

# Research Journal of Pharmaceutical, Biological and Chemical Sciences

## Probiotics And Its Use To Ease The Digestive Tract Problems In Children: A Review.

Sudha M\*, and Auslin S.

Department of Pharmacy Practice, J.K.K.Nattraja College of Pharmacy, Kumarapalayam-638183, Tamil Nadu, India.

### ABSTRACT

Gastrointestinal disease is one of the most important reason for morbidity and mortality among paediatrics within developing countries. This review article proposes about the utilization of probiotics among paediatrics for gastrointestinal disorders. Probiotics are active living microorganisms that are taken by paediatrics for their preventive or therapeutic effects on a wide variety of diseases, particularly for gastrointestinal disorders such as functional intestinal disorders, diarrhea, necrotizing enterocolitis, inflammatory bowel disease, infant colic and irritable bowel syndrome. Probiotics produce its beneficial effect by enhancing the gut barrier function and modulation of immune function. Examples of some specific probiotic organisms essential for infants includes *Lactobacillus rhamnosus*, *Lactobacillus casei*, *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Bifidobacterium lactis* and *Bifidobacteria infantis*. Administration of probiotics to children's through mouth can decreases the extent of gastrointestinal symptomps like diarrhoea. Because of its beneficial effect they are extensively used in medical practice.

**Keywords:** probiotics in pediatrics, gastrointestinal disorders, probiotic therapy

<https://doi.org/10.33887/rjpbcs/2019.10.6.22>

*\*Corresponding author*

## INTRODUCTION

Gastrointestinal disease is common among paediatrics and it is one of the most important reason for morbidity and mortality among paediatric population in developing countries.[1] Gastrointestinal diseases such as chron’s disease, ulcerative colitis and irritable bowel syndrome can induce diarrhoea. Diarrhoea is one of the chief cause for death in infants of age not more than 5 years.[2] Human gut consists of various types of microbe which is called as gut microbials. They are absent at the moment of birth.[2] Breast milk gives the most tremendous protection for infants as it contains beneficial bacteria which colonize in babies gut after birth. Disruption of gut microbata leads to occurrence of various gastrointestinal diseases which commonly affect the paediatric population. During such condition treating the paediatric population with probiotics decreases the progression of disease.[3]

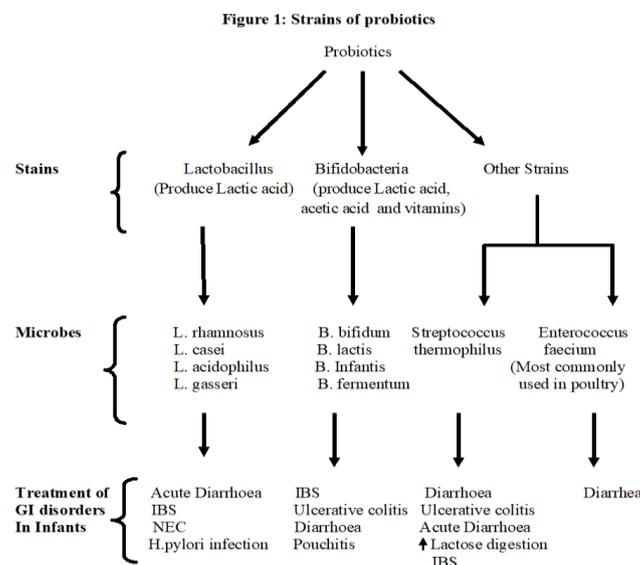
Probiotics can be defined as living microorganisms which gives health related benefit to the patients when administered in enough amount.[2] These probiotic microorganisms are obtained by fermentation process which is non-pathogenic and helpful.[3] Non-pathogenic bacteria are also present naturally in human gut. This bacterial flora in intestine produces some beneficial effect by involving in digestion of foods and metabolism of carcinogen. It act as a barrier by fighting against pathogenic organisms.[3]

Probiotics are utilized to treat a broad range of diseases that affect animals and humans. It rebuilds the normal balance of living organism in the intestinal tract.[2] The gut of human have a germ free environment until birth. After birth, they are exposed to a broad diversity of bacteria. These bacteria will be there for the rest of the individual’s life. During early childhood, the gastrointestinal immune system will recognize some bacteria as good and some as bad. Later on, any intake of such harmful bacteria will alter the normal gut microbial flora and initiate the immune response against the harmful bacteria. [4]

