Original Article

Efficacy of probiotic therapy in full-term infants with critical illness

Yu Wang MD, Li Gao MD, Yu-hua Zhang MB, Chang-song Shi MM, Chun-ming Ren MB

Department of Pediatrics, the People's Hospital of Henan Province, Zhengzhou, Henan Province, China

Background: Probiotics are microbial supplements that have shown efficacy in a wide range of applications. To assess the safety and effects of enteral probiotics in critically ill neonates. **Methods**: A double-blind, randomized controlled trial was conducted in 100 full-term infants with critical illness according to scores of neonatal acute physiology. Fifty neonatal intensive care patients were randomly assigned to receive probiotics three times daily after birth for 8 days, and fifty patients were not given probiotics, but who received a placebo. The incidence of sepsis, multiple organ dysfunction syndrome (MODS), nosocomial pneumonia, and necrotizing enterocolitis were recorded. The prognosis of probiotic treatment was determined based on the rate of recovery and hospital days. Serum IgA, IgG, and IgM concentrations were measured on days 4 and 8. **Results**: Infants in the probiotics group showed a significantly reduced rate of nosocomial pneumonia (18% versus 36%) and multiple organ dysfunction syndrome (6% versus 16%) compared with the placebo group ($p<0.05$). Significant results were demonstrated in favour of the probiotics for days of hospital stay (13±3.5 d versus 15.8±5.3 d) ($p<0.05$). However, there were no significant differences in the occurrence of sepsis, necrotizing enterocolitis, and recovery rate. Patients given probiotics had significantly greater levels of IgA than those in the placebo group ($p<0.05$). No serious adverse effects in the study population were noted. **Conclusions**: Supplements of probiotics to critically ill neonates could enhance immune activity, decrease occurrence of nosocomial pneumonia and MODS, and reduce days in hospital.

Key Words: intestinal microbiota, multiple organ dysfunction syndrome, intensive care, nosocomial pneumonia, infant

INTRODUCTION

Probiotics are "live microbes which when administered in adequate amounts confer a health benefit to the host" according to the World Health Organisation.[1] These are normal commensal inhabitants of the human intestine and colonize the colon better than others. In particular, proper acquisition of gut microflora after birth promotes nutrition and enhances the gut's epithelial barrier in newborn children.[2] Critical illness and its treatment creates a hostile environment in the gut and alter the gut flora, favouring growth of pathogens. Dysbiosis of the intestine, or imbalance of the gut microbiota, increases the risk of sepsis and necrotizing enterocolitis (NEC) in neonates. These clinical conditions prolong hospital stay, increase the cost of care, and place the infant at greater risk for morbidity and mortality. Probiotics normally function as colonizers and create an unfavourable environment for pathogens by multiple mechanisms, including immune and antibacterial effects. Early feeding of probiotics prevents and treats antibiotic-associated diarrhea, NEC, and MODS.[3-5] Recently, there has been an increasing amount of attention paid by clinicians to the application of probiotics.[6,7] However, their potential role in bio-ecological modification of pathological internal milieu of the critically ill is still under evaluation. Infants are different from adults in physiology. Many clinical characteristics, optimum dosage, and contraindications for probiotics are still unclear. We conducted a clinical trial to investigate the effect and safety of enteral probiotics in critically ill neonates.

METHODS

Study participants

Patients admitted between February of 2010 and December of 2011 to the neonatal intensive care unit (NICU) of the People's Hospital of Henan Province were eligible for the study.

The study was conducted at the People's Hospital of Henan Province where the maternity unit is a reference centre for high-risk pregnancies for the whole province. All the neonates included in this study were born locally and admitted to the NICU at the gestational ages of 37 to 42 weeks. They were transferred to the NICU during their first hour of life by the neonatologist in the delivery room. The score of neonatal acute physiology (SNAP)[8] was calculated using data obtained within 24 h, and the following parameters were measured for each individual system: 1)

