World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/1007-9327office
wjg@wjgnet.com
doi:10.3748/wjg.v17.i24.2890

World J Gastroenterol 2011 June 28; 17(24): 2890-2896
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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TOPIC HIGHLIGHT

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Probiotics in hepatology

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Received: December 13, 2010 Revised: February 18, 2011
Accepted: February 25, 2011
Published online: June 28, 2011

Abstract

The paper provides a basic review of intestinal microflora and its importance in liver diseases. The intestinal microflora has many important functions, above all to maintain the microbial barrier against established as well as potential pathogens. Furthermore, it influences the motility and perfusion of the intestinal wall, stimulates the intestinal immune system and therefore also the so-called common mucosal immune system, reducing bacterial translocation and producing vitamins. Immune homeostasis at mucosal level results from a controlled response to intestinal luminal antigens. In liver cirrhosis, there are many changes in its function, mostly an increase in bacterial overgrowth and translocation. In this review, probiotics and their indications in hepatology are generally discussed. According to recent knowledge, these preparations are indicated in clinical practice only for cases of hepatic encephalopathy. Probiotics are able to decrease the permeability of the intestinal wall, and decrease bacterial translocation and endotoxemia in animal models as well as in clinical studies, which is extremely important in the prevention of complications of liver cirrhosis and infection after liver transplantation. Probiotics could limit oxidative and inflammatory liver damage and, in some situations, improve the histological state, and thus non-alcoholic steatohepatitis could be considered as another possible indication.

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Key words: Intestinal microflora; Probiotics; Liver encephalopathy; Non-alcoholic steatohepatitis; Liver cirrhosis

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Lata J, Jurankova J, Kopacova M, Vitek P. Probiotics in hepatology. *World J Gastroenterol* 2011; 17(24): 2890-2896 Available from: URL: http://www.wjgnet.com/1007-9327/full/v17/i24/2890.htm DOI: http://dx.doi.org/10.3748/wjg.v17.i24.2890

INTRODUCTION

In recent years, probiotics have become a promising alternative for the treatment of gastrointestinal and various other diseases. Despite their initially described negative influence on the course of disease, as in the case of acute pancreatitis[1], these medicines are considered safe and their beneficial effects have also been intensively studied and described in hepatology[2].

INTESTINAL MICROFLORA

The average length of an average human adult intestine

is approximately 10 m and its irregular surface is covered with one layer of epithelial cells that represent a surface area of approximately 200 m^2. The intestinal microflora above all plays a very important role in the immune reactions of the body. During fetal development, the intestine is sterile and becomes colonized with the first microorganisms after the passage of the fetus through the birth canal. After birth, the intestine is very quickly colonized with various microorganisms, the composition of which is highly variable during the first few days of life. After the first week, the intestinal microflora achieves a stable composition that depends on the method of birth, environment and type of nutrition. In breast-fed infants, there is a predominance of bifidobacteria, while in infants on milk formula, the number of bifidobacteria can be several times lower. Breast-fed infants are therefore colonized sooner with bacterial strains whose composition resembles that of the intestinal microflora of an adult[3]. The initial colonization of the intestine also plays a very important role in further development of the individual, as the bacteria present may modulate gene expression of epithelial cells and thus create a favorable environment for themselves[4]. The primary colonizers are permanently settled in the intestine and determine intestinal colonization with further bacterial strains later in life, which are important for the final composition of intestinal microflora in adulthood.

Major changes in the features of the intestinal ecosystem occur after weaning[5]. During this period, anaerobic bacteria such as *Bacteroides spp*. and *Clostridium spp*. achieve a strong position and the intestinal ecosystem evolves into its stable form. The intestinal microflora contains a large amount of microbes that weigh more than 1 kg; this quantity exceeds the number of cells in the human body 10-fold. The microbial community of the intestine consists of more than 500 species, most of which have not been cultivated, and many that have not been identified so far. The intestinal microflora contains both bacteria that are fixed in the intestine (autochthonous, resident) and bacteria that only pass through the intestine (transient allochthonous)[6]. Most of the bacteria in the intestine form an anaerobic bioreactor that helps to digest difficult polysaccharides and synthesizes micronutrients including vitamins and short-chain fatty acids. The fermentation products of these bacteria can provide up to 10% of the daily energy needed by an individual[7]. The composition of human gastrointestinal microflora is given in Table 1.

