www.jpnim.com Open Access eISSN: 2281-0692
Journal of Pediatric and Neonatal Individualized Medicine 2017;6(2):e060205
doi: 10.7363/060205
Received: 2016 Nov 01; revised: 2017 Mar 17; accepted: 2017 May 20; published online: 2017 Jun 09

Review

Microbiota and probiotics

Mara Corpino

Pediatric Clinic, Thalassemia and Rare Diseases, AO Brotzu, Cagliari, Italy

Abstract

Microbiota, the collection of microorganisms peacefully coexisting with their human host, colonize virtually every surface of the human body exposed to the external environment. The complex community of microorganisms living in the digestive tract, the gut microbiota, is determined by the delivery mode, prematurity, sex, genetics and subsequent environmental exposures (diet, drugs).

It has also been claimed that the constant interaction between the host and the gut microbiota influences the health of the host. Probiotics are defined as live non-pathogenic microorganisms that, when administered in adequate amounts can replicate and colonize in sufficient numbers the gastrointestinal tract. This is the main reason for the use of probiotics in different clinical settings where they may act as biomodulators of the intestinal microbiota. The therapeutic efficacy of probiotics has been evaluated in randomized controlled trials for various diseases. In this paper, the usage and the efficacy of probiotics in different conditions like necrotizing enterocolitis, sepsis, diarrhea, functional gastrointestinal disorders, inflammatory bowel disease, allergies are analyzed.

The usefulness of a probiotic treatment is affected by many factors including: bacterial strain, duration of administration, disease and age and not all products marketed as probiotics provide the same safety and efficacy. Therefore, comparative studies to assess the most effective formulations, timing and the optimal length of therapy are mandatory.

Keywords

Microbiota, probiotics, infant, biomodulator, dysbiosis.

Corresponding author

Mara Corpino, Pediatric Clinic, Thalassemia and Rare Diseases, AO Brotzu, Cagliari, Italy; email: mara.corpino@aob.it.

How to cite

Corpino M. Microbiota and probiotics. J Pediatr Neonat Individual Med. 2017;6(2):e060205. doi: 10.7363/060205.

Microbiota

The collection of microorganisms peacefully coexisting with their human host is defined microbiota. The microbiota colonizes virtually every surface of the human body that is exposed to the external environment and it has been recently estimated that the human body contains $4x10^{13}$ colonizing bacteria and $3x10^{13}$ own cells, a ratio roughly equal one to one. Gut microbiota is the complex community of microorganisms that live in the digestive tract. The human intestinal microbiota contains more than 10^{13} microbes subdivided in different species of bacteria, with large inter-individual variability [1, 2]. The diversity of gut microbiota has been revealed by the application of high-throughput sequencing of the microbial ribosomal RNA or DNA [3]. Metagenomic analyses and 16s rRNA gene sequences have shown that although to date more than 50 bacterial phyla have been described, only two are those prevailing: the *Bacteroidetes* and the *Firmicutes*, followed by *Proteobacteria* and *Actinobacteria* [1]. Most of the bacteria reside in the lower part of the digestive system, especially in the large intestine, because in the proximal tract the gastric juice, bile and pancreatic secretions are toxic or not favorable for the growth of most microorganisms. After birth, the composition of microbiota of newborns is constituted by *Bacteroidetes*, derived from the maternal microbiota colonizing the urogenital tract and the skin, and influenced by environmental factors, such as diet (formula versus breastfeeding). Also, the mode of delivery and subsequent environmental exposures influence the composition of microbiota in the infant [4]. After the initial establishment of the intestinal microbiota and during the first year of life the microbial composition of the mammalian gut is relatively simple and varies widely between different individuals. After the first year of age the intestinal microbiota undergoes a second transformation until it is fairly stabilized in its composition, very similar to that of the adult [5].

There are different factors that influence gut microbiota: prematurity, treatment of the mother or the baby with antibiotic, sex, genetic factors (for example HLA haplotype), diet [5]. Direct evidence concerning the impact of diet on the gut microbiota has been observed. Diet influences the production of micronutrient by the intestinal microbiota. Short-chain fatty acid (SCFAs), such as butyrate, acetate and propionate, products of carbohydrate fermentation by the gut microbiota, support barrier function in the intestine. The intestinal microbiota is involved in normal digestion and affects energy salvaging from the diet, fermenting unavailable energy substrates such as fibers to SCFAs [5, 6].

