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ROLE OF PROBIOTICS AND PREBIOTICS IN PREVENTION AND TREATMENT OF DISEASES IN CHILDREN: AN EVIDENCE BASED CRITICAL ANALYSIS

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ABSTRACT

Probiotics are commonly used in pediatric office practice. The purpose of this clinical report is to review uses of probiotics and prebiotics in children and summarize what is currently known about their health benefits supported by evidence-based medicine. The guidance in this report will help paediatricians to make appropriate decisions regarding which prebiotic and probiotic to use in a particular disease and at what dose. Probiotics are beneficial for treating some diseases such as acute rota viral diarrhoea, antibiotic associated diarrhoea and preventing Necrotizing Enterocolitis. There might also be a beneficial effect in patients with colic and Irritable Bowel Syndrome. The role of probiotics remains unproven in preventing or treating atopic diseases. Caution should be exercised in giving probiotics to patients with immunodeficiency. The efficacy of probiotics is both strain, disease and dose-specific.

KEY WORDS: Probiotics, prebiotics, health benefits, children

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INTRODUCTION

Probiotics are typically members of the genera *Lactobacillus*, *Bifidobacterium* and *Streptococcus*. Their inherent biological features enable them to predominate and prevail over potential pathogenic microorganisms in the human digestive tract. The most studied probiotic to date include *Lactobacillus rhamnosus GG* (*LGG*), *Bifidobacterium lactis* and *Streptococcus thermophilus*.[1] Some yeasts are frequently used as probiotic agents such as *Saccharomyces boulardii*. Prebiotics are dietary substances that nurture a selected group of microorganisms in the gut. They favour the growth of beneficial bacteria over that of harmful ones. Unlike probiotics, most prebiotics are used as food ingredients especially in dairy products. Synbiotics are appropriate combinations of prebiotics and probiotics. A synbiotic product exerts both a prebiotic and probiotic effect. However, much ambiguity and confusion exist in the minds of the practitioners as regards the choice and dose of various strains of probiotics to be used in a specific disease. An attempt has been made on the basis of evidence based studies and reviews to update available knowledge so that a more rational approach can be made in decision making.

MATERTIALS AND METHODS

Various index journals, grey literatures, electronic database and references from previous reviews were extensively studied. Data from well-conducted randomized-controlled trials supporting the health benefits of probiotics in children were analyzed. In addition, the Cochrane database of Systematic Reviews was also searched. The results of various searches and reviews have been analysed for health effects of specific strains of probiotics in specific disease conditions at an appropriate dose in children.

RESULTS

Prevention of infectious diseases

In a recent observational study (771 infants), the group receiving a formula supplemented with synbiotics had significantly less overall infectious diseases (ID) compared with the control group (31.0% versus 40.6%; $P < 0.05$), whereas if analyzed for specific ID, frequency of gastrointestinal infections only remained significantly less (3.5% versus 6.8%; $P = 0.03$).[2] A randomized-controlled trial (RCT) demonstrated 30% reduction in the total number of ID in the probiotic group compared with the control group (incidence rate ratio: 0.70; $P = 0.003$). There was no effect on overall febrile episodes between the intervention and the control group in this study.[3] Fayol-Messaoudi et al [4] reported that *L. plantarum* strain ACA-DC287 displayed in vitro killing activity against Salmonella, similar to that exhibited by probiotic strains *L. rhamnosus GG* and *L. casei Shirota. L. rhamnosus* has shown to be a promising probiotic in preventing the colonization of the gastrointestinal tract by pathogenic bacteria such as *enteropathogenic E. coli, enterotoxigenic E. coli and Klebsiella pneumoniae* .[5] An RCT (571 children; 1–6 years of age) showed no difference in the occurrence of otitis media (OM) between the intervention group using *Lactobacillus rhamnosus GG* (*LGG*) and the control group [72% versus 65%; odds ratio = 1.48 (95% CI: 0.87– 2.52)] but difference towards the lower incidence of recurrent (≥4) upper respiratory tract infections (URTI) was demonstrated [odds ratio = 0.56 (95% CI: 0.31–0.99)].[6] 10 RCTs (including 8 RCTs involving children) from a recent Cochrane systematic review demonstrated that probiotics were better than placebo with regard to the incidence of URTI.[7]Infants who received formula supplemented with prebiotics for the first 6 months of life had a reduced risk for URTI [14/102 versus 30/104; RR: 0.5 (95% CI: 0.3–0.8)], and a reduced rate of recurrent respiratory tract infections [3% versus 10%; RR: 0.3 (95% CI: 0.09–0.99)].[8]