### NATURE OF MICROBIAL FLORA PRESENT IN GUT

The gut microflora is considered as a diversified ecosystem which helps in supporting the structure in addition to the functioning of the mucosa in intestine. The bacteria present in intestine acts as a filtering aid to the gut by fighting against many pathogenic bacteria, amplifying mucin secretion, diminishing the gut porosity and by modifying the gut’s immune function.[5] The colonic bacteria helps in metabolizing the unabsorbed carbohydrates into short chain fatty acids (SCFA). Short chain fatty acid is a favourable form of energy for the enterocytes. Colonic bacteria also involve in acidification of colonic content by production of SCFA and further increase the amount of water absorption. It produces antitoxins and antimicrobial compounds. Probiotics compete with other bacteria for adhesion receptors within cell surface and act as a physical barrier.[6] They also helps in absorption of iron, magnesium, calcium and synthesis of folic acids, vitamin B and K.[5]

### Strains of probiotics



**Lactobacillus:** Lactobacillus is also recognized as Lactic acid bacteria, which is one among the largely essential probiotic microorganism that is present in the gastrointestinal tract. Examples of some specific probiotic lactobacillus essential for infants comprises: Lactobacillus rhamnosus (also called Lactobacillus GG), Lactobacillus casei and Lactobacillus acidophilus.[7] Lactobacillus acidophilus has its effect against some microbial organisms such as Staphylococcus aureus, Salmonella, Escherichia Coli and Candida albicans. Lactobacillus brevis, is a probiotic which produces lactic acid by using an enzyme called lactase. It also involves in synthesizing Vitamins D and K. Lactobacillus rhamnosus is another probiotic flora which is highly tolerable to bile salts, surviving in less than favorable environments. So it has beneficial activity for infants and elderly people. Rhamnosus assist with lactose intolerance, it also involves in protecting the small intestine.[8]

**Bifidobacteria:** Bifidobacterium bifidum is one of the familiar probiotic flora belonging to category bifidobacteria. It inhibits the invading of pathogenic bacteria. Bifidobacterium bifidum lives inside the lining of mucus in large intestine produces some organic acids such as lactic acid and acetic acid which prevent the development of harmful bacteria.[8] It also produce some vitamins such as folic acid which helps to absorb nutrients. This species catalyse the absorption of iron, calcium, magnesium and zinc. Examples of some specific probiotic bifidobacteria includes Bifidobacterium bifidum, Bifidobacterium lactis and Bifidobacteria infantis.[7]

**Other Strains:** Streptococcus thermophilus is another probiotic which is utilized in making of yogurt and cheese. It break lactose inorder to create lactase, which is the enzyme that involves in digestion of milk sugars. These strains of bacteria also produce some antibiotic chemicals which can keep away from infections like C. Difficile , pneumonia and also help to prevent ulcers. Other strains of Streptococcus include faecium. cremoris and infantis. Some studies has shown that enterococcus faecium can relieve diarrhoea and also decrease the duration of symptoms.[7,8]

#### **FEATURES OF AN IDEAL PROBIOTIC MICROFLORA**

An ideal probiotic must be non pathogenic. It must stick on to epithelium present in intestine and generate antimicrobial substances. It must contain sufficient number of workable cells which shouldn't be affected by gastric acid or bile or technical processing. A good probiotic flora must be alive in the gastrointestinal tract, even for a short period of time. It must be able to adapt to immune responses.[9]

#### **SHIELDING PROPERTY OF PROBIOTICS**

The shielding property of probiotics takes place by direct antagonism towards the harmful pathogens through the competitive adherence to mucosa and epithelium and thereby strengthen the intestinal epithelial barrier. It also modulate the immune system by stimulating the cytokine production and enhancing the production of immunoglobulin secreting cells in the intestinal mucosa. Probiotics involve in transporting of antigens to submucosal lymphocytes to ensure immediate immune reaction against pathogens.[9,10]

The frequently utilized probiotics include Lactobacillus and Bifidobacterium species which produce propionic acid, acetic acid, and lactic acid which involve in lowering the intestinal pH and control the growth of different pathogenic bacterial organisms and thereby restore the equilibrium of the gut flora.[7]