The relationships between the host and their microflora bacteria also play an important role in postnatal development, maturation of the intestine and development of the mucosal immune system.

The intestinal microflora has many important functions, in particular to maintain the microbial barrier against established as well as potential pathogens, and furthermore, it influences the motility and perfusion of the intestinal wall, stimulates the intestinal immune system, and therefore also the so-called common mucosal immune system, reducing bacterial translocation and producing vitamins.

The digestive tract microflora is continuously influenced by numerous physical, chemical and biological factors that can affect its balance, and therefore it represents a constant potential source of digestive tract and whole-body disease. Changes in the total amount, localization, strain or species structure and in the metabolic activity of microorganisms may occur. Impairment of digestive tract microflora physiology can lead to disease or act as its cofactor (infectious, medication-associated, post-antibiotic and post-radiation diarrhea and colitis, functional diseases of the digestive tract-chronic constipation, irritable bowel syndrome, inflammatory bowel diseases, immunodeficiencies, colorectal carcinoma, some extraintestinal diseases and last, but not least, also liver diseases)[8]. In patients with liver cirrhosis, abnormal colonization of the small intestine with colonic bacteria has been reported, while the amount of these bacteria in the small intestine of healthy individuals is small. There is a reciprocal regulatory activity between intestinal microflora and the motility of the small intestine, where the motility is regulated by the presence of intestinal bacteria. Inhibition of gastric acid production induces bacterial overgrowth in the small intestine, whereas the overgrowth of its proximal part correlates with bacterial translocation into the extraintestinal space, such as the mesenteric lymph nodes, liver and spleen.

CHANGES IN INTESTINAL MICROFLORA IN PATIENTS WITH CHRONIC LIVER DISEASES

Intestinal bacterial overgrowth was described in approximately one-third of patients with alcoholic cirrhosis, ascites or advanced liver dysfunction. The main causes are considered to be anchylosis and hypochlorhydrosis, a decrease in IgA secretion and malnutrition caused by liver dysfunction, and possibly alcoholism. Also, the decrease in intestinal motility associated with cirrhotic liver damage facilitates bacterial overgrowth in the small intestine. The impaired immune mechanisms of the mucous membrane of the small intestine facilitating bacterial overgrowth can be one explanation of the repeated and common infections in patients with liver cirrhosis. In particular, the spontaneous infection of ascites-spontaneous bacterial peritonitis (SBP)-is a frequent and severe condition[9,10]. In contrast, suppression or eradication of intestinal facultative anaerobic gram-negative bacteria prevents their translocation and SBP, both in cirrhotic rats and in liver cirrhosis patients.

As a result of bacterial overgrowth, bacterial translocation may occur, and portal hypertension also plays an important role. It leads to vasodilation of the intestinal mucous membrane, edema of the lamina propria, fibromuscular proliferation and hypertrophy of the muscularis mucosae. Furthermore, the integrity of the intestinal mucous membrane is compromised; toxic influences of alcohol, disturbances in biliary secretion, malnutrition, decrease in growth factor secretion (insulin-like growth factor I),

Table 1 Composition of the human gastrointestinal tract microflora (from Nord and Kager, 1984)