Corresponding Author: Dr Yu Wang, Department of Pediatrics, the People's Hospital of Henan Province, No 7, Weiwu Road, Zhengzhou 450003, Henan Province, China.
Tel: +86-371-65897581; Fax: +86-371-65964376
Email: wangyugirl2004@126.com
Manuscript received 25 December 2013. Initial review completed 29 January 2014. Revision accepted 17 May 2014.
doi: 10.6133/apjcn.2014.23.4.14

respiratory (RR, partial pressure of oxygen/fraction of inspired oxygen), 2) renal (serum creatinine, electrolytes), 3) hepatic (bilirubin), 4) cardiovascular (blood pressure and heart rate), 5) hematological (WBC and platelets), and 6) neurological (epilepsy). One hundred patients with critical illness were enrolled in the present study according to the SNAP score (≤15). None of the neonates had major congenital malformations, previously diagnosed life-threatening chromosomal alterations, or congenital infections or congenital metabolic disorders. Consent was provided by the parents of the infants. The Ethics Committee for Medical Research at the People's Hospital of Henan Province approved the study protocol.

Intervention

Infants who met the inclusion criteria were randomly allocated to the probiotics group or control group. Infants of the probiotics group received probiotics for 8 consecutive days from the second day after birth (n=50). Infants given probiotics were compared with 50 patients without probiotics. Infants in the probiotics group received 3 mL of 5% glucose liquid to which one tablet was added three times daily. Each tablet of probiotics contained 30 billion viable lyophilized bacteria, consisting of 2 strains of Lactobacillus (L casei and L acidophilus), Bacillus subtilis and Enterococcus faecalis. Infants in the control group received the same volume of glucose liquid without probiotics. The glucose liquid was offered in glass receptacles or through a nasogastric feeding tube, even if the nutrition regime had been suspended. Neither the medical and nursing staff responsible for monitoring the infants nor the researchers were aware of which group the infants were allocated to. If the patient discontinued enteral nutrition or was ready to be discharged from hospital before study completion, the study was discontinued prematurely.

Study design

Enteral feeding of formula milk powder was initiated and progressed according to a strict NICU protocol. This protocol was followed by all infants in this study. A volume of 2-3 mL of specific formula milk for full-term infants was begun every 2-3 hours when infants had stable vital signs. An increase in the daily enteral feeding did not exceed 20 $mL \cdot kg^{-1} \cdot d^{-1}$. The enteral feeding was interrupted if there were signs of intolerance, defined as the presence of gastric residuals exceeding 25% of the volume offered within the previous 6 h, abdominal distension, or blood in the stool. Feeding was then resumed and continued until 150 $mL \cdot kg^{-1} \cdot d^{-1}$ was achieved. A parenteral supply of amino acids was initiated for all children within the first 24 h of life, and total parenteral nutrition was maintained until it reached 100 $mL \cdot kg^{-1} \cdot d^{-1}$. All patients in the study received concomitant therapy, including antibiotics, as considered appropriate by the attending physician.

Outcome measures

Infants were monitored every day for eight days after commencement of treatment. The occurrence of nosocomial pneumonia, sepsis (deterioration of clinical condition with positive blood culture),[9] MODS, NEC, and diarrhea were recorded. Nosocomial pneumonia and MODS were defined according to the criteria of Bradley[10] and Goldstein,[11] respectively. The occurrence of NEC was defined by Bell's criteria and modified by Walsh and Kliegman as stage II.[12] For these staging criteria, the radiographic findings of pneumatosis intestinal is with or without metabolic (acidosis) and hematological changes (thrombocytopenia) are defined as NEC stage II. In stage I, radiographic findings are limited to mild intestinal dilation and dysmotility. Stage III includes infants with stage II criteria plus respiratory or cardiovascular deterioration, or required surgical intervention. Precoded forms were used to record hospital stays and recovery rate. Systemic concentrations of immunoglobulin (Ig) A, IgM, and IgG were measured on day 4 (4 days after initiation of the study treatment) and at the completion of the study (day 8).

Statistical analysis

Data are expressed as individual values or mean±SD. Data were analyzed by using the statistical software package STATA (STATA ver 4.0 Statistical Software, Stata Corporation). Reported p values are two-tailed and p values<0.05 were considered significant for all statistical tests. The Mann-Whitney U test was used to compare continuous variables, and the chi-square test was used to compare categorical variables.