Treatment of Acute Infectious Diarrhoea

In a recently published Cochrane systematic review including 56 studies with children, the authors conclude that probiotics have clear beneficial effects in shortening the duration of acute infectious diarrhoea by a median of 24.76 hours (95% CI: 15.9–33.6 hours; 35 trials; >4500 participants) and in reducing mean stool frequency on day 2 (mean difference 0.8; 0.45–1.14; 20 trials; >2700

participants).[9] Results from an updated meta-analysis of RCTs (5 RCTs; 944 participants) investigating the impact of *Saccharomyces boulardii* on treatment of acute (viral) gastroenteritis in children also demonstrated a reduction in the duration of diarrhoea by a median of 1.08 days (95% CI: −1.64 to −0.53) in the probiotic intervention group compared with the control group.[10]

Prevention of Antibiotic-Associated Diarrhoea

A meta-analysis of 6 RCT results demonstrated a reduced risk for developing antibiotic-associated diarrhoea from 28.5% to 11.9% [RR: 0.44 (95% CI: 0.25–0.77); *P* = 0.006; number needed to treat = 7].[11]A re-cently published Cochrane systematic review also demonstrated that high-dose prebiotics had a protective effect towards preventing antibiotic-associated diarrhoea in children in comparison with placebo [prevalence 8% versus 22%; RR: 0.40 (95% CI: 0.29–0.55); benefit observed in 1 in 7 children treated].[12]According to 1 reported meta-analysis, probiotic treatment significantly reduced odds of antibiotic-associated diarrhoea as compared with placebo [odds ratio (OR): 0.39 (95% CI: 0.25–0.62); *P* < .001] for both the yeast by-products *S boulardii* and *LGG*.[13]

Treatment of Antibiotic-Associated Diarrhoea

No published RCT of children has investigated the effect of probiotics for the treatment of antibiotic-associated diarrhoea. Thus, their use cannot be recommended. An adult meta-analysis found no evidence to support the use of probiotics in the treatment of *Clostridium difficile*.[14] Till date there has been no pediatric RCT.

Role in critical illness

Marrow *et al*[15] conducted a prospective, randomized, double-blind, placebo-controlled trial of 146 mechanically ventilated patients at high risk of developing ventilator associated pneumonia (VAP) treated with *Lactobacillus rhamnosus GG* at a dose of 2×10^9 CFU who were significantly less likely to develop microbiologically confirmed VAP compared with patients treated with placebo. Patients treated with probiotics had fewer days of antibiotics prescribed for VAP and for *C. difficile* –associated diarrhoea. A trial of 65 critically ill, mechanical ventilated, polytrauma patients by Kotzampassi *et al*[16] showed that Synbiotic Forte for 15 days significantly reduced rate of infections, severe sepsis and mortality. ICU stay and duration of mechanical ventilation were also significantly reduced. In view of conflicting reports on beneficial effects and lack of details about the dose and strain, probiotics cannot be recommended currently for prevention of Multi Organ Dysfunction Syndrome, VAP and nosocomial infections

Prevention of Atopic Disease

Two RCTs suggested that *LGG* supplementation before delivery for pregnant mothers with a family history of atopy and subsequent supplementation while breastfeeding or formula feeding later, reduced the risk of developing atopic dermatitis in their infants.[17,18] However, a recent meta-analysis concluded that there was insufficient evidence to recommend adding probiotics to infant feeds to prevent allergic disease or food hypersensitivity.

