Effect of *Lactobacillus johnsonii* La1 and antioxidants on intestinal flora and bacterial translocation in rats with experimental cirrhosis

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**Background/Aims:** Probiotics and antioxidants could be alternatives to antibiotics in the prevention of bacterial infections in cirrhosis. The aim of the present study was to determine the effect of *Lactobacillus johnsonii* La1 and antioxidants on intestinal flora, endotoxia, and bacterial translocation in cirrhotic rats.

**Methods:** Twenty-nine Sprague–Dawley rats with cirrhosis induced by CCl₄ and ascites received *Lactobacillus johnsonii* La1 10⁹ cfu/day in vehicle (antioxidants: vitamin C + glutamate) (n = 10), vehicle alone (n = 11), or water (n = 8) by gavage. Another eight non-cirrhotic rats formed the control group. After 10 days of treatment, a laparotomy was performed to determine microbiological study of ileal and cecal feces, bacterial translocation, endotoxemia, and intestinal malondialdehyde (MDA) levels as index of intestinal oxidative damage.

**Results:** Intestinal enterobacteria and enterococci, bacterial translocation (0/11 and 0/10 vs. 5/8, P < 0.01), and ileal MDA levels (P < 0.01) were lower in cirrhotic rats treated with antioxidants alone or in combination with *Lactobacillus johnsonii* La1 compared to cirrhotic rats receiving water. Only rats treated with antioxidants and *Lactobacillus johnsonii* La1 showed a decrease in endotoxemia with respect to cirrhotic rats receiving water (P < 0.05).

**Conclusions:** Antioxidants alone or in combination with *Lactobacillus johnsonii* La1 can be useful in preventing bacterial translocation in cirrhosis.

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**Keywords:** Experimental cirrhosis; Bacterial translocation; Antioxidants; Probiotics; *Lactobacillus johnsonii*; Spontaneous bacterial peritonitis

1. Introduction

Bacterial translocation of microorganisms from the intestinal lumen to extraintestinal sites appears to be a key step in the development of bacterial infections, mainly spontaneous bacterial peritonitis (SBP), in cirrhosis [1–5]. Intestinal bacterial overgrowth of aerobic bacteria [6–10] and impairment in several antimicrobial mechanisms [11–13] including disturbances in the intestinal mucosal barrier [10,14] seem to be important factors to explain bacterial translocation in cirrhosis.

In the last 15 years, the administration of antibiotics to suppress aerobic intestinal flora has proven effective in the prevention of bacterial infections in rats with experimental cirrhosis [15,16], as well as in cirrhotic patients [17–20]. However, bacterial resistance to antibiotics is a growing problem, mainly when antibiotic prophylaxis is performed over long periods of time [20–24]. Therefore, alternative non-antibiotic approaches are currently being evaluated in several situations where antibiotics were used [7,10,25–30]. Microbial interference therapy (MIT) consists of maintaining or restoring health by introducing living microorganisms (probiotics) into the host to stabilize the balance of
intestinal flora [25,31]. As probiotics can decrease intestinal bacterial overgrowth [27,32] and improve the immunological defence mechanisms [33,34], it has been suggested that they could be useful in the prevention of bacterial infections from intestinal origin in different settings [25–29,35]. *Lactobacillus johnsonii* La1 is a lactic acid bacteria able to adhere to intestinal cells [36], inhibits cell attachment and invasion by enterovirulent bacteria [36], and improves phagocytic activity of granulocytes [33].

On the other hand, intestinal mucosal oxidative damage probably due to hypoperfusion and hypoxia has been implicated in impaired intestinal barrier contributing to bacterial translocation in several experimental models of portal hypertension, including cirrhosis [37–39]. Antioxidants have been shown to be useful in the prevention of bacterial translocation in rats with prehepatic portal hypertension and common bile duct ligated rats [37,38].

The aim of the present study was to determine the effect of a probiotic strain (*Lactobacillus johnsonii* La1) (La1) and antioxidants on intestinal flora, intestinal mucosal oxidative damage, endotoxemia and bacterial translocation in an experimental model of cirrhosis in rats.