#### **PROBIOTIC MICROFLORA ATTENUATING THE DIGESTIVE DISORDERS**

##### **Probiotic bacterium for infectious diarrhoea**

Diarrhoea is the foremost reason for morbidity and death among children's beneath 5 years of age in worldwide.[2,11] Probiotics are used for the treatment of acute diarrhoeal infection which is triggered by bacteria, but there are some variance in the results considering the outcome of probiotics use in viral diarrhoea. Administration of probiotics through mouth decreases the extent of acute infectious diarrhoea caused by bacteria in children nearly by one day. It was found that lactobacillus reduces the extent of acute diarrhoeal episodes, and decreases the stool frequency.[12]

One of the most significant virus that largely cause acute diarrhoeal episodes is rotavirus. The probiotic therapy has found to normalise the gut permeability in infectious diarrhoea after rotavirus infection,

and also amplify the expression of mucin and IgA-secreting cells which has the ability to work against rotavirus.[13]

Clinical studies have revealed that probiotics such as *L. reuteri*, *L. casei* Shirota, *L. rhamnosus* GG and *Bifidobacterium lactis* Bb12 are safe for the nutritional management of patients with acute infectious diarrhoea. It has been established that paediatrics with more severe diarrhoea has no provable benefit. [14]

#### **Probiotic bacterium for Antibiotic-associated diarrhoea**

Antibiotic associated diarrhoea (AAD) is diarrhoea that often occurs when antibiotics are taken with the omission of other etiologies. AAD is one of the main problem among paediatrics owing to the overuse of antibiotics among them.[15] Antibiotic therapies involves in altering the biological equilibrium of bacterial microflora in intestine, which bring into various clinical symptoms, mainly diarrhoea. AAD occurrence among children's is about 10 % in 1<sup>st</sup> line treatment with antibiotics. Children under 2 years of age are more prone to suffer from an events of AAD, particularly those who are treated with antibiotics like amoxicillin or its combination such as amoxicillin and clavulanic acid.[16] AAD possibly will occur following a few weeks and can even occur after a few months after antibiotics administration.[15]

Several studies proposed that probiotics, such as *Saccharomyces boulardii* CNCM I-745 and *L. rhamnosus* GG, prevent AAD.[17] However the exact mechanism is not clear. But some studies propose that antibiotics induce some disruption in gut microflora which further leads to reduction of SCFA production and Na dependent fluid absorption. So probiotics when given in required amount produces beneficial effect among paediatric populations.[16]

The suggested dose of *L. rhamnosus* GG is 10<sup>11</sup> CFU/capsule given twice daily and the dose of *Saccharomyces boulardii* is 250 mg twice daily.[17] Investigations have revealed that probiotic use has reduced the mean period of diarrhoea by three-quarters of a day.[18]

#### **Probiotic bacterium for Traveler's diarrhoea**

Children moving to areas with hot climates and underdeveloped countries might experience a high occurrence of diarrhea.[19] There are no paediatric studies/ evidences regarding the decrease in episodes of traveller's diarrhoea using probiotics. A meta-analysis on adult trials illustrated a statistically significant shielding effect for different types of probiotics, but the majority of these studies had major limitations. It has been carry out to assess probiotic in stopping of traveler's diarrhoea. Mainly *Lactobacillus* GG has been utilized and it has considerably decreased the incidence of traveler's diarrhea.[20]

#### **Probiotic bacterium for Infant colic**

Infantile colic can be defined as the paroxysm of crying owing to abdominal pain for  $\geq 3$  hours a day, which occur 3 days or more per week for 3 weeks, among healthy infants aged from 2 weeks to 3 months. Colic is a disturbing condition in infants that often requires medical consultation and treatment.[21] It affects about 5% of newborns and 19 % of infants in the initial months of life.[22] Due to changes in gut microbata, dysbiosis play a role in the pathophysiology of infant colic. It affects the gut motor functions and gas production, which further result in abdominal pain among infants. Probiotics has been recommended to treat infants with colic crying.[23] Roos et al., [24] concluded that higher level of gut microbata in infants had reduced colicky. Probiotics supplementation, particularly *L. Reuteri* in infants of age beneath 6 months with the dose of 10<sup>8</sup> CFU once daily seems to be harmless and effective in the treatment of infantile colic pain without causing any notable side effects.[25] Early management with probiotics in newborns with colic provided relief from their crying and fussing however, delayed management with probiotics in newborns might increase the risk of irritability. [25]

