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Application of Probiotics to Ameliorate Ill Conditions from, Preterm Infants to the Elderly People

Yuichiro Yamashiro[1]* and Satoru Nagata[1,2]

[1]Probiotics Research Laboratory, Juntendo University Graduate School of Medicine, Tokyo, Japan
[2]Department of Pediatrics, Tokyo Women's Medical University, Tokyo, Japan

The human gut microbiota consists of trillions of microorganisms including 150-200 prevalent and approximately 1,000 less common bacterial species, harbouring over 100- fold more genes than those present in the human genome [1]. Recent renewed interest in the structure and function of gastrointestinal tract (GIT), which is the most heavily colonized organ of human body, has illuminated its functions essential to health maintenance. Inadequate gut colonization and dysbiosis, especially in extremely low birth weight (ELBW) infants and oncology patients undergoing chemotherapy, may lead to an increased risk of mucosal damage and inflammation which are important mechanisms to develop bacterial translocation that can result in systemic infection including septicemia.

Elderly people are especially prone to infection, as many physiological and immune responses as well as organ functions decline with age. Probiotics are live microorganisms which, when administered in sufficient doses, confer a health benefit on the host. In this review, we discuss the role played by GIT microbiota and probiotics in human health and disease based on our study in conjunction with the current knowledge.

Establishment of Bacterial Colonization

Colonization of the human gut with microorganisms begins immediately at birth. Upon passage through the birth canal, infants are exposed to a complex microbial population, and the immediate contact with microorganisms during birth can affect the development of the GIT microbiota and this probably occurs since the GIT microbiota of infants and the vaginal microbiota of their mothers are similar [2]. However, most preterm infants who have been delivered by Caesarian section for various reasons, can be colonized easily by abnormal bacteria (dysbiosis) such as *Klebsiella* and enterobacteria, because the transfer of bacteria from mother to infant is completely absent during Caesarean deliveries [3].

The following sections briefly introduce the results of our probiotics research conducted in the last 5 years.

Clinical studies on probiotics

Prevention of septicemia and NEC due to probiotic administration in preterm infants: Premature birth or Caesarean delivery may result in abnormal GIT colonization causing premature infants to be susceptible to gut colonization by pathological bacteria because of their daily exposure to nosocomial bacteria and the likelihood of exposure to antibiotics on admission to the neonatal intensive care unit (NICUs) [4]. Immature intestinal cells seem to have a propensity for exaggerated inflammatory responses to pathogenic stimuli, and it is postulated that, developmentally, the deficient expression of the NF-κB inhibitor IκB might allow greater NF-κB activity. Such an exaggerated inflammatory response which might be caused by immature or abnormal pattern recognition receptor (PRR) could cause increased celluar inflammation and potentially uncontrolled tissue damage [5]. Increased cellular inflammation and tissue damage can lead to intestinal permeability or a "leaky gut" that promotes bacterial product(s) translocation resulting in systemic complications such as septicemia and brain damage. Furthermore, the tissue damage may cause development of necrotizing enterocolitis (NEC) which is one of the most common devastating gastrointestinal emergency in preterm infants.

A total of 338 infants (220 with extremely low birth weight [ELBW] and 118 very low birth weight [VLBW] infants) who received *Bifidobacterium breve* supplementation (Bifido group) were admitted to our neonatal intensive care unit (NICU), and a total of 226 infants (101 ELBW and 125 VLBW infants) who were not supplemented with *B. breve* (control group).

Infants in the Bifido group were supplemented with *B. breve* with a daily dose of 1×10^9 colony forming units (CFU) dissolved in their own mother's milk alone or combined with formula for premature infants, 30 minutes before feeding. Administration of *B. breve*, was started within several hours (mean 7.2 hours) after birth and continued until discharge from the NICU. The control group was fed with their own mother's milk alone or mixed with formula for premature infants without the addition of probiotic. The incidence rate of NEC and infection was compared in the two groups.

There was a significant difference ($P<0.01$) in the incidence of NEC in the Bifido group (no cases) as compared to the control group where 6 cases (2.6%) developed NEC. In this study, it was also confirmed that there was not only a significant reduction in infection rate from 28.8% in the control group to 20.7% as compared to the Bifido group ($P<0.05$) was there, but also that mortality from infection (13.8% in the controls vs. 0.6% in the Bifido) and the mortality ratio from infection in the total mortality (23.7% in the controls vs. 5.1% in the Bifido, $P<0.05$) were lower in the Bifido group [6]. A major strategy for preventing NEC is to find a means to reduce the excessive immature inflammatory response and to accelerate the maturation of intestinal defenses, which should also contribute to prevent bacterial translocation leading to systemic infection and/ or sepsis. Previously, we have demonstrated that supplement of VLBW infants with *B. breve*, initiated during the early hours of life, promoted the establishment of bifidobacteria predominated gut microbiota, leading to an intestinal environment where concentrations of lactate and acetate were higher but butyrate was lower, and also facilitating the development of gut immune function [3,7,8].