2. Materials and methods

2.1. Induction of cirrhosis

Thirty-seven male Sprague–Dawley rats with an initial weight of 100–120 g were included in the study. Rats were individually caged at a constant room temperature of 21°C, exposed to a 12:12 light/dark cycle, and allowed free access to water and standard rodent chow B/K ad libitum. Induction of cirrhosis was performed in 29 rats as previously described by Runyon et al. [15]. Briefly, rats were treated with phenobarbital (1.5 mmol/l) in tap water. After they gained weight to >200 g (in 10–14 days), weekly doses of CCl4 (JT Baker Inc., Phillipsburg, NJ, USA) were given intragastrically using a feeding tube (Popper and Sons Inc., New Hyde Park, NY, USA). The first dose of CCl4 was 20 μl and subsequent doses were adjusted based on changes in weight 48 h after the last dose as previously reported [15]. After ascites appeared, the dose was reduced to 40 μl per week until laparotomy. The eight rats from the control group received standard diet and water with phenobarbital throughout the study.

2.2. Experimental design

Once cirrhotic rats developed ascites (approximately 18 weeks after beginning of the induction of cirrhosis) confirmed by paracentesis under anesthesia with 10 mg/kg xylazine (Rompun, Bayer) and 50 mg/kg ketamine (Ketolar, Park-Davis), they were randomized into three groups. Each group of cirrhotic ascitic rats received a different treatment, by daily gavage of a probiotic strain (*Lactobacillus johnsonii* La1) (La1) and antioxidants on intestinal flora, intestinal mucosal oxidative damage, endotoxemia and bacterial translocation in an experimental model of cirrhosis in rats.

2.3. Laparotomy

All ascitic cirrhotic rats were sacrificed at the end of treatment. All control rats were sacrificed at 18 weeks after they began to drink water with phenobarbital. Laparotomy was performed under anesthesia with the same drugs and doses used for paracentesis in strictly sterile conditions. Abdominal fur was removed with a depilatory and the skin was sterilized with iodine. A short incision in the abdominal wall was performed and a sample of ascitic fluid was obtained for bacterial culture. The abdomen was then opened widely and the remaining ascitic fluid was evacuated. If no free ascitic fluid was present, sterile swabs were passed over the parietal peritoneal surface and then plated. Samples of pleural fluid were also collected for microbiological study. The mesenteric lymph nodes from the ileo-cecal area were aseptically dissected, removed, weighed, and then liquefied in sterile saline for bacterial culture. Samples of cecal feces, ileal feces, and ileum wall weighing 0.2 g were collected, homogenised and diluted with normal saline. Blood was collected from the cava vein to determine endotoxemia in a non-additive sterile interior vacutainer (Becton Dickinson Vacutainer Systems Eur., Meylan Cedex, France). In addition, samples of jejunal, ileal, and cecal walls were collected and immediately frozen in dry ice until malondialdehyde (MDA) level determination, as index of mucosal oxidative damage [37,38]. The rats were then euthanised with intravenous sodium thiopentate (Penthotal, Abbott Laboratories).

2.4. Bacterial translocation

Samples of mesenteric lymph nodes, particularly those draining lymph from ileum and cecum, ascites and pleural fluid were collected in sterile conditions before death of the rat, and cultured in Mac Conkey agar (Oxoid), Columbia sheep blood (Oxoid) and Esculin-Bile-Azide agar (MERCK), and incubated at 37°C for 48 h. Bacterial translocation was defined as the positivity of cultures of mesenteric lymph nodes, ascites, or pleural fluid.

2.5. Microbiological intestinal study

Samples of cecal and ileal feces and ileal wall were collected under sterility before death of the rat, frozen in several cryotubes, and stored at −80°C until microbiological analysis in Nestle Research Center, Laussanne, Switzerland. Bacteria were detected on selective media. Serial decimal dilutions were performed in Ringer solution containing 0.5% of cystein, from −2 to −8. Petri dishes of various selective media were inoculated and incubated. Enterobacteria were detected in Drigalski (Sanofi Diagnostics Pasteur, France) for 24 h at 37°C, lactobacilli in MRS (Difco, MI, USA) + antibiotics (phosphomycin 79.5 mg/l + sulfamethoxazole 0.93 mg/l + trimethoprim 5 mg/l) during 48 h at 37°C in anaerobic atmosphere, Bacteroides in Schaedler Neo-Vanco (bioMérieux) for 48 h at 37°C in an anaerobic atmosphere, and enterococci in Azide Agar (Difco) for 24 h at 37°C in an aerobic atmosphere.

The anaerobic atmosphere was obtained using Anaerocult A (MERCK). After incubation, the colonies were counted and further identified if necessary. Lactobacilli were identified by microscopy and API 50 CH gallery (bioMérieux). Counts are expressed as log10 cfu/g of fresh fecal sample or ileal wall with a detection limit at 3 cfu/g.