Treatment of Atopic disease

Although early probiotics studies showed promising results for the treatment of atopic dermatitis with *LGG* and *L reuterii* in children with moderate to severe eczema, three subsequent meta-analyses concluded that reductions in eczema severity from probiotic treatment were modest and clinically insignificant.[19]

Treatment of H. Pylori eradication

A meta-analysis in adult patients with *H. pylori* infection concluded that there is evidence to recommend the use of *S. boulardii* along with standard triple therapy as an option for increasing the eradication rates and decreasing overall therapy-related side effects, particularly diarrhea[20] But results from RCTs in children are inconclusive.[21]

Irritable bowel syndrome

In a single published RCT of the treatment of irritable bowel syndrome (IBS) in children, *LGG* decreased abdominal distension and was more likely to improve symptoms of patients with IBS than a placebo.[22]

Infantile colic

Two trials showed a significant reduction of crying in infants receiving *L reuteri*.[23,24] While there may be a role for probiotics in treating infantile colic, there is insufficient evidence to recommend for or against using probiotics to manage this condition.

Preventing necrotizing enterocolitis

A 2008 Cochrane review based 9 RCTs showed that enteral probiotic supplementation significantly reduced both the incidence of NEC (stage II or more) [RR: 0.32 (95% CI: 0.17– 0.60)] and mortality [RR: 0.43 (95% CI: 0.25– 0.75)] in preterm infants weighing > 1 kg.[25]The severity and incidence of NEC was lower in infants given a mixture of *Bifidobacterium infantis*, *B bifidus* and *S thermophilus*.[26,27]

Table 1
Summary of Evidence-based positive health benefits of probiotics and prebiotics in children

Disease/ Action	Probiotic strain/ Prebiotic	Recommended dose	Evidence level	Ref	Comments
Treatment of acute infectious diarrhoea	*Lactobacillus Rhamnosus GG*	10^{10}–10^{11} cfu, twice daily	1a	28	Meta-analysis of RCTs ; SPGHAN/ESPID recommendation
	Saccharomyces boulardii, strain of *S. cerevisiae*	200 mg, three times daily	1a	29	Meta-analysis of RCTs ; SPGHAN/ESPID recommendation
	Indian Dahi containing *L. lactis cremoris* and *Leuconostoc mesenteroides cremoris*	10^{10} cfu of each strain, 2 or 3 times per day	2b	30	
Prevention of antibiotic associated diarrhoea	*S. boulardii,* strain of *S. cerevisiae*	250 mg, twice daily	1a	31	Meta-analysis of RCTs
	L. rhamnosus GG	10^{10} cfu, OD or twice daily	1b	32	
	Bifidobacterium lactis + *Streptococcus thermophiles*	10^{7} + 10^{8} cfu/g of formula	1b	33	
	L. rhamnosus	2 × 10^{10}, twice daily	1b	34	
Prevention of common gastro-intestinal infections	*L. casei* in fermented milk	10^{10} cfu, once daily	1b	35	
	B. lactis or *L. Reuteri*	10^{7} cfu/g of formula powder	1b	36	
	L. casei Shirota in fermented milk	10^{10} cfu, once daily	1b	37	
Adjuvant therapy for *H. pylori* eradication	*L. casei* in fermented milk	10^{10}-10^{12} cfu daily, for 14 days	1b	38	The probiotic was given together with a 7-day course of eradication triple therapy with omeprazole, amoxicillin and clarithromycin
Alleviates some symptoms of functional bowel disorders	*L. rhamnosus GG*	10^{10}–10^{11} cfu, twice daily	1a	39	Meta-analysis of RCTs
	L. reuteri	10^{8} cfu, twice daily	1b	40	
Infantile colic	*L. reuteri*	10^{8} cfu/day	1b	41	
Prevention of necrotizing enterocolitis in preterm infants	*B. bifidum , L. acidophilus*	10^{9} cfu each strain, twice daily	1b	42	Meta-analysis of pooled data from RCTs testing different probiotic preparations confirms significant benefits of probiotic supplements in reducing death and disease in preterm neonates[45]
	L. acidophilus + *B. infantis*	10^{8} cfu each, twice daily	1b	43	
	B. infantis, B. bifidum, S. thermophilus	10^{9} cfu each, once daily	1b	44	