Microorganisms	Numbers of microorganisms (CFU/mL or CFU/g)			
	Stomach	Jejunum	Ileum	Colon
Total bacterial count	$0\text{-}10^3$	$0\text{-}10^5$	$10^3\text{-}10^9$	$10^{10}\text{-}10^{12}$
Aerobically growing agents				
Family *enterobacteriaceae*	$0\text{-}10^2$	$0\text{-}10^3$	$10^2\text{-}10^7$	$10^4\text{-}10^{10}$
Streptococci	$0\text{-}10^3$	$0\text{-}10^4$	$10^2\text{-}10^6$	$10^5\text{-}10^{10}$
Staphylococci	$0\text{-}10^2$	$0\text{-}10^3$	$10^2\text{-}10^5$	$10^4\text{-}10^9$
Lactobacilli	$0\text{-}10^3$	$0\text{-}10^4$	$10^2\text{-}10^3$	$10^6\text{-}10^{10}$
Yeasts	$0\text{-}10^3$	$0\text{-}10^2$	$10^2\text{-}10^4$	$10^4\text{-}10^6$
Anaerobic bacteria				
Bacteroides	Rare	$0\text{-}10^3$	$10^3\text{-}10^7$	$10^{10}\text{-}10^{12}$
Bifidobacteria	Rare	$0\text{-}10^4$	$10^3\text{-}10^9$	$10^4\text{-}10^{11}$
Peptostreptococci	Rare	$0\text{-}10^3$	$10^2\text{-}10^6$	$10^{10}\text{-}10^{12}$
Clostridia	Rare	Rare	$10^2\text{-}10^4$	$10^6\text{-}10^{11}$
Eubacteria	Rare	Rare	Rare	$10^{10}\text{-}10^{12}$

changes in bile composition and flow or increased levels of nitric oxide may be present, as well as portal hypertension. The increase in intestinal permeability is conspicuously proportionate to the degree of portal hypertension, but it is independent of severity and etiology of liver impairment[11]. In patients with liver cirrhosis and portal hypertension, vascular resistance decreases and splanchnic flow increases. These changes lead to hypoperfusion and hypoxia of the mucous membrane further compromising the vascular wall. As a consequence of this, translocation of intestinal bacteria occurs easily[12].

The term bacterial translocation was used for the first time in 1979[13]. Bacterial translocation is defined as active or passive penetration of live microorganisms and their toxic products across the epithelial layer of the mucous membrane to the lamina propria mucosae. Microorganisms then migrate to the lymph nodes and/or into extraintestinal locations. Under normal conditions, this refers to the small amount of bacteria that are destroyed by the immune system of the lamina propria. Translocation is only possible when there are a high number of bacteria; the literature reports up to 10^8 bacteria in 1 g of stool[14].

Bacteria that escape phagocytes, as well as destruction by complement, can reach the circulation. *Enterobacteria, staphylococci* and *enterococci* are able to translocate, i.e. pass alive across the intestinal epithelium into the mesenteric lymph nodes, blood and other organs, while most other anaerobic microorganisms lack this ability. Bacterial translocation can be verified by positive cultivation from mesenteric lymph nodes. The main mechanisms leading to translocation include a deficit in the local immune response of the mucous membrane, a decrease in phagocytic activity of macrophages as well as neutrophils, an increase in the permeability of the intestinal barrier, and intestinal bacterial overgrowth[15].

Factors that influence bacterial translocation can be divided into 3 groups. These are the bacterial factor, comprising the nature of the translocating agent and the status of the surrounding physiological microflora, the morphological and functional state of the intestinal wall, and not least the so-called defensive factors, i.e. local and systemic antibacterial activities of the organism[16,17]. All of these systems are impaired in patients with liver cirrhosis[18].

PROBIOTICS

The history of probiotics started at the beginning of the last century with Metchnikoff[19]; however, German authors often report a study by Döderlein as the first description of a possible probiotic 16 years before Metchnikoff proposed the use of vaginal lactate-producing bacteria for the inhibition of pathogenic bacteria growth, and attributed the higher average age of certain ethnic groups to the increased intake of fermented milk products and recommended their use.

Probiotics were originally defined as "microorganisms causing growth of other microorganisms", and later on as "live microorganisms that cause or support the beneficial balance of autochthonous microbial population of the gastrointestinal tract (GIT)". These microorganisms do not have to be an essential permanent component of the GIT, but should have a "beneficial influence on the general and health status of an individual". Currently, probiotics are defined more precisely as "monocultures or mixed cultures of live microorganisms that, if administered to a person, positively influence the host by improving the properties of his/her own microflora"[20].