2.6. Endotoxemia

Endotoxemia was assessed in blood from cava vein using a spectrophotometric method provided in a Limulus Amebocyte Lysate COATEST Plasma–Endotoxin assay available commercially (BioWhittaker, Walkersville, MD), according to the manufacturer’s instructions. Endotoxemia is expressed as EU/ml.

2.7. MDA levels

MDA formation by thiobarbiturate reaction was determined in samples
of jejunal, ileal, and cecal walls according to the method previously described [40]. MDA levels are expressed as nmol/mg of protein.

2.8. Statistical analysis

Results are expressed as mean ± SEM or proportions. Comparison of quantitative variables was performed using the non-parametric Mann–Whitney test. Comparison of qualitative variables was performed with the Fisher test. A P value less than 0.05 was considered statistically significant.

All animals received humane care and the protocol was approved by the Animal Research Committee of the Institut de Recerca of the Hospital de la Santa Creu i Sant Pau.

3. Results

3.1. Characteristics of rats at study onset

When the different protocol treatments were initiated, the age of the rats was: 17.0 ± 1.4 weeks in group 1, 18.2 ± 2.0 in group 2, 17.2 ± 1.9 in group 3, and 17.2 ± 0.4 in group 4 (P NS). The weight of cirrhotic rats at the beginning of the treatments was: 419 ± 26 g in group 1, 425 ± 17 g in group 2, and 468 ± 28 g in group 3 (P NS between the three groups). The weight of control rats was 585 ± 13 g (P = 0.001 with respect to group 1, P < 0.001 with respect to group 2 and P = 0.01 with respect to group 3). The total dose of CCl₄ administered during the induction of cirrhosis was similar in the three groups of cirrhotic rats (6747 ± 1554 µl in group 1, 10212 ± 2950 µl in group 2, and 7020 ± 1813 µl in group 3, P NS).

3.2. Presence of ascites, bacterial translocation, and bacterial peritonitis (Table 1)

At the moment of laparotomy, 7/11 cirrhotic rats from group 1, 4/10 cirrhotic rats from group 2, and 7/8 cirrhotic rats from group 3 had detectable ascitic fluid (P NS). Cultures of mesenteric lymph nodes were negative in all eight control rats (group 4). Cultures of mesenteric lymph nodes, ascitic fluid, and pleural fluid were also negative in all cirrhotic rats from groups 1 and 2. Considering cirrhotic rats from group 3, 5/8 rats showed bacterial translocation (any positive culture) to mesenteric lymph nodes or ascitic fluid or pleural fluid (P < 0.01 with respect to groups 1 and 2); two to pleural fluid, two to mesenteric lymph nodes, and only one had more than one site with positive culture (pleural and ascitic fluid and mesenteric lymph nodes). Bacteria isolated were: two Escherichia coli, two E. coli + Enterococcus, and one E. coli + Streptococcus viridans.

3.3. Microbiological intestinal study

The results of the microbiological study are shown in Table 2. There was a trend to higher bacterial counts of enterobacteria and enterococci in the cecum, ileal content, and ileal wall in group 3 as compared to group 4, without reaching statistical significance. The bacterial counts of enterococci and enterobacteria in the cecum, ileal content, and ileal wall were lower in groups 1 and 2, compared to group 3. These differences achieved statistical significance, except for cecal enterobacteria in the two groups and ileal wall enterococci in group 2. No relevant differences were observed in the counts of lactobacilli between group 1 and the remaining groups. In contrast, a somehow paradoxical effect was observed since group 1 and group 2 showed a trend toward lower lactobacilli counts in cecum and ileum than group 4.

3.4. Endotoxemia

Endotoxemia levels are shown in Fig. 1. Rats from group 3 showed higher levels of endotoxemia than rats from group 4 (0.82 ± 0.17 vs. 0.51 ± 0.12 EU/ml), although without reaching statistical significance. There was a statistically significant decrease in endotoxemia in group 1 with respect to group 3 (0.36 ± 0.12 vs. 0.82 ± 0.17 EU/ml, P < 0.05), whereas it was similar in group 2 and group 3 (0.78 ± 0.17 vs. 0.82 ± 0.17 EU/ml, P NS).