The gut microbiota is also easily altered by pathogens, antibiotics, changes in environment [5].

In the healthy gut, the intestinal microbiota is constantly monitored by the mucosal immune system. In addition to the physical barrier between the gut-epithelium and the bacteria in the lumen, there is a thick mucus layer formed by antimicrobial peptides, secretory IgAs, lamina propria-resident macrophages and dendritic cells (DCs) that survey the mucosal surfaces for unwanted or pathogenic bacteria. Intestinal macrophages are involved in direct killing of bacteria via phagocytosis, whilst DCs intervene by presenting antigens to T and B cells thus priming B and T cells, against mucosal pathogens to add another layer of protection at the mucosal surface. On the other hand, gut microbiota directly affects the development of the immune system [7]. Indeed, the gut microbiota plays important roles in shaping the immune system during infancy. The commensal microbes and their products interact with immune cells to create and maintain host tolerance and influence both innate and adaptive immune response [8-11].

Gut microbiota provides its host with a physical barrier to incoming pathogens by competitive exclusion, such as occupation of attachment sites, consumption of nutrient sources and production of antimicrobial substances. It also stimulates the host to produce various antimicrobial compounds [8]. The metabolic trophic action is achieved with the synthesis of vitamins, the absorption of ions, the production of trophic function compounds for the enterocyte [8].

The intestinal microbiota plays a detoxifying function due to the ability to synthesize enzymes for the transformation and neutralization of xenobiotics [8].

The constant interaction between the host and the resident microbes influences the health of the host, with a combination of bacterial species that favors non-pathogenic symbionts.

Changes in the composition of the gut microbiota or an increased proportion of certain

phyla over others (dysbiosis) have been implicated as potential trigger for various disorders. The probiotics with prebiotics, symbionts and postbiotic are considered biomodulators of the intestinal microbiota.

It has been suggested that the increase of some bacterial species of intestinal microbiota considered "favorable" to the health of the organism, such as *Bifidobacterium* and *Lactobacillus*, is correlated with a reduction in the incidence and severity of different disorders of the gastrointestinal tract.

Probiotics

Probiotics are defined as live non-pathogenic microorganisms (bacteria or yeasts) that, when administered in adequate amounts, can replicate and colonize in sufficient numbers the gastrointestinal tract and may confer health benefit on the host [12]. Microorganisms, to be defined as probiotic, should be of human origin, resists to the gastric acid pH, the bile and survive in the gastrointestinal tract by adhering to the intestinal mucosa. They should be able to replicate into the gastrointestinal tract and must be tolerated by the intestinal immune system; in addition, they should have beneficial effects on health, antagonizing pathogenic microorganisms and producing antimicrobial molecules. A wide variety of probiotic products and strains exist and it is important to consider the term "probiotics" for a group of microorganisms with different properties and effects.

Probiotic organisms can provide a beneficial effect on intestinal epithelial cells in numerous ways. Some strains can block pathogen entry into the epithelial cell by providing a physical barrier, referred to as "colonization resistance" [13-15], or create a mucus barrier by causing the release of mucus from goblet cells. Other probiotics maintain intestinal permeability by increasing the intercellular integrity of apical tight junctions, for example, by upregulating the expression of zona-occludens [16] or by preventing tight junction protein redistribution [17], thereby stopping the passage of molecules into the lamina propria. Some probiotic strains have been shown to produce antimicrobial factors. Other stimulate the innate immune system by activating dendritic cells, which then travel to mesenteric lymph nodes and lead to the induction of T regulatory (Treg) cells and the production of anti-inflammatory cytokines, including IL-10 and TGF-β [18].

The probiotics most commonly used are *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* [19-21].

Clinical benefits of probiotics depend on strain selection, dose and duration of administration, preservation in the gastrointestinal tract, and perhaps, combination of probiotics.

Probiotics and necrotizing enterocolitis and sepsis

Necrotizing enterocolitis (NEC) remains the most common gastrointestinal complication in premature infants with high mortality and long-term morbidity. The disease is characterized by extensive intestinal tissue necrosis and high serum level of proinflammatory cytokines. Current thinking suggests that NEC is not a single disease. Risk factors include prematurity of the innate and adaptive immune-responses, enteral feeding, an altered intestinal microbiota, and variation in intestinal perfusion [22]. A 2014 Cochrane review of trials, in preterm infants with less than 37 weeks gestation or birth weight (BW) less than 2,500 g, reported that preparations that contained bacterial strain of *Lactobacillus* alone or in combination with *Bifidobacterium* reduced the risk of NEC and mortality but had no effect on the rate of nosocomial sepsis. There was no conclusive evidence on the strain and on the optimal dose because there was a great deal of heterogeneity amongst the studies [23].