***Corresponding author:** Yuichiro Yamashiro, Probiotics Research Laboratory, Juntendo University Graduate School of Medicine, Tokyo, Japan, Tel: +81-3-5689-0082; E-mail: yamasiro@juntendo.ac.jp

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The present findings, together with those of others [9,10], suggest that *B. breve* supplemented as a probiotic to ELBW and VLBW infants may modulate the composition of the intestinal microbiota and production of SCFA to the benefit of the host. Thus, probiotic treatment is suggested as a very effective method to promote prevention of NEC and infection in ELBW and VLBW infants.

Probiotic therapy to ameliorate chemotherapy-induced mucositis in children with cancer: Mucositis, also referred to as mucosal barrier injury, is one of the most debilitating side effects of chemotherapy for treatment of cancer. Clinically, mucositis is presented with stomatitis and ulcer and is associated with severe pain, appetite loss, diarrhea, high fever/ bacteremia, and malnutrition. These complications often require total parenteral nutrition, and intravenous (i.v.) infusion of broad-spectrum antibiotics. Chemotherapeutics have a detrimental effect on the intestinal microbial composition by drastically reducing the numbers of anaerobic bacteria leading to bacterial translocation, together with intestinal mucosal damage.

For the purpose of alleviation of signs and symptoms of mucositis, the effect of *B. breve* administration in children with malignancy undergoing chemotherapy was investigated. A placebo-controlled trial was conducted and patients with malignancies admitted in our hospital for chemotherapy (n=42) were randomized into 2 groups receiving either the probiotic or a placebo.

The frequency of fever and the use of i.v. antibiotics were lower in the probiotic group as compared to the placebo group and probiotic administration enhanced the growth of anaerobes. Disruption of the intestinal microbiota after chemotherapy resulting in an increase in population levels of Enterobacteriaceae in the placebo group as compared to the probiotic group. The concentration of total organic acids was maintained at the normal level, which resulted in the fecal pH being below 7.0 in the probiotic group [11].

Risk management of long-term inpatients at health service facilities for the elderly by continuous intake of probiotic: With age, there are a variety of physiological problems resulting in a decline in organ function and immune response leading to a number of problems, which result in an increased requirement for health care facility. The patients become susceptible to infection that often becomes very severe leading to mortality. The possibility of spread of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* infection through contact between staff carriers and inpatients at the healthcare service facility is very high and hence an efficient strong strategy for infection control that is safe and economical is strongly desired. The effectiveness of continuous intake of *Lactobacillus casei* strain Shirota (LcS)-fermented milk in open trials that compared the results of pre- and post-intake of the probiotic on the inpatients living at a facility for the elderly (n=42, 82 ± 10 years) was evaluated. LcS-fermented milk was consumed continuously for 6 months. It was observed that the number of days that the inpatients in the probiotic group suffered from fever, diarrhea, and constipation was reduced during the post-intake period as compared to the pre-intake period. This was accompanied by an increase in Bifidobacteria count and a decrease in Clostridium species in the inpatients in the probiotic group after intake.

No MRSA was detected in the fecal samples after the intake of the probiotic drink. There were no cases of nosocomial infection among the staff. LcS-fermented milk is therefore considered to be useful for improving clinical conditions, the enteric microflora, and environment in such inpatients [12].

Effects of prophylactic intake of probiotic for norovirus infection: An open case-controlled study to evaluate the effect of the intake of LcS-fermented milk on norovirus gastroenteritis was also undertaken among the elderly people who were the same subjects who participated in study 3. Continuous intake of LcS-fermented milk could positively contribute to the alleviation of fever caused by norovirus gastroenteritis by correcting the imbalance of the intestinal microflora typical of the elderly, although it did not protect them from the disease [13].