DISCUSSION

1) Use of probiotics in overall reduction of infectious diseases is significant. Probiotics might help to reduce childhood respiratory illnesses. Review of 21 clinical trials by Popova *et al* has shown positive outcome in 17 cases and no beneficial effects in 4 cases.[46]
2) The benefit of probiotics in acute infectious diarrhoea is strain and dose dependent. *LGG* is the most effective probiotic reported. Probiotics also seem to be more effective when given early in the course of diarrhoea. It is mostly helpful for otherwise healthy infants and young children with watery diarrhoea secondary to viral gastroenteritis but not invasive bacterial infections. While there is currently no evidence to support using probiotics to treat *C difficile* in children, there might be a role for probiotics in preventing relapse in patients with recurrent *C difficile* infection to prevent antibiotic associated diarrhoea. However, there is enough evidence to prevent antibiotic associated diarrhoea if probiotics are used from day 1 of antibiotic therapy.
3) Despite the encouraging results of some studies, there is insufficient evidence to warrant the routine supplementation of probiotics to either pregnant women or infants to prevent allergic diseases in childhood.
4) At the present time, the sustained or long-term benefit of using probiotics for treating IBS requires further RCTs and cannot be recommended in children. There may be some benefit of treating *H. Pylori* gastritis and infantile colic with probiotics in childhood, but further studies are necessary.
5) Clinical trials have shown that probiotic supplementation reduces the risk of necrotizing enterocolitis in preterm neonates. Systematic reviews of randomized controlled trials have also shown a reduced risk of death in probiotic treated groups. Probiotics can be considered for the prevention of NEC in preterm infants >1 kg who are at risk for NEC. There are currently no data for infants weighing <1000g.

CONCLUSION

Benefits of one probiotic cannot be generalized to another. Use of a combination of probiotics is not evidence based in all clinical situations. There are conflicting evidence for possible beneficial effects of probiotics toward overall infectious disease. Choice of strain and dose of probiotics in different disease conditions in children may be followed by practitioners as depicted in Table 1. A significant shortening of acute watery rotavirus-induced diarrhoea has been demonstrated with *Lactobacillus rhamnosus GG* (*LGG*) and *Saccharomyces boulardii*. Probiotics could be useful against antibiotic-associated diarrhoea if started on day 1 of antibiotic therapy. Probiotics and prebiotics can decrease the incidence and recurrence of URTI. Similarly incidence of VAP has been found to be less when *LGG* was used in a dose of 2×10^9 CFU. Treatment childhood *Helicobacter pylori* gastritis, irritable bowel syndrome, infantile colic and prevention of childhood atopy using probiotics, although encouraging, are preliminary and require further confirmation. There are also safety concerns with the use of probiotics in infants and children who are immunocompromised, chronically debilitated or seriously ill. Keeping in mind that the effect of probiotics is both strain, disease and dose-specific, physicians should recommend correct dose and strain of probiotics for specific diseases.

REFERENCES

1. Wadher K.J, Mahore J.G, Umekar M.J, et al. Probiotics: Living medicines in health maintenance and disese prevention. Int J Pharma. Bio. Sci, 85: 1-9, (2010)
2. Picaud JC, Chapalain V, Paineau D, et al. Incidence of infectious diseases in infants fed follow-on formula containing synbiotics: an observational study. *Acta Paediatr*, 99: 1695–1700, (2010).