In a 2016 meta-analysis of 37 trials, probiotics were associated with a small, but statistically significant, reduction in the risk of late onset sepsis compared with placebo or no treatment [24]. In a subsequently multicenter double-blinded randomized trial involving > 1,300 preterm neonates (gestational age 23 to 30 weeks), treatment with the probiotic *Bifidobacterium breve* BBG-001 was not associated with reduction in sepsis or mortality compared with placebo [25].

The beneficial effect of probiotics is not apparent in infants with birth weights < 1,000 g. Further studies should be directed to the modulating gut microbes, or the products they produce, to prevent NEC [26].

Probiotics and diarrhea

Acute gastroenteritis has been defined by the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) as

a decrease in the consistency of stools and/or an increase in the frequency of evacuations (typically 3 in 24 hours), with or without fever or vomiting lasting 10-14 days. In 2014 the Working Group (WG) on Probiotics of the ESPGHAN recommended *Lactobacillus rhamnosus* GG (low Quality of Evidence [QoE], strong recommendation) and *Saccharomyces boulardii* (low QoE, strong recommendation) in acute gastroenteritis treatment in addition to rehydration therapy. The evidence is strong for these two probiotics in decreasing acute gastroenteritis duration and severity in children [27]. Less evidence is available for *Lactobacillus reuteri* DSM 17938 (very low QoE, weak recommendation) and heat-inactivated *Lactobacillus acidophilus* LB (very low QoE, weak recommendation) in acute gastroenteritis treatment in addition to rehydration therapy [27].

A 2015 Cochrane review acknowledged to *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* (at 5 to 40 billion colony forming units/day) a preventive role in diarrhea associated with antibiotic therapy [28].

The WG on Probiotics of the ESPGHAN in 2016, for the use of probiotics for the prevention of antibiotic-associated diarrhea in children, recommends using *Lactobacillus rhamnosus* GG (moderate QoE, strong recommendation) or *Saccharomyces boulardii* (moderate QoE, strong recommendation). If the use of probiotics for preventing *Clostridium difficile*-associated diarrhea is considered, the WG suggests using *Saccharomyces boulardii* (low QoE, conditional recommendation) [29].

A Cochrane review of 2013 recognized the ability of probiotics, given with antibiotic, to prevent diarrhea caused by *Clostridium difficile* but not in reducing its incidence [30, 31].

Probiotics and pediatric functional gastro-intestinal disorders

Alteration of the gut microbiota has been considered as a possible mechanism for the development of functional gastro-intestinal disorders (FGID). Dysbiosis might alter visceral perception, intestinal motility and fermentation and gut permeability leading to FGID-specific symptoms [32]. The Child/Adolescent Committee for Rome IV quoted two papers supporting the utility of probiotics in the treatment of irritable bowel syndrome (IBS) [33, 34]. However, they recommended pathophysiology studies of microbiome-brain-gut axis for the future research [35].

Infant colic has been described as a behavioral syndrome in 1- to 4-month-old infants involving long periods of crying and, although self-limiting and benign, it is stressful for the family and difficult to treat. The pathogenesis is still unclear. Probiotics have been used in different clinical trials for treatment and prevention of infant colic in breastfed or formula-fed infants. Systematic reviews and meta-analysis concluded that *Lactobacillus reuteri* DSM 17938 might have a role in treating but not in prevention of infant colic in breastfed infants (low QoE) [32] and other studies have confirmed that *Lactobacillus reuteri* DSM 17938 can reduce infant crying relative to controls [36]. However, the absence of clear data and regional differences in gut microbioma in the different studies might explain why there is no clear position of Societies and Institutions for the use of probiotics and prebiotics in infant colic [36, 37].

IBS is a FGID characterized by the association of abdominal pain with a change in stool pattern in which the symptoms cannot be fully explained by another medical condition.