#### **Probiotic bacterium for Inflammatory Bowel Disease (IBD)**

IBD is a term for two conditions such as ulcerative colitis and crohn's disease. In ulcerative colitis (UC) the inflammatory response is restricted to the mucosa and submucosa of colon whereas in Crohn's disease (CD), the whole intestinal tract can involve and the inflammation can persist throughout the intestinal wall

from mucosa to serosa.[26] The correct etiology of IBD is unknown, however both genetic and environmental factors are considered to be some factors. The bacterial flora in intestine is considered to be a significant factor in the development and reappearance of IBD.[27] The theory of dysbiosis is an inequality among 'protective' and 'harmful' bacteria present in intestine is an etiologic factors of IBD. Preliminary reports specify that there are advantages achieved by probiotic intervention in reversing some immunological disturbances, in modification of disease activity and in normalisation of increased intestinal permeability in children with Crohn's disease.[28]

For ulcerative colitis, advantageous effect have been illustrated for a combination of Bifidobacterium, Lactobacillus and Streptococcus probiotic species for reduction of disease activity in mild to moderately severe ulcerative colitis.[29] In paediatrics with ulcerative colitis probiotics must be started during onset of exacerbation of the disease and should be continued for one to two weeks until resolution of symptoms.[27]

#### **Probiotic bacterium for Pouchitis**

Pouchitis is a chronic inflammation in ileal reservoir formed after colectomy and ileal pouch anal anastomosis.[30] Probiotics play a most promising role in treatment of pouchitis among paediatrics. There are some evidences regarding utilization of probiotics like Lactobacilli, Bifidobacteria and Streptococcal for preventing an initial attack of pouchitis, and further prevent its relapse after remission.<sup>31</sup> Probiotics are also recommended for paediatrics with pouchitis having mild activity and for patients with remission as maintenance therapy.[31]

#### **Probiotic bacterium for Irritable Bowel Syndrome (IBS)**

IBS is one of the common disorders among paediatrics due to irritation of bowel which is mainly caused due to alteration of gut microbial flora, which can be common among paediatric populations. The symptoms include bloating, cramps, abdominal pain, and disturbed bowel habits.[32] Many studies suggested that prescribing the paediatrics with probiotics reduced the incidence of IBS and also reduced the symptom's like abdominal boating and flatulence by suppressing the low grade inflammation corresponding to IBS and also by normalizing the immune function .[33,32]

#### **Probiotic bacterium for Helicobacter pylori infection (H.pylori)**

H.pylori is a spiral shaped gram negative bacterium which is pathogenic for infants. It affects the GI tract by colonizing in gut mucosa. H.pylori affects more than half of the population in world wide.[34] Many invitro studies propose that various strains of probiotics particularly lactobacillus exhibit antagonistic property against H.pyloric infections.[35] Intestine consist of lactic acid bacteria which produces volatile fatty acids, this fatty acids have antibacterial property and there by fight against infections.[36]

Bacteriocin is a substance produced by bifidobacteria, a probiotic bacterium which has anti H.pyloric property and also fight against gram positive and gram negative pathogenic bacteria.[37]

Certain lactobacilli can put forth their antiadhesion action against H.pylori by producing some antimicrobial substances. However, strains such as L. reuteri can be able to inhibit H. pylori growth by opposing with adhesion receptors. It has been recommended that intake of probiotic supplements can strengthen the mucosal barrier by inducing the synthesis of mucin. However, probiotics alone can give only minimal effect on against H. pyloric infection, so it is recommended to be given along with antibiotics.[38]