3.5. MDA levels

MDA levels (Fig. 2) in the jejunum wall were similar in the four groups. 0.5 ± 0.1 nmol/mg protein in group 1, 0.6 ± 0.09 nmol/mg in group 2, 0.7 ± 0.1 nmol/mg in group 3, and 0.7 ± 0.3 nmol/mg in group 4, P NS). MDA

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Incidence of ascites and bacterial translocation in the three groups of cirrhotic rats*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 (n = 11) La1 in vehicle</td>
<td>Group 2 (n = 10) vehicle</td>
</tr>
<tr>
<td>Ascites</td>
<td>7/11</td>
</tr>
<tr>
<td>Positive culturesb (MLN, ascites or pleural fluid)</td>
<td>0</td>
</tr>
<tr>
<td>MLN</td>
<td>0</td>
</tr>
<tr>
<td>Ascites</td>
<td>0</td>
</tr>
<tr>
<td>Pleural fluid</td>
<td>0</td>
</tr>
</tbody>
</table>

* La1, Lactobacillus johnsonii La1. Group 1, cirrhotic rats treated with La1 in vehicle containing antioxidants; group 2, cirrhotic rats treated with vehicle; and group 3, cirrhotic rats treated with water. MLN, mesenteric lymph nodes. **P < 0.01 with respect to the other two groups. One rat from group 3 had positive cultures in MLN, ascites, and pleural fluid.

b No. of rats with a positive culture.
levels in the ileum were higher in group 3 than in group 4 (1.8 ± 0.2 vs. 0.6 ± 0.1, P < 0.01), and lower in group 1 (0.8 ± 0.2) and in group 2 (0.7 ± 0.1) than in group 3 (1.8 ± 0.2, P < 0.01 with respect to groups 1 and 2). MDA levels in the cecum were higher in group 3 than in group 4 (1.2 ± 0.2 vs. 0.4 ± 0.09, P < 0.01), and lower in group 1 (0.9 ± 0.2) and group 2 (0.7 ± 0.06) than in group 3 (1.2 ± 0.2, P < 0.03 with respect to group 2, NS with respect to group 1).

4. Discussion

The main finding in the present study is that vehicle containing antioxidants, alone or in combination with *Lactobacillus johnsonii* La1, decreases the rate of bacterial translocation in ascitic cirrhotic rats. Several experimental and clinical data support the importance of bacterial translocation in the pathogenesis of bacterial infections, mainly SBP, in cirrhosis [1–5]. The decrease in bacterial translocation observed in the present study could be due to several mechanisms.

First, both treatments (antioxidants with or without La1) produced a decrease in the concentrations of enterobacteria and enterococci in the cecum and in the terminal ileum. It has been suggested that bacterial translocation in cirrhosis would occur at this level of the intestinal wall [4]. On the other hand, intestinal bacterial overgrowth has been considered an important factor for the development of bacterial translocation in experimental cirrhosis [7], and it also seems to be relevant in the development of SBP in cirrhotic patients [6,8]. Actually, the decrease in intestinal bacterial overgrowth with antibiotics results in a decrease in bacterial translocation and SBP in experimental cirrhosis [15,16], and several oral antibiotics have been observed to be useful in the prevention of SBP and other infections in different clinical trials including cirrhotic patients [17–20]. Therefore, the changes in intestinal flora observed in both groups

