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Cover Page Footnote

The authors declare that there are no conflicts of interest to be disclosed for this article. All authors have equal contributions.

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Review

The relationship between gut microbiota and spontaneous bacterial peritonitis in patients with liver cirrhosis - a literature review

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Abstract

Gut microbiota is an essential component in the pathogenesis of liver cirrhosis and its complications. There is a direct relationship between the gut and the liver called the gut-liver axis through which bacteria can reach the liver through the portal venous blood. However, it remains unclear how bacteria leave the intestine and reach the fluid collection in the abdomen. A series of mechanisms have been postulated to be involved in the pathogenesis of spontaneous bacterial peritonitis (SBP) and other complications of liver cirrhosis, including bacterial translocation, bacterial overgrowth, altered intestinal permeability and dysfunctional immunity. The hepatic function may also be affected by the alteration of intestinal microbiota composition. Current treatment in SBP is antibiotic therapy, but lately, probiotics have been the useful treatment suggested to improve the intestinal barrier and prevent bacterial translocation. However, studies are contradictory regarding their usefulness. In this review, we will summarize the literature data on the pathogenesis of spontaneous bacterial peritonitis concerning the existence of a relationship with the microbiota and the useful use of probiotics.

Keywords

: gut microbiota, bacterial translocation, spontaneous bacterial peritonitis, probiotics

Highlights

- ✓ Bacterial overgrowth is the consequence of delayed intestinal transit in patients with liver cirrhosis.
- ✓ Probiotics are useful in treating and preventing hepatic encephalopathy, but this therapy seems to have an essential role in liver cirrhosis, non-alcoholic steatohepatitis and alcoholic liver disease.

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Introduction

Spontaneous bacterial peritonitis is the infection of the ascitic fluid by excluding possible surgical causes that can be treated. In 1970, the term was used by Harold Conn and Runyon to describe a large number of unexplained deaths before this infection was suspected in patients with an altered condition and ascites (1, 2). In patients with ascites, monitored throughout a year, spontaneous bacterial peritonitis (SBP) has had an incidence of 10-30% and a hospital mortality rate of approximately 20% (3-5). The diagnosis of SBP is made due to the presence of more than 250/mm³ of polymorphonuclear leukocytes in the ascitic fluid and the isolation of a single germ from the bacteriological cultures (6-8). SBP is the most common type of infection in patients with hepatic cirrhosis, and 70-80% of cases have gram-negative bacteria such as *E. coli* and *Klebsiella pneumoniae* as etiologic agents (9-11).

The unfavorable evolution and prognosis of patients developing SBP suggest the idea of preventing the occurrence of this complication in cirrhotic patients. The current review aims to study the relationship between gut microbiota and pathogenic mechanisms involved in SBP, as well as the benefit of using probiotics to prevent SBP.

We examined the literature data provided by MEDSCAPE and PubMed portals, and we chose the most reliable data provided by 38 studies and articles focusing on microbiota, probiotics, and SBP. We have eliminated those articles with uncertain statistics and with unclear design.

Discussions

Gut microbiota and pathogenic mechanism involved in spontaneous bacterial peritonitis

With the help of the gut-liver axis, the intestine supplies blood to the portal system and activates the functions of the liver. Conversely, the liver produces bile and facilitates the intestinal function (12). Gut microbiota contains a considerable amount of microbes that exceed ten times the number of cells in the body, and many of them have not yet been identified (13). It also has many functions including bile acid degradation, vitamin synthesis and protection against pathogens with immunity (14, 15). Approximately 50% of patients with liver cirrhosis have experienced bacterial overgrowth compared to healthy people. By stimulating intestinal motility, one can reduce the number of bacteria (16). The key mechanism in SBP pathogenesis is bacterial translocation (BT). Usually, bacterial translocation is the passage of bacteria from the gut lumen into extra

intestinal mesenteric lymph nodes (17). BT measurement can be performed indirectly by using surrogate parameters such as lipopolysaccharide (bacterial wall component), bacterial DNA or LPS binding protein (18). Usually, there is a smaller microbial density in the small intestine compared to the colon. However, there seems to be an increase in the bacteria count of the small intestine in patients with liver cirrhosis (19). An essential role in destroying the first defense mechanism of the mucosal barrier is nitric oxide. It triggers changes in the intestinal wall by enlarging the tight junctions in cultivated intestinal epithelial cells (20). There is also the destruction of the second defense mechanism represented by the expansion of the intercellular space between junctions (21). A recently discovered molecule critical in maintaining the intestinal barrier is the farnesoid X receptor (FXR) (22). The FXR synthetic antagonist can achieve BT cessation (23) and implicitly lower portal hypertension in animal models with cirrhosis (24), but experience in humans is still inexistent. Another factor contributing to the promotion of bactericidal translocation is deficient immunity, proved by an animal study that showed an increased intraepithelial lymphocyte with a low capacity to produce interferon and low proliferative activity (25). In conclusion, bacteremia and inoculation of ascitic fluid occur due to deficient immunity. The risk of developing SBP results from a low complement level in the ascitic fluid activity (26). Typically, local macrophages along with neutrophils contribute to the destruction of bacteria in the bloodstream. In cirrhotic patients, because of portal hypertension, circulating bacteria do not come in contact with Kupffer cells, and this leads to the occurrence of bacteremia. Thus, SBP is favored by neutrophil changes and low serum complement (27).