Daily intake of probiotic-fermented milk may prevent influenza infection: Study results were retrieved from information provided by a local group of people living in a southern-most island of Japan where there had been an interesting rumor associated with an influenza A (H1N1) epidemic in 2009 in a local town along the lines of "Drinking of a special milk (in fact: LcS-fermented milk) may have prevented flu from occurring among school teachers of primary school". One of the authors subsequently visited the school teachers including the Principal four months after settling the epidemic, to investigate and to ask whether they agreed to be enrolled in the clinical study to investigate effects of the fermented milk on the influenza infection. All gave an informed consent for the enrollment and provided blood samples for antibody analysis for the virus. They had been diagnosed of their influenza infections by doctors at a local hospital which was the only hospital in the area, based on clinical signs and symptoms in addition to the antibody of the nasal smear.

The pertinent data are shown in Table 1.

Two of the 9 subjects who had not taken the fermented milk became infected but the remaining 7, who had been drinking it did not. These results suggest that probiotic, LcS-fermented milk, may be useful for prophylaxes of influenza infection.

Subjects	Gender	Age	Drinking LcS-fermented milk (m; month till the epidemic)	Infection	H1N1 titer*
1	F	20s	No	Yes	01:32
2	F	30s	No	Yes	0.086111111
3	F	40s	Yes (>1 m)	No	01:10
4	M	40s	Yes (>1 m)	No	< 1:10
5	M	50s	Yes (>1 m)	No	01:20
6	F	50s	Yes (>6 m)	No	01:20
7	M	50s	Yes (>1 m)	No	01:10
8	F	50s	Yes (>1 m)	No	01:40
9	F	30s	Yes (>6 m)	No	01:10

* Positive titer; 1:40 or more
(Kindly analyzed at National Institute of Infectious Diseases,Tokyo, Japan)

Table 1: Effects of LcS-Fermented Milk on Influenza A H1N1 Infection in 2009.

Discussion and Conclusion

This brief review provides an update on probiotic effects on treatment or prevention of important disorders in immunocompromised hosts, based on our clinical studies, such as in preterm infants, cancer patients receiving chemotherapy, and elderly people, who are mostly accompanied by dysbiosis. When they are burdened with stresses, inflammation, infection etc., bacterial translocation from the intestine to the systemic circulation tends to be induced and resulting in systemic diseases including septicemia.

In preterm infants with dysbiosis, we demonstrated that earlier administration of *B. breve* led to earlier gut colonization of bifidobacteria predominantly [3]. And thus, daily supplement of *B. breve* initiated within several hours of early life has routinely introduced in our NICU for more than 10 years [6]. In addition to the probiotic supplement, mother's breast milk should be given to the infant as early as possible. This remedy is also emphasized by others [9,10]. *B. breve* supplement accelerates the feeding schedule probably due to promotion of gut motility [6].

Chemotherapeutics for cancer therapy have a detrimental effect on the intestinal microbial composition, by drastically reducing the numbers of anaerobic bacteria [14] resulting in its discontinuity, thereby promoting bacterial translocation [15]. These findings strongly suggest that the commensal microbiota might play a pivotal role in chemotherapy-induced mucositis. Restoring dysbiosis is possible by interventions, and would attenuate intestinal mucositis. Considering the complexities of the mechanisms that underlie its etiology, it seems that probiotics supplementation may be an effective therapy for mucositis, however further clinical studies are clearly needed because data is still limited.

Age is associated with immune dysfunction, which results in an increased infection rate. In elder care facilities, it is highly likely that an infection, after it emerges, will spread easily among residents. It has therefore become a major challenge for residential long-term care homes for the elderly to take measures to prevent infections among their elderly residents. Our study showed that daily intake of probiotic-fermented milk was quite useful to manage the elderly people's health care at the nursing home, although viral infection, such as norovirus gastroenteritis was not prevented. Regarding viral diarrhea, it is well known that probiotics such as *Lactobacillus* GG reduces the incidence of rotavirus gastroenteritis [16] but the effect of probiotics on norovirus gastroenteris, which is very common infectious gastroenteritis globally [17] is not well known. The probiotic, LcS may be effective for the prophylaxis of influenza infection in healthy adults by improving natural killer cell activity with the intake of LcS-fermented milk [18], but not in elderly people [19].

Regarding expanding application of probiotics for modification of dysbiosis and for immunomodulation to prevent disorders in the host has potential, based on our experience, for example the application for metabolic syndrome including type 2 diabetes. At the same time, research on the roles of gut microbiota in health and disease should be further conducted in more depth.