RESULTS

Participant characteristics

No significant differences in gestational age, sex, birth weight, or the rate of cesarean delivery were observed between the groups. The diagnoses of infants included neonatal asphyxia, ARDS, HIE, MAS, intracranial hemorrhage, thrombocytopenia, and arrhythmia. Most mothers of patients had various obstetrical complications, such as gestational hypertension, placenta previa, placental abruption, fetal distress in the uterus, and premature rupture of the membranes. The baseline characteristics of the infants are presented in Table 1.

Infectious complications

A significant reduction in MODS was seen in the probiotic group (p<0.05). Nosocomial pneumonia was significantly reduced in the probiotic group compared with controls (p<0.05). Infants in the probiotics group (4%) had less sepsis than the control group (8%), but there was no significant difference between them. The occurrence of NEC in the probiotics group was 4%, which was lower than that in the control group (6%), but no significant difference was observed between the two groups. The incidence of diarrhea in the probiotics group (6%) was lower than that in the control group (10%), with no significant difference (Table 2).

Other clinical parameters

In the group given probiotics, 92% of the patients (46/50) recovered and were discharged from the NICU. In the placebo group, 76% of patients (38/50) improved after illness prior to discharge. There was no significant difference in the recovery rate between the two groups. However, infants in the probiotics group demonstrated a significant decrease in the number of days spent in hospital

than the control group (p<0.05). The time achieved to full enteral nutrition in neonates given probiotics was significantly shorter than the other group (p<0.05). (Table 2)

Immune system variables

The probiotics group had a significantly greater increase in IgA than the control group (p<0.05, Table 3). No significant changes in IgG values and IgM concentrations were found between the two groups (p>0.05).

Adverse events

No adverse effects were recorded during the probiotics therapy. No infants with the treatment developed Lactobacillus-induced sepsis.

DISCUSSION

Gastrointestinal dysfunction in patients with critical illness is common in practice, but is always underestimated by most of us even now.[13-15] Impaired gastrointestinal motility is important in the progression of critical illness, and it could result in many subsequent complications, such as intolerance to enteral feeding, enhanced permeability of the intestinal mucosa, systemic inflammatory response syndrome, sepsis, and MODS. Many studies have shown that bioecological treatment with probiotics can regulate the status of the intestinal mucosa. However few trials using probiotics have specifically focused on neonates in the critical care unit. Furthermore, establishing an intestinal microbiome is particularly important for intestinal development and defense in neonates.[16] Therefore, pediatricians have attempted to search for a new strategy for improvement of the digestive system.

Nosocomial infections are common complications among critically ill patients. Severe sepsis associated with MODS is the main reason leading to death in intensive care units. Bacterial translocation from the gastrointestinal tract is an important pathway leading to the sepsis. Some studies have shown that feeding probiotics can maintain the balance of microbial communities with positive effects on intestinal permeability and bacterial translocation in infants.[17,18] However, the effects of probiotics on reducing the incidence or severity of sepsis have been equivocal.[19] In our study, no difference was found in the occurrence of sepsis between the probiotics and control groups. However positive effects of probiotics should not be completely discounted according to the results because the underlying mechanism of sepsis is complex.[20] Low birth weight, maintenance of vessels catheters, and a long duration of parenteral nutrition all play important roles in the development of neonatal sepsis.[21] It is likely that probiotics alone will be difficult to accomplish the task of preventing sepsis. On the other hand, though probiotics are not expected to eliminate potentially pathogenic microorganisms as antibiotics, the use of probiotics delays the moment of colonization while the patients are intubated and ventilated.[22] Recent trials have shown that probiot-

Table 1. Baseline characteristics of full-term infants in two groups (n=50)

	Probiotics group	Placebo group	*p* value
Boys, n (%)	36 (72)	34 (68)	0.663
GA (weeks)	38.8±1.1	38.2±1.1	0.512
Birth weight (g)	3084±494	3044±604	0.719
Cesarean delivery, n (%)	38 (76)	40 (80)	0.629
Apgar score at 1 min	7.3±1.1	7.2±1.8	0.435
Twins, n (%)	3 (6)	2 (4)	0.646
SANP	10.2±1.8	11.1±1.1	0.760

GA: gestational age; SANP: score of acute neonatal physiology.

