N=1128, RR 0.52, 95% CI 0.4-0.65) as proved in another review (14). The daily dose was between 250 and 750 mg (14). The Cochrane review showed similarly that *S. boulardii* reduced the risk of diarrhea lasting ≥4 days (6 RCTs, N=606, RR 0.37, 95% CI 0.2-0.65) (12).

Another strain, *Lactobacillus reuteri DSM 17938* (and the original strain *ATCC 55730*) has been shown to have a positive effect in AEG treatment (11). A systematic review from 2014 (15) found 2 RCTs on 196 participants that evaluated *L. reuteri DSM 17938* and 3 RCTs on 156 participants that evaluated the original strain *L. reuteri ATCC 55730.* The results showed that both strains reduced the duration of diarrhea (MD-32 hours, 95% CI -41 to -24) and increased the chance of a cure on day 3 (RR 3.5, 95% CI 1.2-10.8). The results were similar in the analysis of *L. reuteri DSM 17938* from 2016 that evaluated 8 RCTs (N=1229) (16).

Summarizing all the data, the use of LGG and *S. boulardii* is strongly recommended as an adjunctive treatment in AEG despite the low quality of evidence provided, and *L. reuteri DSM 17938* has a weak recommendation with very low quality of evidence (11). Ideally, probiotics should be initiated early in the course of diarrhea (2, 3, 5). There are

still no data that can recommend any other strain as a single microorganism or a mixture of strains for treatment of AEG in children.

Treatment of Functional Gastrointestinal Disorders

Chronic recurrent pain is one of the most common problems in children. Its prevalence in Europe and the United States ranges from 0.3%-19% (17). The great majority are functional in nature, which means that no specific organic cause can be found (18, 19). In a recent meta-analysis with almost 200,000 participants, the prevalence of functional gastrointestinal disorders (FGIDs) varied widely, from 1.6% to 41.2%, and the pooled prevalence was 13.5% (95% CI 11.8–15.3) (20). In the pediatric age group the most common entities were functional abdominal pain (FAP) and irritable bowel syndrome (IBS) (21). The Rome criteria are used to define a large spectrum of functional abdominal pain, with Rome III criteria (22) defining FAP as an episodic or continuous abdominal pain occurring at least once per week for at least 2 months, with no evidence of inflammatory, anatomic, metabolic, or neoplastic process, while IBS is defined as abdominal pain or discomfort associated frequently with relief after defecation, change in stool frequency, and/or a change in stool consistence. According to the latest evidence, diagnosing FGIDs by exclusion of organic diseases has been changed to a symptom-based diagnosis, so in 2016 the Rome IV criteria were published (23). The main difference from the Rome III criteria is that the phrase "no evidence of an inflammatory, anatomic, metabolic, or neoplastic process that explain the subject's symptoms" has been removed and changed to "after appropriate medical evaluation, the symptoms cannot be attributed to another medical condition". The pathogenesis of FGIDs is complex and encompasses visceral hypersensitivity, psychosocial factors, visceral motility and intestinal dysbiosis with low-grade inflammation (24-26). There is only symptomatic therapy for FGIDs, and probiotics have been shown to reduce the manifestations of the disorder through modification of enzymatic and metabolic function, with limited data on the pediatric population (3).

Very recent data exist from a panel of experts organized by the European Paediatric Association, the Union of the National European Paediatric Societies and Associations (EPA/UNEPSA) in 2018 that highlight two probiotic strains that could be effective in FGIDs, LGG and *L. reuteri DSM 17938* (2). According to a Cochrane meta-analysis probiotics in general can significantly reduce abdominal pain frequency (6 RCTs, N=523, standardized mean difference (SMD) -0.55, 95% CI 0.98 to -0.12), without performing strain-specific analysis (27). A strain-specific meta-analysis was undertaken by Horwath and colleagues in 2011 and found LGG to be effective in FGIDs; in 3 RCTs with 290 participants LGG reduced pain in the overall population with abdominal pain-related functional gastrointestinal disorders (RR 1.31, 95% CI 1.08-1.59) and in irritable bowel syndrome (IBS) subgroup (3 RCTs, N=167; RR 1.70, 95% CI 1.27-2.27), but not in other subgroups of FGIDs (28). The same expert group (2) found some evidence from several RCTs that *L. reuteri DSM 17938* could reduce the pain in FGIDs, both FAP and IBS (21, 29).

Summarizing all the data, due to the limitations of the available evidence, no recommendations can be provided for the use of probiotics in the treatment of FGIDs (2). Latin-American experts came to similar conclusions with 2c grade of recommendation for LGG in improving symptoms in IBS (3), with the addition of VSL#3 with the same indication, on the basis of the trial by Guandalini, et al. in 2010 (30).