3. Maldonado J, Cañabate F, Sempere L, et al. Human milk probiotic *Lactobacillus fermentum* CECT5716 reduces the incidence of gastrointestinal and upper respiratory tract infections in infants. *J Pediatr Gastroenterol Nutr*, 54:55–61, (2012).
4. Fayol-Messaoudi D, Coconnier-Polter M, Lievin-Le Moal V, Atassi F, Berger CN and Servin AL, The Lactobacillus plantarum strain ACA-DC287 isolated from a Greek cheese demonstrates antagonistic activity in vitro and in vivo against Salmonella enterica serovar Typhimurium. J Appl Microbiol, 103: 657–665, (2007).
5. Mengi B, .Kotwal S.K, Singh M, et al. Probiotics and infectious agents. Int J Pharma. Bio. Sci, 2: 119 -134, (2011).
6. Hatakka K, Blomgren K, Pohjavuori S, et al. Treatment of acute otitis media with probiotics in otitis-prone children-a double-blind, placebo-controlled randomised study. *Clin Nutr*, 26:314–321, (2007).
7. Hao Q, Lu Z, Dong BR, et al. Probiotics for preventing acute upper respiratory tract infections. *Cochrane Database Syst Rev*, 9:CD006895, (2011).
8. Arslanoglu S, Moro GE, Boehm G. Early supplementation of prebiotic oligosaccharides protects formula-fed infants against infections during the first 6 months of life. *J Nutr*, 137: 2420–2424, (2007).
9. Allen SJ, Martinez EG, Gregorio GV, et al. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*, 11: CD003048, (2010).
10. Szajewska H, Skórka A. *Saccharomyces boulardii* for treating acute gastroenteritis in children: updated meta-analysis of randomized controlled trials. *Aliment Pharmacol Ther*, 30:960–961, (2009).
11. Szajewska H, Ruszczynski M, Radzikowski A. Probiotics in the prevention of antibiotic-associated diarrhoea in children: a meta-analysis of randomized controlled trials. *J Pediatr*, 149:367–372, (2006).
12. Johnston BC, Goldenberg JZ, Vandvik PO, et al. Probiotics for the prevention of pediatric antibiotic-associated diarrhoea. *Cochrane Database Syst Rev*, 11: CD004827, (2011).
13. D'Souza AL, Rajkumar C, Cooke J, Bulpitt CJ. Probiotics in prevention of antibiotic associated diarrhoea: meta-analysis. *BMJ*,324(7350):1361, (2002).
14. Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. Cochrane Database Syst Rev, (1); CD004611, (2008).
15. Morrow LE, Kollef MH, Casale TB. Probiotic prophylaxis of ventilator-associated pneumonia: a blinded, randomized, controlled trial. *Am J Respir Crit Care Med*, 182(8):1058-1064, (2010).
16. Kotzampassi K, Giamarellos-Bourboulis EJ, Voudouris A, Kazamias P, Eleftheriadis E: Benefits of a synbiotic formula (Synbiotic 2000Forte) in critically Ill trauma patients: early results of a randomized controlled trial. World J Surg, 30: 1848-55, (2006).
17. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: A randomised placebo-controlled trial. Lancet,357(9262): 1076-9, (2001).
18. Kalliomäki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet, 361(9372): 1869-71, (2003).
19. Boyle RJ, Bath-Hextall FJ, Leonardi-Bee J, Murrell DF, Tang ML. Probiotics for treating eczema. Cochrane Database Syst Rev, (4); CD006135, (2008).
20. Szajewska H, Horvath A, Piwowarczyk A. Meta-analysis: the effects of *Saccharomyces boulardii* supplementation on *Helicobacter pylori* eradication rates and side effects during treatment. Aliment Pharmacol Ther, Nov;32(9):1069-1079, (2010).
21. Szajewska H, Albrecht P, Topczewska-Cabanek A. Randomized, double-blind, placebo-controlled trial: effect of lactobacillus GG supplementation on *Helicobacter pylori* eradication rates and side effects during treatment in children.