#### **Probiotic bacterium for Necrotizing enterocolitis (NEC)**

One of the most frequently emerging gastrointestinal problem with ischemic necrosis in intestinal mucosa is necrotizing enterocolitis (NEC). In necrotizing enterocolitis, severe inflammation occurs along with invading of enteric gas-forming organisms, and dissection of gas into the portal venous system and the intestinal wall.[39] NEC causes some changes in intestinal permeability which further affects the intestinal bacteria.[40] The relationship of NEC with acid suppressants and long term utilization of antibiotics can alter the infant's microbial flora in intestine, and also supports the abnormal gut bacteria.[41] Probiotic supplementation decreases the probability for occurrence of necrotizing enterocolitis among preterm

neonates. A meta-analysis of probiotic studies conducted on strains of *Saccharomyces*, *Bifidobacterium*, *Lactobacillus*, and *S thermophilus* to prevent necrotizing enterocolitis states that, there is a drop in frequency and overall mortality rate among infants.[42] So probiotic therapy can be started in those at risk of NEC and it should be continued as long as the risk persists.[41]

### **Probiotic bacterium for Food allergies**

A meta-analysis on “Probiotics as treatment for food allergy among paediatric” states that, probiotics can effectively relieve allergic symptoms in infants caused due to cow’s milk. However, there is reduction in confidence due to imprecise results.<sup>43</sup> Many studies states that *Lactobacillus rhamnosus* GG administration in paediatrics induces acceptance among infants for suspected cow’s milk allergy. [44,45]

### **Safety and Precaution**

Probiotics are considered to be safe and efficient among pediatric populations, but special care must be given for vulnerable population. Due to its beneficial effect they are widely used in medical practice.[46] However, as they are living microorganisms they are capable of producing active infections, but the risk quite low.[47] The most frequently reported adverse effect of probiotics are sepsis and fungemia. Critically ill infants in ICU and immune compromised patients are at high risk for sepsis due to probiotics.[47] *Lactobacillus* Sepsis have been reported on intake of probiotic supplements especially in immune compromised patients and in patients with endocarditis. So probiotics must be prescribed after considering the risk-benefit ratio in infants.[48]

### **CONCLUSION**

This review demonstrates the scientific evidence in both the beneficial and risky use of probiotics among paediatric population. Probiotics are found to be useful in treatment of various gastrointestinal disorders, including infectious diarrhoea, antibiotic associated diarrhoea, and traveler's diarrhoea which occur in pediatric population but the strain specificity of probiotics play a major role in it. Most of the available literature and data’s showed that, probiotics are most effective in treatment of GI disorders. There by we conclude that probiotics are found to reduce the gastrointestinal discomfort among paediatrics and is also considered to be safe in children with some precaution.

### **REFERENCES**

- [1] Fischer Walker CL, Perin J, Aryee MJ, Boschi-Pinto C, Black RE. Diarrhea incidence in low- and middle-income countries in 1990 and 2010: a systematic review. *BMC Public Health*. 2012; 12: 220.
- [2] Salminen S, Gibson C, Bouley MC, Cummings JH, Franck A, Gibson GR, Isolauri E, Moreau MC, Roberfroid M, Rowland. *Gastrointestinal physiology and function: the role of prebiotics and probiotics*. *British Journal of Nutrition*. 1998; 80(1): S147–171.
- [3] The scoop on probiotics. *Consumer Reports on Health*. 2015; 27(8): 9.
- [4] Vanderhoof JA, Young R. Probiotics in the United States. *Clinical Infectious Disease*. 2008; 46(2): S67-S72.
- [5] Mack DR, Michail S, Wei S, McDougall L, Hollingsworth MA. Probiotics inhibit enteropathogenic *E. coli* adherence in vitro by inducing intestinal mucin gene expression. *American Journal of Physiology*. 1999; 276(1) :G941-50.
- [6] Cebra JJ, Periwal SB, Lee G, Lee F, Shroff KE. Development and maintenance of the gut-associated lymphoid tissue (GALT): The roles of enteric bacteria and viruses. *Developmental Immunology*. 1998; 6(1-2): 13-18.
- [7] N. T. William. “Probiotics,” *American Journal of Health System*. 2010; 67(6): 449–458.
- [8] Dash, S. K. *The Consumer’s Guide to Probiotics: The Complete Source Book*. Topanga, CA: Freedom Press. 2005.
- [9] Borchers, A., Selmi, C, Meyers, F., Keen, C., Gershwin M. Probiotics and immunity. *Journal of Gastroenterology*. 2009; 44(1), 26-46.
- [10] Indriyani S. Effects of live versus heat-killed probiotics on acute diarrhea in young children. *Paediatrica Indonesiana*. 2012; 52: 249–254.