Treatment and Prevention of Infantile Colic

Infantile colic is a common problem that affects up to 30% of healthy infants (2, 3, 31). The first definition given in 1954 as paroxysms of irritability, fussing or crying lasting for a total of more than three hours a day and occurring on more than three days in any one week, in an otherwise healthy and thriving infant, is still used (32). More recently Rome IV criteria defined infant colic as recurrent and prolonged periods of crying, fussing or irritability in otherwise healthy infants under the age of 5 months, occurring without obvious cause and which cannot be prevented or resolved by caregivers (33). The cause is still unclear, but there is strong evidence that intestinal dysbiosis has an important role (2, 31, 34).

Latin-American Guidelines from 2015 found *L. reuteri DSM 17938* to be effective for colic treatment and prevention (3). A more recent systematic review of 7 RCT (N=471) with low risk of bias, compared probiotics with a placebo in healthy full-term infants with infantile colic who were less than 6 months of age (31). Treatment success, defined as the percentage of children who achieved a reduction in the daily average crying time >50%, and the duration of the crying time were evaluated at the end of the intervention. Data from 5 RCTs found *L. reuteri DSM 17938* increased treatment success (RR=1.67, 95% CI: 1.10 - 2.51.), but only in breastfed infants (4 RCTs, N=345, RR=2.11, 95% CI: 1.22–3.66). The same strain reduced the duration of crying at the end of the intervention by almost 50 min (5 RCTs, MD = –50, 95% CI: –66 to –33) (31).

One RCT (N=30) found LGG not to have any significant effect on treatment success (RR=0.10, 95% CI: 0.01–1.76) and the duration of crying (MD=1 min, 95% CI: –62 to 60) (31). Data from one RCT (N=50) showed that administration of a symbiotic containing 7 probiotic strains (*L. casei, L. rhamnosus, S. thermophilus, B. breve, L. acidophilus, B. infantis, L. bulgaricus*) and fructooligosaccharides increased the treatment success (RR=1.96, 95% CI: 1.18 - 3.24) and reduced the duration of crying (MD=–35, 95% CI: –40 to –29) (31).

There is still no strong evidence to support the use of probiotics in infantile colic prevention, although there are some promising data on *L. reuteri DSM 17938* (2, 34).

Conclusion

There have been numerous clinical investigations that have tried to prove the use of probiotics not only in gastrointestinal diseases, but in diseases affecting many other organs. It is of the utmost importance to choose a probiotic strain with clinically proven efficacy in well-controlled randomized clinical trials. From a gastroenterological point of view, there are only small number of illnesses where the use of the probiotics has been proved to be beneficial. Two strains are recommended for AAD prevention and treatment of acute gastroenteritis: LGG and *S. boulardii*. For the strain *L. reuteri DSM 17938* there is a weak recommendation for AGE treatment. Among FGIDs, *L. reuteri DSM 17938* has been found to be effective in the treatment of infantile colic in breastfed infants. Probiotics are generally found to be safe, but in certain clinical conditions, such as in immunocompromized, premature and critically ill patients, they should be used with extreme caution.

Conflict of Interest: The author declares that she has no conflict of interest.

References

1. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B, et al. Expert consensus document. The International Scientific Association for Pro-

biotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroetnerol Hepatol 2014;11:506-14.