Table 2. Clinical outcomes of full-term infants in two groups (n=50)

	Probiotics group	Control group	RR [95% CI]	*p* value
Sepsis, n (%)	2 (4)	4 (8)	0.65 (0.21~2.1)	0.400
MODS, n (%)	3 (6)	8 (16)	0.52 (0.19~1.38)	0.044
Nosocomial pneumonia, n (%)	8 (16)	18 (36)	0.54 (0.29~0.99)	0.023
NEC, n (%)	2 (4)	3 (6)	0.79 (0.27~2.36)	0.471
Diarrhea, n (%)	3 (6)	5 (10)	0.73 (0.29~1.84)	0.461
Hospital stays (day)	13.0±3.5	15.8±5.3	-4.61~-1.08	0.030
Recovery rate, n (%)	46 (92)	38 (76)	2.19 (0.92~5.23)	0.123
Age when enteral feeding began (day)	2.6±1.2	2.9±1.1	-0.77~0.13	0.327
Time to full enteral feeding (day)	8.2±2.6	10.9±4.3	-4.16~-1.36	0.009

MODS: multiple organ dysfunction syndrome; NEC: necrotizing enterocolitis.

Table 3. Comparison of the level of IgA, IgG and IgM between two groups (n=50)

	IgA		IgG		IgM	
	Day 4	Day 8	Day 4	Day 8	Day 4	Day 8
Probiotics group	58.7±9.5	65.7±10.4	8.4±2.9	8.1±2.6	0.39±0.2	0.42±0.2
Control group	56.9±12.4	58.8±12.4	8.4±2.5	8.4±2.8	0.37±0.2	0.41±0.2
95% CI	-4.33~7.97	1.58~14.2	-1.48~1.2	-1.57~1.04	-0.1~0.12	-0.11~0.14
p value	0.556	0.023	0.854	0.621	0.869	0.811

ics reduced the risk of nosocomial gastrointestinal and respiratory tract infections in a pediatric ward.[23] In our study, recipients of probiotics had fewer infectious episodes, such as nosocomial pneumonia. Probiotics also reduce the incidence of all-cause diarrhea in hospitalized infants.[2]

Few researches have evaluated the effects of probiotics in the prevention of MODS. A randomized clinical trial explored the role of combined supplementation of B. breve and L. casei in term infants. In this study, infants who received probiotics had a reduced incidence of MODS after 8 days of treatment.[24] Similar to that study, the utilization of probiotics appears to decrease the occurrence of MODS in NICU patients with critical illness.

Some meta-analyses have also reported the benefits of probiotics in preventing NEC.[25] However, probiotics had no significant effect on NEC in full-term infants in our study. It was found that most publications studied preterm neonates, but full-term infants were seldom involved. Therefore, the variations in outcome may result from the different populations observed. Research on animal models has shown that ischemia and hypoxic injury play important roles in the development of NEC in full-term infants. However intestinal injury of preterm neonates is mainly caused by the presence of food substrate in immature and inadequately colonized intestine. Effects of probiotics on maturation of the gastrointestinal tract may contribute to the benefit for pre-term neonates.

Studies have suggested that probiotics may be related to immune-modulating activity in innate and adaptive immunity. In our study, application of probiotics significantly increased serum IgA levels. High concentrations of IgA activity in the gut are critical for sustaining a barrier against pathogen translocation, especially gram-negative bacterials.[26] Some studies[27-29] have indicated that activation of macrophages and improvement in natural killer cell increase the numbers of IgA-, IgM-, and IgG-secreting cells, and provide benefits for the balance of proinflammatory and anti-inflammatory cytokine secretion. However, we did not find any increases in IgG and IgM concentrations. This is because neonates cannot produce considerable quantity of IgG and IgM by themselves untill four to eight weeks after birth. Therefore the quantity of IgG and IgM did not significantly increase just like adult patients during probiotic treatment.[3]

Probiotics regulate the innate and adaptive immune system in a dose- and strain-dependent manner.[30,31] Some Lactobacilli and Bifidobacteria strains have been reported to promote the secretory IgA and IgG particularly.[30] A similar finding[31] showed that viable L. casei and L. acidophilus raised the number of IgA cells in the intestine of mice much more than non-viable bacterial cells. In our study, acidophilus was also introduced to infants as previously used in most studies. As no defined protocol has been generally accepted, many factors still need to be identified in terms of the strain selection, the time point to treat, and optimal dose.