UTILIZATION OF PROBIOTICS IN HEPATOLOGY

In the Cochrane Library Review, there is currently no unambiguous recommendation for administration of probiotics in any indication in hepatology. According to the World Gastroenterology Organisation Practice Guideline "Probiotics and prebiotics" are probiotics in hepatology indicated only for hepatic encephalopathy[21], and in clinical practice, probiotics are now administered in principle only in the above-mentioned treatment of hepatic encephalopathy, with the disadvantage of a higher price compared to the standard treatment. The use of

probiotics in the treatment of non-alcoholic steatohepatitis and in prophylaxis of infections, or some complications in patients with liver cirrhosis, can be expected in the future.

Liver encephalopathy

It is believed that gut-produced ammonia plays a key role in the pathogenesis of hepatic encephalopathy because of the failure of the diseased liver to clear toxic products. Small intestinal overgrowth and delayed gastrointestinal transit time in cirrhotic patients plays an important role[22].

Lactulose and non-absorbable antibiotics currently hold a dominant position in the treatment of liver encephalopathy. One of the effects of lactulose may be a probiotic effect on lactobacilli that reduce the activity of bacterial ureases, resulting in a decrease in hyperammonemia. Probiotics can also have a similar effect and are already included in some recommendations for the treatment of minimal liver encephalopathy[23].

As early as the 1960s, the beneficial effect of *Lactobacillus acidophilus* was described on the course of liver encephalopathy in patients with liver cirrhosis[24]. In a more recent study on 97 patients, the beneficial effect of a synbiotic (mixture of a probiotic and prebiotic) on minimal liver encephalopathy was observed, with a decrease in ammonium levels as well as the improvement of symptoms of encephalopathy[25]. Minimal liver encephalopathy is described as an otherwise inexplicable impairment of cognitive functions such as prolonged psychomotor tempo, lack of attention, impairment of fine motor functions and the perception of visual sensations that can only be detected using special neurophysiological tests, and is present in 30%-70% of patients with liver cirrhosis without liver encephalopathy. In the treatment of advanced liver encephalopathy, a beneficial effect of *Enterococcus faecium* was observed, the administration of which led to an improvement in clinical status, electroencephalogram findings and a reduction of ammonium levels[26]; the treatment of the *Enterococcus* strain SF69[27] also had a similar effect. A mixture of probiotics[28] may have an even better effect. A combination of *Bifidobacterium* + fructo-oligosaccharides also demonstrated a significant reduction in the Trail Making Test B, a significant increase in the Symbol Digit Modalities Test and Block Design Test and improvement in some laboratory findings[29].

A study confirming improvement of liver encephalopathy during long-term administration of probiotic yogurts with the advantage of excellent adherence with potential for long-term adherence[30] is also of interest.

So far, there are only very few experimental studies, however, the studies comparing the efficacy of probiotic preparation *Golden Bifid* and lactulose on an experimental rat model of minimal hepatic encephalopathy induced by thioactamide showed excellent effects in lowering the level of ammonemia and endotoxemia, improving hepatic histopathology of rats, and decreasing the incidence of minimal hepatic encephalopathy[31].

The use of probiotics in common clinical practice as well as evaluation of the economic effect of the treatment will, however, require further studies. At the moment, a study titled "Probiotic *Lactobacillus* GG (LGG) in Patients with Minimal Hepatic Encephalopathy" is being conducted at Virginia Commonwealth University and we can only hope it will bring novel, positive results.

Effects on bacterial intestinal translocation, reduction in infections or prophylaxis of liver cirrhosis complications

Infectious complications are very frequently caused by bacterial strains that originate from the digestive tract. Bacterial overgrowth, as well as the associated translocation of microbes across the dysfunctional mucous membrane barrier, occurs for the above-mentioned reasons, especially in liver cirrhosis. The small gut of cirrhotic rats is contaminated by colonic microflora, which translocate to mesenteric lymph nodes, and is the most important cause of infection of ascites and spontaneous bacterial peritonitis. The identity of microbial strains in the gut, mesenteric lymph nodes and ascites was demonstrated by analysis of macrorestricted fragments DNA[32].