2. Hojsak I, Fabiano V, Pop LP, Goulet O, Zuccotti GV, Çokuğraş FC, 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):927-37.
3. Cruchet S, Furnes R, Maruy A, Hebel E, Palacios J, Medina F et al. The use of probiotics in pediatric gastroenterology: a review of the literature and recommendations by Latin-American experts. Paediatr Drugs. 2015;17(3):199-216.
4. Kolaček S, Hojsak I, Berni Canani R, Guarino A, Indrio F, Orel R, et al. Commercial Probiotic Products: A Call for Improved Quality Control. A Position Paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2017;65:117-24.
5. Hojsak I. Probiotics in Children: What Is the Evidence? Pediatr Gastroenterol Hepatol Nutr. 2017;20:139-46.
6. Bartlett JG. Antibiotic-Associated Diarrhea. N Engl J Med. 2002;346:334-9.
7. Szajewska H, Berni Canani R, Guarino A, Hojsak I, Indrio F, Kolacek S, et al. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children. J Pediatr Gastroenterol Nutr. 2016;62:495-506.
8. Arvola T, Laiho K, Torkkeli S, Mykkänen H, Salminen S, Manula L, et al. Prophylactic Lactobacillus GG reduces antibiotic-associated diarrhea in children with respiratory infections: a randomized study. Pediatrics. 1999;104(5):e64.
9. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet. 2010;375(9730):1969-87.
10. Guarino A, Ashkenazi S, Gendrel D, Lo Vecchio A, Shamir R, Szajewska H. European Society for Pediatric Gastroenterology, Hepatology, and Nutrition/European Society for Pediatric Infectious Diseases Evidence-Based Guidelines for the Management of Acute Gastroenteritis in Children in Europe: Update 2014. J Pediatr Gastroenterol Nutr. 2014;59:132-2.
11. Szajewska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, et al. Use of probiotics for management of acute gastroenteritis: a position paper by the ESPGHAN Working Group for Probiotics and Prebiotics. J Pediatr Gastroenterol Nutr. 2014;58(4):531-9.
12. Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. Cochrane Database Syst Rev. 2010;(11):CD003048.
13. Szajewska H, Skórka A, Ruszczyński M, Gieruszczak-Białek D. Meta-analysis: Lactobacillus GG for treating acute gastroenteritis in children--updated analysis of randomised controlled trials. Aliment Pharmacol Ther. 2013;38(5):467-76.
14. Dinleyici EC, Eren M, Ozen M, Yargic ZA, Vandenplas Y. Effectiveness and safety of Saccharomyces boulardii for acute infectious diarrhea. Expert Opin Biol Ther. 2012;12(4):395-410.
15. Szajewska H, Urbańska M, Chmielewska A, Weizman Z, Shamir R. Meta-analysis: Lactobacillus reuteri strain DSM 17938 (and the original strain ATCC 55730) for treating acute gastroenteritis in children. Benef Microbes. 2014(3):285-93.
16. Urbańska M, Gieruszczak-Białek D, Szajewska H. Systematic review with meta-analysis: Lactobacillus reuteri DSM 17938 for diarrhoeal diseases in children. Aliment Pharmacol Ther. 201643(10):1025-34.
17. Chitkara DK, Rawat DJ, Talley NJ. The epidemiology of childhood recurrent abdominal pain in Western countries: a systematic review. Am J Gastroenterol. 2005;100(8):1868-75.
18. Di Lorenzo C, Colletti R, Lehmann H, Boyle JT, Gerson WT, Hyams JS, et al. Chronic abdominal pain in children: a technical report of theAmerican Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition: AAP Subcommittee and NASPGHAN Committee on Chronic Abdominal Pain. J Pediatr Gastroenterol Nutr. 2005;40:249-61.
19. Spee LA, Lisman-Van Leeuwen Y, Benninga MA, Bierma-Zeinstra SM, Berger MY. Prevalence, characteristics, and management of childhood functional abdominal pain in general practice. Scand J Prim Health Care. 2013;31(4):197-202.
20. Korterink JJ, Diederen K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. PLoS One. 2015;10(5):e0126982.
21. Jadrešin O, Hojsak I, Mišak Z, Kekez AJ, Trbojević T, Ivković L, et al. Lactobacillus reuteri DSM 17938 in the Treatment of Functional Abdominal Pain in Children: RCT Study. J Pediatr Gastroenterol Nutr. 2017;64: 925-9.

22. Rasquin A, Di Lorenzo C, Forbes D, Guiraldes E, Hyams JS, Staiano A, et al. Childhood functional gastrointestinal disorders: child/adolescent. Gastroenterology 2006;130:1527-37.

23. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology 2016;150:1456-68.

24. Farmer AD, Aziz Q. Mechanisms and management of functional abdominal pain. J R Soc Med. 2014;107(9): 347-54.

25. Drossman DA, Camilleri M, Mayer EA, Whitehead WE. AGA technical review on irritable bowel syndrome. Gastroenterology.2002;123:2108-31.

26. Simre´n M, Barbara G, Flint HJ, Spiegel BM, Spiller RC, Vanner S, et al. Intestinal microbiota in functional bowel disorders: a Rome foundation report. Gut. 2013;62:159-76.

27. Newlove-Delgado TV, Martin AE, Abbott RA, Bethel A, Thompson-Coon J, Whear R, et al. Dietary interventions for recurrent abdominal pain in childhood. Cochrane Database Syst Rev. 2017;3:CD010972.

28. Horvath A, Dziechciarz P, Szajewska H. Meta-analysis: Lactobacillus rhamnosus GG for abdominal pain-related functional gastrointestinal disorders in childhood. Aliment Pharmacol Ther. 2011;33:1302-10.

29. Weizman Z, Abu-Abed J, Binsztok M. Lactobacillus reuteri DSM 17938 for the Management of Functional Abdominal Pain in Childhood: A Randomized, Double-Blind, Placebo-Controlled Trial. J Pediatr. 2016;174:160-4.

30. Guandalini S, Magazzu G, Chiaro A, La Balestra V, Di Nardo G Gopalan S, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. J Pediatr Gastroenterol Nutr. 2010;51:24-30.

31. Dryl R, Szajewska H. Probiotics for management of infantile colic: a systematic review of randomized controlled trials. Arch Med Sci. 2018;14:1137-43.

32. Wessel MA, Cobb JC, Jackson EB, Harris GS, Detwiler AC. Paroxysmal fussing in infancy, sometimes called colic. Pediatrics. 1954;14:421-35.

33. Benninga MA, Faure C, Hyman PE, St James Roberts I, Schechter NL, Nurko S. Childhood Functional Gastrointestinal Disorders: Neonate/Toddler. Gastroenterology. 2016;150:443-55.

34. Pärtty A, Rautava S, Kalliomäki M. Probiotics on Pediatric Functional Gastrointestinal Disorders. Nutrients. 2018;10. pii: E1836. doi: 10.3390/nu10121836.