J Pediatr Gastroenterol Nutr, 48:431–436, (2009).
22. Bausserman M, Michail S. The use of *Lactobacillus GG* in irritable bowel syndrome in children: A double-blind randomized control trial. J Pediatr, 147(2):197-201, (2005).
23. Savino F, Pelle E, Palumeri E, Oggero R, Miniero R. *Lactobacillus reuteri* (American Type Culture Collection Strain 55730) versus simethicone in the treatment of infantile colic: A prospective randomized study. Pediatrics, 119(1):e124-30, (2007).
24. Savino F, Cordisco L, Tarasco V, et al. *Lactobacillus reuteri* DSM 17938 in infantile colic: A randomized, double-blind, placebo-controlled trial. Pediatrics, 126(3):e526-33,(2010).
25. Alfaleh K, Bassler D. Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst Rev*, (1): CD005496, (2008).
26. Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics, 115(1):1-4, (2005).
27. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr, 147(2):192-6, (2005).
28. Szajewska H, Ruszczyński M, Gieruszczak-Białek D. *Lactobacillus GG* for treating acute diarrhoea in children. A meta-analysis of randomized controlled trials. Aliment Pharmacol Ther, 25:177–84, (2007).
29. Szajewska H, Skorka A, Dylag M. Meta-analysis: *Saccharomyces boulardii* for treating acute diarrhoea in children. Aliment Pharmacol Ther, 25:257–64, (2007).
30. Agarwal KN, Bhasin SK. Feasibility studies to control acute diarrhoea in children by feeding fermented milk preparations Actimel and Indian Dahi. Eur J Clin Nutr, 56 Suppl 4:S56–99, (2002).
31. Kotowska M, Albrecht P, Szajewska H. *Saccharomyces boulardii* in the prevention of antibiotic-associated diarrhoea in children: a randomized double-blind placebo-controlled trial. Aliment Pharmacol Ther, 21:583–90, (2005).
32. Arvola T, Laiho K, Torkkeli S, et al. Prophylactic *Lactobacillus GG* reduces antibiotic associated diarrhoea in children with respiratory infections: a randomized study. Pediatrics, 104:1–4, (1999).
33. Correa NB, Peret Filho LA, Penna FJ, Lima FM, Nicoli JR. A randomized formula controlled trial of *Bifidobacterium lactis* and *Streptococcus thermophilus* for prevention of antibiotic-associated diarrhoea in infants. J Clin Gastroenterol, 39:385–89, (2005).
34. Ruszczyński M, Radzikowski A, Szajewska H. Clinical trial: effectiveness of *Lactobacillus rhamnosus* (strains E/N, Oxy and Pen) in the prevention of antibiotic-associated diarrhoea in children. Aliment Pharmacol Ther, 28:154–61, (2008).
35. Merenstein D, Murphy M, Fokar A, et al. Use of a fermented dairy probiotic drink containing *Lactobacillus casei* (DN-114 001) to decrease the rate of illness in kids: the DRINK study. Eur J Clin Nutr , 64:669–77, (2010).
36. Weizman Z, Asli G, Alsheikh A. Effect of a probiotic infant formula on infections in child care centers: comparison of two probiotic agents. Pediatrics, 115: 5–9, (2005).
37. Sur D, Manna B, Niyogi SK, et al. Role of probiotic in preventing acute diarrhoea in children: a community-based, randomized, double-blind placebo-controlled field trial in an urban slum. Epidemiol Infect, 139: 919–26, (2011).
38. Duman DG, Bor S, Ozütemiz O, et al. Efficacy and safety of *Saccharomyces boulardii* in prevention of antibiotic-associated diarrhoea due to *Helicobacter pylori* eradication. Eur J Gastroenterol Hepatol, 17:1357–61, (2005).
39. Horvath A, Dziechciarz P, Szajewska H. Systematic review and meta-analysis of randomized controlled trials: *Lactobacillus rhamnosus GG* for abdominal pain-related functional gastrointestinal disorders in childhood. Aliment Pharmacol Ther, 33: 1302–10, (2011).

40. Coccorullo P, Strisciuglio C, Martinelli M, Miele E, Greco L, Staiano A. *Lactobacillus reuteri* (DSM 17938) in infants with functional chronic constipation: a double-blind, randomized, placebo-controlled study. J Pediatrics, 157:598–602, (2010).
41. Savino F, Cordisco L, Tarasco V, et al. *Lactobacillus reuteri* DSM 17938 in infantile colic: a randomized, double-blind, placebo-controlled trial. Pediatrics, 126:e526–33, (2010).
42. Lin HC, Hsu CH, Chen HL, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight preterm infants: a multicenter, randomized, controlled trial. Pediatrics, 122:693–700, (2008).
43. Lin HC, Su BH, Chen AC, et al. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics,115: 1–4,(2005).
44. Bin-Nun A, Bromiker R, Wilschanski M, et al. Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr ,147: 192–6,(2005).
45. Deshpande G, Rao S, Patole S, Bulsara M. Updated meta-analysis of probiotics for preventing necrotizing enterocolitis in preterm neonates. Pediatrics, 125:921–30, (2010).
46. Popova M, Molimard P, Courau S et al. Beneficial effects of probiotics in upper respiratory tract infections and their mechanical actions to antagonize pathogens. J Appl Microbiol, 113(6): 1305-18, (2012).