In 50%-70% of patients with liver cirrhosis, bacterial overgrowth occurs in the small intestine as a result of gram-negative colon microflora contamination. As a result, an impairment of the intestinal barrier with increased bacterial translocation occurs. Apparently, it is the most important point of entry of infection in cirrhotic patients; generally, infections are very common in liver cirrhosis and can be involved in many complications associated with the disease. In the first animal studies with short term application of *Lactobacillus* GG, the treatment did not prevent translocation of colonic microflora, although it was able to colonize the cecum in 90% of cirrhotic rats[33]. In later studies, preventive treatment with *Lactobacillus plantarum* inhibited an increase in permeability after subsequent application of *E. coli*[34], and *Lactobacillus johnsonii* La1 with antioxidants were able to decrease endotoxemia and prevent bacterial translocation in cirrhotic rats[35].

In clinical studies, administration of a symbiotic reduced the endotoxemia, which is an indicator of the degree of translocation[11]. In our study, a reduction in endotoxemia was achieved through administration of *E. coli* Nissle for 42 d[36]. The clinical significance of this has yet to be verified, but the beneficial influence on the prophylaxis of severe infectious complications, such as spontaneous bacterial peritonitis, can be expected.

In both the above-mentioned papers, an improvement in functional liver capabilities was observed, evaluated according to the Child-Pugh classification. It can be presumed that the recovery of physiological microflora in the digestive tract will reduce the liver load of toxic metabolites, above all endotoxin, which might potentially be absorbed. It stimulates secretion of cytokines. The cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1 and interleukin-6 can influence the formation and degradation of the extracellular matrix, which is important for the development of liver fibrosis as well as during cirrhotic rearrangement[37]. Apart from the above-

mentioned decrease in endotoxin levels, a direct decrease in cytokine levels after administration of VSL#3 probiotic has also been reported[38]. There are some data showing, that Se-enriched *Lactobacillus* can intervene in carbon tetrachloride-induced liver injury in mice by enhancing macrophage function to maintain normal and beneficial effects, elevating antioxidant-enzyme activities, reducing lipid peroxidation reaction and inhibiting excessive release of TNF-α[39]. However, this extremely important finding will have to be confirmed. Another study with VSL#3, presenting a trend of a reduction in plasma endotoxin, on the other hand showed no change in the hepatic venous pressure gradient or intestinal permeability[40].

In liver cirrhosis of alcoholic etiology, the alcohol itself may play a role, such as increased gut permeability, endotoxemia, and TNF-α production[41]. In rats, *Lactobacillus* GG has been shown to reduce alcohol induced gut leakiness and steatohepatitis[42]. The same group also found that the mucosa-associated microflora was altered in rats on a high alcohol diet, and this dysbiosis could be counteracted by *Lactobacillus* GG or oat supplementation[43]. In a rat model of acute pancreatitis, synbiotic (*Lactobacillus acidophilus*, *Lactobacillus helveticus* and *Bifidobacterium* in an enriched medium) and metronidazole were able to effectively protect against endotoxin/bacterial translocation, as well as liver damage in the course of acute pancreatitis and concomitant heavy alcohol consumption. The beneficial effect of synbiotics on liver histology seems to be correlated with endotoxemia. Metronidazole did not produce such a beneficial effect; in fact, it further worsened liver damage when alcohol was added to the background of ongoing acute pancreatic inflammation[44].

However, no large randomization study has been carried out as yet which would be relevant for clinical practice, although a recent study again confirmed the theoretic presumptions for beneficial action in this field[45]. The "Probiotics for the Prevention of Major Complications of Cirrhosis" study, carried out in the Meir Medical Center in Israel, was finished last year but its results have not yet been published.