In the current study, probiotics did not affect the recovery rate, but they did appear to shorten the duration of hospitalization. So probiotics have been proposed to favourably influence the course of critically ill patients. Besides this, difficulties of enteral nutrition are greater in patients with serious illness because of gut dysmotility and hypoperfusion. Our study also found that probiotics improved the function of gastrointestinal tract and hastened the establishment of intestinal feeding. In this way probiotics not only shorten the time of intravenous nutrition but also may have avoided many complications related to the function of gastrointestinal tract.

Similar to previous clinical trials,[32-34] the present study found no complications associated with probiotics. However, Ohishi[35] reported a case of sepsis caused by B. breve during probiotic administration in a neonate. Therefore, probiotics should be used with care in vulnerable patients as to the potential pathogenicity. While feeding probiotics to newborns has been suggested to be safe and increase resistance to respiratory infections during the first 5 years of life,[2,36] the clinical benefits and safety of prenatal and postnatal probiotic treatments still remain unclear. So more studies are required to confirm long-term effects of probiotic use in ICU neonates. In addition, the absolute power and effect size were low in all outcome measures, indicating that the study needs to be replicated in a larger sample size to be conclusive. The third limitation of the study was the heterogeneity of the ICU patients enrolled. Future studies may consider attempting to enroll patients with a similar disease profile.

In summary, the early establishment of commensal flora in neonates is more important than in adults, and probiotic treatment should be started as early as possible before pathogens colonize or antibiotics destroy the prevailing commensals.

ACKNOWLEDGEMENTS

We thank the parents of the infants who took part in this study and the medical staff at the NICU for their cooperation. None of the authors had a financial or personal conflict of interest.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

REFERENCES

1. FAO/WHO. Food and Argricultural Organization/World Health Organization Report - Health and Nutritional Properties of Probiotics in Food including Powder Milk with Live Lactic Acid Bacteria (2001), Cordoba, Argentina.
2. Thomas DW, Greer FR. American Academy of Pediatrics Committee on Nutrition; American Academy of Pediatrics Section on Gastroenterology, Hepatology, and Nutrition. Probiotics and prebiotics in pediatrics. Pediatrics. 2010;126: 1217-31. doi: 10.1542/peds.2010-2548.
3. Alberda C, Gramlich L, Meddings J, Field C, McCargar L, Kutsogiannis D, Fedorak R, Madsen K. Effects of probiotic therapy in critically ill patients: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2007;85:816-23.
4. Braga TD, da Silva GA, de Lira PI, de Carvalho Lima M. Efficacy of Bifidobacterium breve and Lactobacillus casei oral supplementation on necrotizing enterocolitis in very-low-birth-weight preterm infants: a double-blind, randomized, controlled trial. Am J Clin Nutr. 2011;93:81-6. doi: 10.3945/ajcn.2010.29799.
5. Friedman G. The role of probiotics in the prevention and treatment of antibiotic-associated diarrhea and Clostridium difficile colitis. Gastroenterol Clin North Am. 2012;41:763-79. doi: 10.1016/j.gtc.2012.08.002.
6. Delia P, Sansotta G, Donato V, Messina G, Frosina P,