The etiology of IBS is still debated but recent research suggests a complex interaction between the microbiome, the gut and the brain. The enteric bacteria may modulate visceral pain responses via neurologic, endocrine or immunologic activities [35-38]. A meta-analysis concluded that the use of *Lactobacillus rhamnosus* GG moderately increases treatment success in children with FGID, particularly with IBS. A recent systematic review on non-pharmacologic treatment of FGIS concluded that although high quality studies are lacking, some evidence shows efficacy of probiotics (*Lactobacillus rhamnosus* GG and VSL#3®) in reducing the frequency and severity of abdominal pain in children with IBS [33, 37-40].

Functional constipation is a common problem in childhood. Constipation is associated with symptoms such as painful defecation, abdominal pain and fecal incontinence. In 2014, the ESPGHAN and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) developed an evidence-based management of children with constipation and evaluated different treatment options and probiotics. The analysis of the literature showed no effect of probiotics in improving constipation in children [32, 41].

Probiotics and inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic relapsing inflammatory disorder of the gastrointestinal tract, comprising ulcerative colitis (UC) and Crohn's disease (CD).

A recent systematic review in 2014 showed inconclusive evidence of a beneficial role of probiotics in the induction or maintenance of remission in CD. Well-designed randomized controlled trials are needed to determine if there is any benefit with the use of probiotics in the treatment of CD [42].

There is some evidence to support the use of probiotics for induction and maintenance of remission in UC [43]. For pouchitis, the evidence appears to support a role for VSL#3® as a maintenance therapeutic option when pouchitis is in remission. However, the limited data available do not support the use of probiotics as primary therapy for pouchitis [42].

In UC, *Escherichia Coli* Nissle 1917 (200 mg daily) is equivalent to standard doses of mesalazine in maintaining remission and therefore may be an option for patients who are unable to take mesalazine [43].

Future studies are needed to confirm whether probiotics, have a definite role in induction or maintenance of remission in CD, UC, and pouchitis [42].

Probiotics and allergy

There is currently no positive recommendation from international scientific medical Societies to use prebiotics or probiotics for treatment of food allergy or other allergic manifestations and for prevention of food allergy, allergic rhinitis, and asthma [44]. Discrepant recommendations exist for probiotics for prevention of eczema in high-risk infants [44].

According to the 2015 World Allergy Organization guidelines, made with Grading of Recommendations Assessment, Development and Evaluation methodology, probiotics are effective in the prevention of atopic dermatitis in pregnant women at high risk for allergy in their children, in woman who breastfeed infants at high risk of developing allergy and in infants at risk of developing allergies (very low QoE) [45].

Conclusion

The effectiveness of a probiotic treatment is affected by many factors including: bacterial strain, duration of administration, disease and age. Not all products, marketed as probiotics provide the same safety and efficacy.

In conclusion, since there is insufficient data regarding the benefits and potential adverse effects of probiotics, comparative studies are mandatory to assess the most effective formulations, timing and the optimal length of therapy.

Acknowledgements

Special thanks to Dr. Mauro Congia for his help in the paper's revision.

Declaration of interest

The Author has no conflicts of interest to declare.

References

1. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M, Gill SR, Nelson KE, Relman DA. Diversity of the human intestinal microbial flora. Science. 2005;308:1635-8.
2. The Human Microbiome Project Consortium. Structure, function and diversity of the health human microbiome. Nature. 2012;486:207-14.
3. Zoetendal EG, Rajilić-Stojanović M, de Vos WM. High-throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut. 2008;57:1605-15.
4. Fallani M, Young D, Scott J, Norin E, Amarri S, Adam R, Aguilera M, Khanna S, Gil A, Edwards CA, Doré J; Other Members of the INFABIO Team. Intestinal microbiota of 6 week old infants across Europe: geographic influence beyond delivery mode, breast feeding and antibiotics. J Pediatr Gastroenterol Nutr. 2010;51:77-84.
5. Rosser EC, Mauri C. A clinical update on the significance of the gut microbiota in systemic autoimmunity. J Autoimmun. 2016;74:85-93.
6. Hamer HM, Jonkers D, Venema K, Vanhoutvin S, Troost FJ, Brummer RJ. Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther. 2008;27:104-19.
7. Cerf-Bensussan N, Routhiau U. The immune system and the gut microbiota: friends or foes? Nat Rev Immunology. 2010;10:735-44.
8. Sekirov I, Russel S, Antunes L, Finlay B. Gut microbiota in health and disease. Physiol Rev. 2010;90:859-904.
9. Kaplan JL, Shi HN, Walker WA. The role of microbes in developmental immunologic programming. Pediatr Res. 2011;69(6):465-72.
10. Vael C, Desager K. The importance of the development of the intestinal microbiota in infancy. Curr Opin Pediatr. 2009;21(6):794-800.
11. Murgas Torrazza R, Neu J. The developing intestinal microbiome and its relationship to health and disease in the neonate. J Perinatol. 2011;31(Suppl 1):S29-34.
12. World Health Organization/Food and Agriculture Organization of the United Nations. Probiotics in food. Health and nutritional properties and guidelines for evaluation. FAO Food and Nutrition Paper 85. Available at www.fao.org/3/a-a0512e.pdf, date of publication: 2006, last access: May 2017.