- [11] Black RE, Cousens S, Johnson HL, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *Lancet*. 2010; 375: 1969–1987.
- [12] Allen, S., Martinez, E., Gregorio, G., Dans, L. (2010). Probiotics for treating acute infectious diarrhoea. *Cochrane Database Systematic Review* .2011; 129(3): 185-185.
- [13] Isolauri E. Probiotics for infectious diarrhoea. *Gut*. 2003; 52: 436–437.
- [14] Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomised, double blind, placebo-controlled trials. *The Journal of Pediatric Gastroenterology and Nutrition* .2001; 33: S17.
- [15] Alam S, Mushtaq M. Antibiotic associated diarrhea in children. *Indian Pediatrics*.2009; 46: 491-496.
- [16] Turck D1, Bernet JP, Marx J, Kempf H, Giard P, Walbaum O, Lacombe A, Rembert F, Toursel F, Bernasconi P, Gottrand F, McFarland LV, Bloch K. Incidence and risk factors of oral antibiotic associated diarrhea in an outpatient pediatric population. *The Journal of Pediatric Gastroenterology and Nutrition*. 2003; 37: 22–26.
- [17] Hickson M. Probiotics in the prevention of antibiotic-associated diarrhoea and *Clostridium difficile* infection. *Therapeutic Advances in Gastroenterology*. 2011; 4: 185-197
- [18] Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JNV, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *The Journal of the American Medical Association*. 2012; 307(18): 1959–1969.
- [19] Oksanen PJ, Salminen S, Saxelin M, et al. Prevention of travellers' diarrhea by *Lactobacillus GG*. *Annals of Medicine*.1990; 22: 53–56.
- [20] Scarpignato C, Rampal P. Prevention and treatment of traveler's diarrhea: A clinical pharmacological approach. *Chemotherapy*.1995; 42: 48-81.
- [21] Harb T, Matsuyama M, David M, Hill RJ. Infant Colic What works: A Systematic Review of Interventions for Breast fed Infants. *The Journal of Pediatric Gastroenterology and Nutrition*. 2016; 62: 668-686.
- [22] Savino F. Focus on infantile colic. *Acta Paediatrica*. 2007; 96: 1259–64.
- [23] Dryl, R.; Szajewska, H. Probiotics for management of infantile colic: A systematic review of randomized controlled trials. *Archives of Medical Science*. 2018; 14: 1137–1143.
- [24] Stefan Roos, Johan Dicksved, Valentina Tarasco, Emanuela Locatelli, Fulvio Ricceri, Ulf Grandin, and Francesco Savino . 454pyrosequencing analysis on faecal samples from a randomized DBPC trial of colicky infants treated with *Lactobacillus reuteri* DSM 17938. *PLoS One*. 2013; 8(2): e56710.
- [25] Anna Peartty, Raakel Luoto, Marko Kalliomeaki, Seppo Salminen, Erika Isolauri. Effects of early prebiotic and probiotic supplementation on development of gut microbiota and fussing and crying in preterm infants: A randomized, double-blind, placebo-controlled trial. *The Journal of Pediatrics*. 2013; 163(5): 1272-7. e2.
- [26] Russel MG, Stockbrugger RW. Epidemiology of inflammatory bowel disease: an update. *The Scandinavian Journal of Gastroenterology*.1996; 31: 417–27.
- [27] Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European collaborative study on inflammatory bowel disease (EC-IBD). *Gut*. 1996; 39: 690–7.
- [28] Isolauri E, Kirjavainen PV, Salminen S. Probiotic role in the treatment of intestinal infection and inflammation? *Gut*. 2002;50:54–9.
- [29] Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, Kamm MA, Weismueller J, Beglinger C, Stolte M, Wolff C, Schulze J. Maintaining remission of ulcerative colitis with the probiotic *Escherichia coli* Nissle 1917 is as effective as with standard mesalazine. *Gut*. 2004; 53: 1617–23.
- [30] Gionchetti P, Venturi A, Brigidi P, Matteuzzi D, Bazzocchi G, Poggioli G, Miglioli M, Campieri M. Oral bacteriotherapy as maintenance treatment in patients with chronic pouchitis: a double-blind, placebo-controlled trial. *Gastroenterology*. 2000; 119: 305-9.
- [31] Guarner F, Khan AG, Garisch J, Eliakim R, Gangl A, Thomson A, Krabshuis J, Lemair T, Kaufmann P, de Paula JA, Fedorak R, Shanahan F, Sanders ME, Szajewska H, Ramakrishna BS, Karakan T, Kim N. World Gastroenterology Organization. World Gastroenterology Organisation Global Guidelines: probiotics and prebiotics October 2011. *Journal of Clinical Gastroenterology* 2012; 46: 468-481.
- [32] Martens U, Enck P, Zieseniss E. Probiotic treatment of irritable bowel syndrome in children. *German Medical Science*. 2010; 8: 07.
- [33] Bauserman M, Michail S. The use of *Lactobacillus GG* in irritable bowel syndrome in children: a double-blind randomized control trial. *The Journal of Pediatrics*. 2005; 147: 197-201.