Pergolizzi S, De Renzis C, Famularo G. Prevention of radiation-induced diarrhea with the use of VSL#3, a new high-potency probiotic preparation. Am J Gastroenterol. 2002;97:2150-2. doi: 10.10 16/S0002-9270(02)04303-4.
7. Bibiloni R, Fedorak RN, Tannock GW, Madsen KL, Gionchetti P, Campieri M, De Simone C, Sartor RB. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis. Am J Gastroenterol. 2005;100:1539-46. doi: 10.1111/j.1572-0241.2005.41794.x.
8. Richardson DK, Gray JE, McCormick MC, Workman K, Goldmann DA. Score for Neonatal Acute Physiology: a physiologic severity index for neonatal intensive care. Pediatrics. 1993;91:617-23.
9. Sankar MJ, Agarwal R, Deorari AK, Paul VK. Sepsis in the newborn. Indian J Pediatr. 2008;75:261-6. doi: 10.1007/s120 98-008-0056-z.
10. Bradley JS. Considerations unique to pediatrics for clinical trial design in hospital-acquired pneumonia and ventilator-associated pneumonia. Clin Infect Dis. 2010;51(Suppl 1): S136-43. doi: 10.1086/653063.
11. Goldstein B, Giroir B, Randolph A. International consensus conference on pediatric sepsis. International pediatric sepsis consensus conference: definitions for sepsis and organ dysfunction in pediatrics. Pediatr Crit Care Med. 2005;6:2-8. doi: 10.1097/00130478-200501000-00049.
12. Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. Pediatr Clin North Am. 1986;33:179-201.
13. Chapman MJ, Nguyen NQ, Deane AM. Gastrointestinal dysmotility: evidence and clinical management. Curr Opin Clin Nutr Metab Care. 2013;16:209-16. doi: 10.1097/MCO. 0b013e32835c1fa5.
14. Codner PA. Enteral nutrition in the critically ill patient. Surg Clin North Am. 2012;92:1485-501. doi: 10.1016/j.suc.2012. 08.005.
15. Hackett TB. Gastrointestinal complications of critical illness in small animals. Vet Clin North Am Small Anim Pract. 2011;41:759-66. doi: 10.1016/j.cvsm.2011.05.013.
16. Patel RM, Lin PW. Developmental biology of gut-probiotic interaction. Gut Microbes. 2010;1:186-95. doi: 10.4161/ gmic.1.3.12484.
17. Sherman MP. New Concepts of microbial translocation in the neonatal intestine: mechanisms and prevention. Clin Perinatol. 2010;37:565-79. doi: 10.1016/j.clp.2010.05.006.
18. Garland SM, Tobin JM, Pirotta M, Tabrizi SN, Opie G, Donath S et al. The ProPrems trial: investigating the effects of probiotics on late onset sepsis in very preterm infants. BMC Infect Dis. 2011;11:210. doi: 10.1186/1471-2334-11-210.
19. Alfaleh K, Anabrees J, Bassler D, Al-Kharfi T. Probiotics for prevention of necrotizing enterocolitis in preterm infants. Cochrane Database Syst Rev. 2011;3:CD005496. doi: 10.10 02/14651858.CD005496.pub3.
20. O'Brien JM Jr, Ali NA, Abraham E. Year in review 2007: Critical Care - multiple organ failure and sepsis. Crit Care. 2008;12:228. doi: 10.1186/cc6950.
21. Wu J, Wu BQ, Huang JJ, Luo L, Tang Y. Risk factors and pathogen distribution in premature infants with nosocomial sepsis. Zhongguo Dang Dai Er Ke Za Zhi. 2012;14:93-6.
22. Schultz MJ, Haas LE. Antibiotics or probiotics as preventive measures against ventilator-associated pneumonia: a literature review. Crit Care. 2011;15:R18. doi: 10.1186/cc99 63.
23. Hojsak I, Abdović S, Szajewska H, Milosević M, Krznarić Z, Kolacek S. Lactobacillus GG in the prevention of nosocomial gastrointestinal and respiratory tract infections. Pediatrics. 2010;125:e1171-7. doi: 10.1542/peds.2009-2568.
24. Huang Y, Shao XM, Neu J. Immunonutrients and neonates. Eur J Pediatr. 2003;162:122-8.
25. Jacobs SE, Tobin JM, Opie GF, Donath S, Tabrizi SN, Pirotta M, Morley CJ, Garland SM; ProPrems Study Group. Probiotic effects on late-onset sepsis in very preterm infants: a randomized controlled trial. Pediatrics. 2013;132:1055-62. doi: 10.1542/peds.2013-1339.
26. Bengmark S. Synbiotics and the mucosal barrier in critically ill patients. Curr Op Gastroenterol. 2005;21:712-6.
27. Rinne M, Kalliomaki M, Arvilommi H, Salminen S, Isolauri E. Effect of probiotics and breastfeeding on the Bifidobacterium and Lactobacillus/Enterococcus microbiota and humoral immune responses. J Pediatr. 2005;147:186-91. doi: 10.1016/j.jpeds.2005.03.053.
28. Viljanen M, Kuitunen M, Haahtela T, Juntunen-Backman K, Korpela R, Savilahti E. Probiotic effects on faecal inflammatory markers and on faecal IgA in food allergic atopic eczema/dermatitis syndrome infants. Pediatr Allergy Immunol. 2005;16:65-71. doi: 10.1111/j.1399-3038.2005.00 224.x.
29. Isolauri E, Arvola T, Sutas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy. 2000;30:1604-10. doi: 10.1046/j.1365-2222.2000.0 0943.x.
30. Perdigon G, Maldonado Galdeano C, Valdez JC, Medici M. Interaction of lactic acid bacteria with the gut immune system. Eur J Clin Nut. 2002;56(Suppl):S21-6. doi: 10.1038 /sj.ejcn.1601658.
31. Galdeano CM, Perdigon G. Role of viability of probiotic strains in their persistence in the gut and in mucosal immune stimulation. J Appl Microbio. 2004;97:673-81. doi: 10.1111/ j.1365-2672.2004.02353.x.
32. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, Yeh TF, Oh W. Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics. 2005;115:1-4. doi: 10.1016/j.jpeds.2005.03.023.
33. Weichert S, Schroten H, Adam R. The role of prebiotics and probiotics in prevention and treatment of childhood infectious diseases. Pediatr Infect Dis J. 2012;31:859-62. doi: 10. 1097/INF.0b013e3182620e52.
34. Samanta M, Sarkar M, Ghosh P, Ghosh JK, Sinha MK, Chatterjee S. Prophylactic probiotics for prevention of necrotizing enterocolitis in very low birth weight newborns. J Trop Pediatr. 2009;55:128-31. doi: 10.1093/tropej/fmn091.
35. Ohishi A, Takahashi S, Ito Y, Ohishi Y, Tsukamoto K, Nanba Y et al. Bifidobacterium septicemia associated with postoperative probiotic therapy in a neonate with omphalocele. J Pediatr. 2010;156:679-81. doi: 10.1016/j. jpeds.2009.11.041.
36. Leyer GJ, Li S, Mubasher ME, Reifer C, Ouwehand AC. Probiotic effects on cold and influenza-like symptom incidence and duration in children. Pediatrics. 2009;124: e172-9. doi: 10.1542/peds.2008-2666.