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References

1. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. (2010) A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464: 59-65.
2. Rahman S Md, Nagata S, Matsuda K (2012) Molecular biological studies of the origin of neonatal fecal Bifidobacterium and Lactobacillus in neonatal feces. Int J of Probiotics Prebiotics 7: 91-98.
3. Li Y, Shimizu T, Hosaka A, Kaneko N, Ohtsuka Y, et al. (2004) Effects of *Bifidobacterium breve* supplementation on intestinal flora of low birth weight infants. Pediatr Int 46: 509-515.
4. Stoll BJ, Gordon T, Korones SB, Shankaran S, Tyson JE, et al. (1996) Early-onset sepsis in very low birth weight neonates: a report from the National Institute of Child Health and Human Development Neonatal Research Network. J Pediatr 129: 72-80.
5. Nanthakumar NN, Fusunyan RD, Sanderson I, Walker WA (2000) Inflammation in the developing human intestine: A possible pathophysiologic contribution to necrotizing enterocolitis. Proc Natl Acad Sci U S A 97: 6043-6048.
6. Satoh Y, Shinohara K, Umezaki H (2007) Bifidobacteria prevents necrotising enterocolitis and infection in preterm infants. Int J Probiotics Prebiotics 2: 149–154.
7. Fujii T, Ohtsuka Y, Lee T, Kudo T, Shoji H, et al. (2006) *Bifidobacterium breve* enhances transforming growth factor beta1 signaling by regulating Smad7 expression in preterm infants. J Pediatr Gastroenterol Nutr 43: 83-88.
8. Wang C, Shoji H, Sato H, Nagata S, Ohtsuka Y, et al. (2007) Effects of oral administration of *Bifidobacterium breve* on fecal lactic acid and short-chain fatty acids in low birth weight infants. J Pediatr Gastroenterol Nutr 44: 252-257.
9. Bin-Nun A, Bromiker R, Wilschanski M, Kaplan M, Rudensky B, et al. (2005) Oral probiotics prevent necrotizing enterocolitis in very low birth weight neonates. J Pediatr 147: 192-196.
10. Lin HC, Su BH, Chen AC, Lin TW, Tsai CH, et al. (2005) Oral probiotics reduce the incidence and severity of necrotizing enterocolitis in very low birth weight infants. Pediatrics 115: 1-4.
11. Wada M, Nagata S, Saito M, Shimizu T, Yamashiro Y, et al. (2010) Effects of the enteral administration of *Bifidobacterium breve* on patients undergoing chemotherapy for pediatric malignancies. Support Care Cancer 18: 751-759.
12. Bian L, Nagata S, Asahara T (2011) Effects of the continuous intake of *Lactobacillus casei* strain Shirota fermented milk on risk management of long-term inpatients at health service facilities for the elderly. Int J Probiotics Prebiotics 6: 12-132.
13. Nagata S, Asahara T, Ohta T, Yamada T, Kondo S, et al. (2011) Effect of the continuous intake of probiotic-fermented milk containing *Lactobacillus casei* strain Shirota on fever in a mass outbreak of norovirus gastroenteritis and the faecal microflora in a health service facility for the aged. Br J Nutr 106: 549-556.
14. van Vliet MJ, Tissing WJ, Dun CA, Kamps WA, de Bont ES, et al. (2009) Chemotherapy treatment in pediatric patients with acute myeloid leukemia receiving antimicrobial prophylaxis leads to a relative increase of colonization with potentially pathogenic bacteria in the gut. Clin Infect Dis 49: 262-270.
15. Sonis ST (2004) The pathobiology of mucositis. Nat Rev Cancer 4: 277-284.
16. Isolauri E, Juntunen M, Rautanen T, Sillanaukee P, Koivula T (1991) A human Lactobacillus strain (*Lactobacillus casei* sp strain GG) promotes recovery from acute diarrhea in children. Pediatrics 88: 90-97.
17. Siebenga JJ, Vennema H, Zheng DP, Vinjé J, Lee BE, et al. (2009) Norovirus illness is a global problem: emergence and spread of norovirus GII.4 variants, 2001-2007. J Infect Dis 200: 802-812.
18. Takeda K, Suzuki T, Shimada SI, Shida K, Nanno M, et al. (2006) Interleukin-12 is involved in the enhancement of human natural killer cell activity by *Lactobacillus casei* Shirota. Clin Exp Immunol 146: 109-115.
19. Van Puyenbroeck K, Hens N, Coenen S, Michiels B, Beunckens C, et al. (2012) Efficacy of daily intake of *Lactobacillus casei* Shirota on respiratory symptoms and influenza vaccination immune response: a randomized, double-blind, placebo-controlled trial in healthy elderly nursing home residents. Am J Clin Nutr 95: 1165-1171.