Non-alcoholic steatohepatitis

Fatty liver disease that develops in the absence of alcohol abuse is increasingly recognized as a major health burden. Non-alcoholic steatohepatitis (NASH) was first described by Ludwig in 1980 as a disease that histologically mimicked alcoholic hepatitis and that also may progress to cirrhosis[46]. The diagnostic criteria for NASH continue to evolve and rely on the histologic findings of steatosis, hepatocellular injury (ballooning, Mallory bodies), and the pattern of fibrosis in patients with minimal intake of ethanol (< 20 g ethanol/d)[47]. Recently, NASH has been studied extensively as it is relatively frequent, and may lead to the development of liver cirrhosis. So far, treatment has not been established and probiotics may play an important role, as the bacterial overgrowth and associated increase of proinflammatory cytokines are important etiopathogenic mechanisms of NASH[48]. Clinical studies so far have been missing in this field, but the positive effect of probiotics has already been described in some laboratory studies. In mice with non-alcoholic liver steatosis, treatment with probiotics or anti-TNF antibodies improved the histological picture of the degree of damage to the liver parenchyma, led to a decrease in the alkaline phosphatase level, improved insulin resistance, and the content of total fatty acids in the liver also dropped. In another study on a model of non-alcoholic liver steatosis, treatment with the probiotic VSL#3 or TNF-α antibodies had a positive influence on histological findings, the fatty acids in hepatocytes were reduced, the ALT level decreased and the expression of TNF-α[49,50] was reduced. Similar data suggesting that VSL#3 administration could limit oxidative and inflammatory liver damage were published in a more recent study[51]. Some previous studies showed that a high fat diet caused obesity, hepatic steatosis and natural killer T-cell (NKT cell) depletion[52]. The VSL#3 was also shown to increase hepatic NKT cell number and reduce inflammatory signaling[53]. Another study indicated that VSL#3 modulates liver fibrosis but does not protect from inflammation and steatosis in NASH. It means, that VSL#3 effects on fibrosis may occur even in the absence of significant changes in markers of inflammation and fat in the liver[54].

In the Cochrane Library Review, there is currently no unambiguous recommendation for administration of probiotics in NASH, even if the results from pilot studies seem promising. Randomized clinical trials are necessary to assess the clinical implication of probiotic therapy in non-alcoholic fatty liver disease and non-alcoholic steatohepatitis[55]. Two clinical studies on the effects of probiotics on NASH are currently being conducted in Hong Kong and in Israel. Hopefully their conclusions will be encouraging.

Prophylaxis of infections after liver transplantation

In the past, several papers were published that confirmed the positive influence of probiotic administration on postoperative course after large abdominal surgery. The studies are mostly of small sample size and exhibit design flaws, but they showed statistically significant differences in infectious complications in favor of synbiotics[56-58], and the synbiotic group did require significantly less days of antibiotic therapy[59].

Patients in the postoperative period after a liver transplant are mainly at risk of infection by organisms, coming in most cases from the digestive tract. As already discussed in the theoretical part of our paper, the translocation of bacteria or their parts across the intestinal wall into the circulation occurs as a result of disturbances in barrier function of the intestine and disturbance of the immune system. Bacteria that translocated from the intestinal tract can be carried through the circulation into more distant systems and cause colonization or infection in extraintestinal locations. A prospective, randomized, double-blind study was published on 66 patients after liver transplantation, whereas half of the patients received a combination of 4 *Lactobacillus spp*. together with the standard enteral

nutrition. In the probiotic group, a significant reduction in postoperative bacterial infection (3% against 48%) was observed and the length of the antibiotic therapy was substantially reduced[60]. In our study on patients after liver transplantation, we demonstrated a correlation between an increase in endotoxin and the subsequent presence of phenotypically as well as genotypically identical strains (originally cultivated from the gastrointestinal tract) in an extraintestinal location[61]. Monitoring serum endotoxin levels can probably confirm bacterial translocation with an increased risk of infectious complications and this result further confirms the positive effect of probiotics in patients after liver transplantation. However, the conclusion is similar from the perspective of evidence-based medicine-use of prebiotics and probiotics in prevention of bacterial sepsis after liver transplantation is promising. Further randomized clinical trials are necessary.

CONCLUSION

Probiotics are becoming part of numerous therapeutic modalities in hepatology, as their effect on intestinal microflora can positively influence many liver diseases. However, verification of the efficiency of this treatment from the perspective of evidence-based medicine will be difficult, as different probiotics can be expected to have different effects in different diseases. With respect to the increasing number of studies on probiotics, the future prospects in this field are optimistic.

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