Evidence regarding probiotic uses in the treatment of spontaneous bacterial peritonitis

Because the most common causes of PBS include *E. coli* and *Klebsiella*, empirical therapy can use third-generation cephalosporins, due to their broad spectrum of action and excellent safety profile.

Cefotaxime is the most commonly used, but other agents such as ceftriaxone and ceftazidime have the same efficacy. Oral fluoroquinolones are an alternative for patients with good digestive tolerance (28). One study demonstrated that there are no significant differences in mortality rates, efficacy and adverse events following treatment with cephalosporins compared to other antibiotics. Although short and long-term treatments offer similar healing rates, the short-term treatment is

recommended (29, 30). Albumin treatment was effective in patients with serum bilirubin > 4 mg/dl, serum creatinine > 1 mg/dl and urea > 30 mg/dl. It is unclear whether they are beneficial in patients with low values of these parameters because the incidence of type 1 hepatorenal syndrome was low in both groups (7% without albumin, 0% albumin) (31). Patients at high risk of developing PBS are patients with proteins from ascitic fluid <1g/dl (primary prevention), patients with active variceal bleeding and those with previous PBS (secondary prevention).

A double-blind randomized placebo-controlled study on patients with severe hepatic disease and proteins from ascites <1.5g/dl and without previous episodes of PBS showed that norfloxacin 400 mg/day reduces the risk of PBS and improves the survival rate (32).

An alternative to antibiotics in the treatment of SBP is the use of probiotics. These drugs have several effects, namely the ability to modulate intestinal flora and improve intestinal barrier function (33, 34). Data from the current literature are contradictory regarding the effectiveness of probiotics (35). The results do not support the idea that probiotics can be used to prevent PBS. In a study on rats with cirrhosis and ascites, they failed to prevent bacterial translocation and ascitic fluid infection (36). Chiva et al. conducted a study on laboratory rats with tetrachloromethane-induced liver cirrhosis. They tested the effects of probiotics such as *Lactobacillus Johnsonii* LA1 combined with antioxidants on the intestinal microbiota and bacterial translocation.

The results showed that there was a decrease of BT in the treated rats compared to the untreated control group. However, the role of probiotics cannot be accurately attributed because antioxidant therapy alone has had the same effects (37). A similar study, but only with probiotic treatment, showed no significant effects on intestinal bacteria and bacterial translocation, suggesting that the beneficial effects in the anterior survey are the result of antioxidant therapy (38). Pande C et al. conducted a study on patients who had previously experienced a PBS episode or were at increased risk of developing this disease. They administered either norfloxacin with probiotics or placebo to norfloxacin and recorded the results for six months, including side effects and mortality rates. Thus, the addition of probiotics with norfloxacin has not been beneficial in terms of primary and secondary prophylaxis of PBS, nor in reducing the mortality rate (39). Instead, the beneficial effect of probiotics on hepatic encephalopathy was proved by a meta-analysis of 9 studies (40). Moreover, Wong et al. surveyed patients

diagnosed with NAFLD using Lepicol probiotic formula treatment and explained that probiotic treatment could improve fatty liver and AST (41). A study on patients with compensated alcoholic cirrhosis treated with *Lactobacillus Casei* Shirota showed that probiotics improve the phagocytic capacity of neutrophils (42).

Conclusions

Considering this close relationship between the microbiota and the liver, the role of the intestinal barrier seems to be the key in the pathogenesis of SBP. Bacterial translocation presents a complex pathogenic mechanism consisting in bacterial overgrowth, changes in the mucosal barrier and a weak local immune response. Bacterial overgrowth is the consequence of delayed intestinal transit in patients with liver cirrhosis. As for probiotics, there is evidence regarding their usefulness in treating and preventing hepatic encephalopathy. Also, this therapy proved its role in liver cirrhosis, non-alcoholic steatohepatitis and alcoholic liver disease. However, few recent studies have demonstrated that probiotic therapy has no benefits in the prevention of primary and secondary SBP. Therefore, more clinical trials are needed to establish their recommendation in SBP management.

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Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

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