Original Article

Efficacy of probiotic therapy in full-term infants with critical illness

Yu Wang MD, Li Gao MD, Yu-hua Zhang MB, Chang-song Shi MM, Chun-ming Ren MB

Department of Pediatrics, the People's Hospital of Henan Province, Zhengzhou, Henan Province, China

益生菌治疗危重足月儿的疗效

目的：益生菌作为微生态调节剂应用广泛而且效果显著,本研究的目的是为了探讨益生菌治疗危重新生儿的有效性及安全性。**方法**：根据急性新生儿生理学评分选取 100 名危重足月新生儿进行双盲、随机对照试验。 随机给予 50 名新生儿口服益生菌治疗，每天三次，连续 8 天，另外 50 名新生儿则给予安慰剂。记录败血症、多器官功能障碍综合征、院内获得性肺炎及坏死性小肠结肠炎的发病率，疾病好转率及住院时间，并分别在治疗后第 4 天及第 8 天测定患儿血浆中 IgA、IgG 和 IgM 的浓度。**结果**：治疗组患儿医院获得性肺炎（18%比 36%）和多器官功能障碍综合征（6%比 16%）显著低于安慰剂组（p<0.05），住院时间（13±3.5 天比 15.8±5.3 天）也较安慰剂组明显缩短（p<0.05）；但两组患儿的败血症和坏死性小肠结肠炎的发病率及好转率没有显著差异；口服益生菌患儿血浆 IgA 水平明显高于安慰剂组；未发现益生菌相关的不良反应。**结论**：危重新生儿补充益生菌可以增强机体免疫功能，降低医院获得性肺炎和多器官功能障碍综合征的发病率，减少住院时间。

关键词：肠道菌群、多器官功能障碍综合征、重症监护、医院获得性肺炎、婴儿