- [34] Rokka, S., S. Myllykangas, V. Joutsjoki. Effect of Specific Colostral Antibodies and Selected Lactobacilli on the Adhesion of *Helicobacter pylori* on AGS Cells and the *Helicobacter*-Induced IL-8 Production. *Scandinavian Journal of Immunology*. 2008; 68(3): p280-286.
- [35] Alsahli M, Michetti P. Lactobacilli for the management of *Helicobacter pylori*. *Nutrition*. 2001; 17: 268-269.
- [36] Collado, M.C, M. Hernandez, and Y. Sanz. Production of bacteriocin-like inhibitory compounds by human fecal *Bifidobacterium* strains. *Journal of Food Protection*. 2005; 68(5): p1034-40.
- [37] Lesbros-Pantoflickova D, Corthésy-Theulaz I, Blum AL. *Helicobacter pylori* and probiotics. *Journal of Nutrition*. 2007; 137: S812-818
- [38] Mukai T, Asasaka T, Sato E, Mori K, Matsumoto M, Ohori H. Inhibition of binding of *Helicobacter pylori* to the glycolipid receptors by probiotic *Lactobacillus reuteri*. *FEMS Immunology and Medical Microbiology*. 2002; 32: 105-110 .
- [39] Neu J, Walker WA. Necrotizing enterocolitis. *New England Journal of Medicine*. 2011; 364: 255.
- [40] Stratiki Z, Costalos C, Sevastiadou S, et al. The effect of a bifidobacter supplemented bovine milk on intestinal permeability of preterm infants. *Early Human Development*. 2007; 83 (9): 5759.
- [41] Carrion V, Egan EA. Prevention of neonatal necrotizing enterocolitis. *Journal of Pediatric Gastroenterology Nutrition*. 1990; 11(3): 317-323.
- [42] Deshpande G, Rao S, Patole S. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. *Pediatrics*. 2010; 125: 921–930.
- [43] Carol Stephanie C, Tan-Lim, Natasha Ann R. Esteban Ipac. Probiotics as treatment for food allergies among pediatric patients: a meta-analysis. *World Allergy Organization Journal*. 2018; 25: 1-13.
- [44] BerniCanani R, Nocerino R, Terrin G, Coruzzo A, Cosenza L, Leone L, et al. Effect of *Lactobacillus GG* on tolerance acquisition in infants with cow's milk allergy: a randomized trial. *Journal of Allergy and Clinical Immunology*. 2012; 129(2): 580–582.
- [45] BerniCanani R, Di Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di Scala C, Granata V, Nocerino R. Extensively hydrolyzed casein formula containing *Lactobacillus rhamnosus GG* reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. *Journal of Allergy and Clinical Immunology*. 2017; 139(6): 1906–1913.
- [46] Doron S, Snyderman DR. Risk and safety of probiotics. *Clinical Infectious Disease*. 2015; 60(2): S129-34.
- [47] Whelan K, Myers CE. Safety of probiotics in patients receiving nutritional support: a systematic review of case reports, randomized controlled trials, and nonrandomized trials. *American Journal of Clinical Nutrition*. 2010; 91(3): 687-703.
- [48] Sharp RR, Achkar JP, Brinich MA, Farrell RM. Helping patients make informed choices about probiotics: a need for research. *American Journal of Gastroenterology*. 2009; 104: 809-813