13. Ingrassia I, Leplingard A, Darfeuille-Michaud A. Lactobacillus casei DN-114 001 inhibits the ability of adherent-invasive Escherichia coli isolated from Crohn's disease patients to adhere to and to invade intestinal epithelial cells. Appl Environ Microbiol. 2005;71:2880-7.
14. Johnson-Henry KC, Nadjafi M, Avitzur Y, Mitchell DJ, Ngan BY, Galindo-Mata E, Jones NL, Sherman PM. Amelioration of the effects of Citrobacter rodentium infection in mice by pretreatment with probiotics. J Infect Dis. 2005;191:2106-17.
15. Ewaschuk JB, Diaz H, Meddings L, Diederichs B, Dmytrash A, Backer J, Looijer-van Langen M, Madsen KL. Secreted bioactive factors from Bifidobacterium infantis enhance epithelial cell barrier function. Am J Physiol Gastrointest Liver Physiol. 2008;295: G1025-34.
16. Ukena SN, Singh A, Dringenberg U, Engelhardt R, Seidler U, Hansen W, Bleich A, Bruder D, Franzke A, Rogler G, Uerbaum S, Buer J, Gunzer F, Westendorf AM. Probiotic Escherichia coli Nissle 1917 inhibits leaky gut by enhancing mucosal integrity. PLoS ONE. 2007;2:e1308.
17. Mennigen R, Nolte K, Rijcken E, Utech M, Loeffler B, Senninger N, Bruewer M. Probiotic mixture VSL#3 protects the epithelial barrier by maintaining tight junction protein expression and preventing apoptosis in a murine model of colitis. Am J Physiol Gastrointest Liver Physiol. 2009;296:G1140-9.
18. Gareau MG, Sherman P M, Walker WA. Probiotics and the gut microbiota in intestinal health and disease. Nat Rev Gastroenterol Hepatol. 2010;7(9):503-14
19. Floch MH, Walker WA, Madsen K, Sanders ME, Macfarlane GT, Flint HJ, Dieleman LA, Ringel Y, Guandalini S, Kelly CP, Brandt LJ. Recommendations for Probiotic Use – 2011 Update: Proceedings and Consensus Opinion. Clin Gastroenterol. 2011;45(Suppl):S168-71.
20. Floch MH, Walker WA, Sanders ME, Nieuwdorp M, Kim AS, Brenner DA, Qamar AA, Miloh TA, Guarino A, Guslandi M, Dieleman LA, Ringel Y, Quigley EM, Brandt LJ. Recommendations for Probiotic Use – 2015 Update: Proceedings and Consensus Opinion. J Clin Gastroenterol. 2015;49(Suppl 1):S69-73.
21. Hsieh MH. The microbiome and probiotics in childhood. Semin Reprod Med. 2014;32:23-7.
22. Mc Elroy SJ, Underwood MA, Sherman MP. Paneth cells and necrotizing enterocolitis: a novel hypothesis for disease pathogenesis. Neonatology. 2013;103:10-20.
23. Alfaleh K, Anabrees J. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2014;CD005496
24. Rao SC, Athalye-Jape GK, Deshpande GC, Simmer KN, Patole SK. Probiotic Supplementation and Late-Onset Sepsis in Preterm Infants: A Meta analysis. Pediatrics. 2016;137(3):e20153684.
25. Costeloe K, Hardy P, Juszczak E, Wilks M, Millar MR. Bifidobacterium breve BBG-001 in very preterm infants: a randomized controlled phase 3 trial. Lancet. 2016;387:649-60.
26. Warner BB, Tarr PI. Necrotizing enterocolitis and preterm infant gut bacteria. Semin Fetal Neonatal Med. 2016;21(6):394-9.
27. Szajeska H, Guarino A, Hojsak I, Indrio F, Kolacek S, Shamir R, Vandenplas Y, Weizman Z. 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.
28. Goldenberg JZ, Lytvyn L, Steurich J, Parkin P, Mahant S, Johnston BC. Probiotics for prevention of pediatric antibiotic associated diarrhea. Cochrane Database Syst Rev. 2015;(12):CD004827.
29. Szajewska H, Canani RB, Guarino A, Hojsak I, Indrio F, Kolacek S, Orel R, Shamir R, Vandenplas Y, van Goudoever JB, Weizman Z; ESPGHAN Working Group for Probiotics Prebiotics. Probiotics for the Prevention of Antibiotic-Associated Diarrhea in Children. J Pediatr Gastroenterol Nutr. 2016;62(3):495-506.
30. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for prevention of Clostridum difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev. 2013;(5):CD006095.
31. Evans CT, Johnson S. Prevention of Clostridium difficile infection with Probiotics. Clin Infect Dis. 2015;60(Suppl 2):S122.
32. Francavilla R, Cristofori F, Indrio F. Indications and Recommendations by Societies and Institutions for the Use of Probiotics and Prebiotics in Paediatric Functional Intestinal Disorders. J Pediatr Gastroenterol Nutr. 2016;63(Suppl 1):S36-7.
33. 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.
34. Guandalini S, Magazzu G, Chiaro A, La Balestra V, Di Nardo G, Gopalan S, Sibal A, Romano C, Canani RB, Lionetti P, Setty M. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo controlled, double bind, crossover study. J Pediatr Gastroenterol Nutr. 2010;51:24-130.
35. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, Van Tilburg M. Childhood functional gastrointestinal disorders: child/ adolescent. Gastroenterology. 2016;150:1456-68.
36. Benninga MA, Nurko S, Faure C, Hyman PE, St James Roberts I, Schechter NL. Childhood functional gastrointestinal disorders: neonate/toddler. Gastroenterology. 2016;150:1443-55.
37. Harb T, Matsuyama M, David M, Hill RJ. Infant colic-what works: a systematic review of interventions for breast fed infants. J Pediatr Gastroenterol Nutr. 2016;62:668-86.
38. Chichlowski M, Rudolph C. Visceral pain and gastrointestinal microbiome. J Neurogastroenterol Motil. 2015;21(2):172-81.
39. 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.
40. Rutten JM, Korterink JJ, Venmans LM, Benninga MA, Tabbers MM. Nonpharmacologic treatment of functional abdominal pain disorders: a systematic review. Pediatrics. 2015;135:522-35.
41. Tabbers MM, DiLorenzo C, BergerMY, Faure C, Langendam MW, Nurkos S, Staiano A, Vandenplas Y, Benninga MA. Evaluation and treatment of functional constipation in infants and children: evidence-based recommendations from ESPGHAN and NASPGHAN. J Pediatr Gastroenterol Nutr. 2014;58:258-74.
42. Ghouri YA, Richards, DM, Rahimi EF, Krill JT, Jelinek KA, DuPont AW. Systematic review of randomized controlled trials of probiotics,

prebiotics, and synbiotics in inflammatory bowel disease. Clin Exp Gastroenterol. 2014;7:473-87.

43. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, Mitton S, Orchard T, Rutter M, Younge L, Lees C, Ho G, Satsangi J, Bloom S. Guidelines for the management of inflammatory bowel disease in adults. Gut. 2011;60:571-607.
44. Koletzko S. Probiotics and Prebiotics for Prevention of Food Allergy: Indications and Recommendations by Societies and Institutions. J Pediatr Gastroenterol Nutr. 2016;63(Suppl 1):S9-10.
45. Fiocchi A, Pawankar R, Cuello-Garcia C, Ahn K, Al-Hammadi S, Agarwal A, Beyer K, Burks W, Canonica GV, Ebisawa M, Gandhi S, Kamenwa R, Wah Lee B W, Li H, Prescott S, Riva JJ, Rosenwasser L, Sampson H, Spigler M, Terracciano L, Vereda-Ortiz A, Waserman S, Yepes-Nuñez JJ, Brożek JL, Schünemann HJ. World Allergy Organization-McMaster University Guidelines for Allergic Disease Prevention (GLAD-P): Probiotics. World Allergy Organ J. 2015;8(1):4.