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**Table 2**

**Microbiological intestinal study**

<table>
<thead>
<tr>
<th>log10 cfu/g</th>
<th>Group 1 (n = 11) La1 in vehicle</th>
<th>Group 2 (n = 10) vehicle</th>
<th>Group 3 (n = 8) water</th>
<th>Group 4 (n = 8) control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cecal Bacteroides</td>
<td>7.4 ± 0.4</td>
<td>7.1 ± 0.2</td>
<td>7.3 ± 0.6</td>
<td>7.6 ± 0.1</td>
</tr>
<tr>
<td>Cecal lactobacilli</td>
<td>8.0 ± 0.2</td>
<td>7.6 ± 0.2*</td>
<td>8.5 ± 0.1</td>
<td>8.5 ± 0.1</td>
</tr>
<tr>
<td>Cecal enterococci</td>
<td>4.5 ± 0.3*</td>
<td>4.3 ± 0.1*</td>
<td>5.7 ± 0.3</td>
<td>5.5 ± 0.2</td>
</tr>
<tr>
<td>Cecal enterobacteria</td>
<td>4.7 ± 0.5</td>
<td>4.1 ± 0.2**</td>
<td>5.5 ± 0.6</td>
<td>4.6 ± 0.3</td>
</tr>
<tr>
<td>Ileal Bacteroides</td>
<td>4.7 ± 0.3</td>
<td>4.8 ± 0.3</td>
<td>5.3 ± 0.5</td>
<td>4.3 ± 0.3</td>
</tr>
<tr>
<td>Ileal lactobacilli</td>
<td>7.8 ± 0.3</td>
<td>7.7 ± 0.3</td>
<td>8.3 ± 0.2</td>
<td>8.5 ± 0.1</td>
</tr>
<tr>
<td>Ileal enterococci</td>
<td>3.5 ± 0.2*</td>
<td>3.4 ± 0.1*</td>
<td>5.4 ± 0.6</td>
<td>4.6 ± 0.2</td>
</tr>
<tr>
<td>Ileal enterobacteria</td>
<td>3.6 ± 0.6**</td>
<td>3.1 ± 0.7*</td>
<td>5.1 ± 0.7</td>
<td>4.2 ± 0.4</td>
</tr>
<tr>
<td>Ileal wall Bacteroides</td>
<td>3.8 ± 0.2</td>
<td>4.0 ± 0.2</td>
<td>3.8 ± 0.3</td>
<td>3.7 ± 0.2</td>
</tr>
<tr>
<td>Ileal wall lactobacilli</td>
<td>6.4 ± 0.3</td>
<td>6.0 ± 0.5</td>
<td>6.5 ± 0.2</td>
<td>6.8 ± 0.3</td>
</tr>
<tr>
<td>Ileal wall enterococci</td>
<td>3**</td>
<td>3.3 ± 0.0</td>
<td>3.9 ± 0.4</td>
<td>3.1 ± 0.1</td>
</tr>
<tr>
<td>Ileal wall enterobacteria</td>
<td>3**</td>
<td>3.6 ± 0.4</td>
<td>3.3 ± 0.2</td>
<td>3.3 ± 0.2</td>
</tr>
</tbody>
</table>

*La1, Lactobacillus johnsonii La1. Group 1, cirrhotic rats treated with La1 in vehicle containing antioxidants; group 2, cirrhotic rats treated with vehicle; group 3, cirrhotic rats treated with water; and group 4, control rats. *P < 0.05 with respect to groups 3 and 4. **P = 0.06 with respect to group 3. ¥P < 0.05 with respect to group 3, and P ≤ 0.01 with respect to group 4. **¥P < 0.05 with respect to group 3. NS in the remaining parameters.*
could, at least in part, explain the decrease in bacterial translocation.

In the present study, cirrhotic rats treated with water showed higher MDA levels, an index of mucosal oxidative damage, in the ileum and the cecum (where bacterial translocation is believed to occur [4]) but not in the jejunum when compared to control rats. Cirrhotic rats receiving antioxidants alone or in combination with La1, however, showed a statistically significant decrease in intestinal MDA probably as a consequence of the effect of antioxidants. These data confirm that intestinal oxidative damage occurs in this experimental model and suggest it could be related to bacterial translocation because treatment with antioxidants decreases both oxidative damage and bacterial translocation, as has been shown in other experimental models of portal hypertension [37,38]. Certainly, increased intestinal oxidative damage and bacterial translocation have been observed in rats with prehepatic portal hypertension and common bile duct ligated rats and these findings were prevented by treatment with antioxidants, such as vitamin C and glutamine [37,38]. The mechanism by which the inhibition of intestinal oxidative damage determines a decrease in bacterial translocation was not evaluated in the present study. However, it has been reported that oxidative damage decreases gastrointestinal motility in several experimental situations [41,42] and the impairment in intestinal motility is one of the main mechanisms implicated in intestinal bacterial overgrowth in cirrhosis [8–10]. Therefore, we can speculate that in the present study the decrease in mucosal oxidative damage observed in the two groups of rats treated with antioxidants would have increased intestinal motility (not determined in the present study) and then contributed to decreasing the intestinal bacterial load. On the other hand, mucosal oxidative damage has been implicated in impaired intestinal permeability leading to bacterial translocation in several experimental models of portal hypertension, including cirrhosis [37–39]. Therefore, another mechanism by which antioxidants could have contributed to decreasing bacterial translocation in the present study is by a possible improvement in the intestinal barrier.

The possible contribution of La1 to the changes in intestinal flora observed in rats receiving antioxidants in combination with La1 is difficult to ascertain because these changes were similar to those observed in rats treated with antioxidants alone. It has been observed that the administration of probiotics decreases intestinal bacterial concentration of aerobic bacteria and bacterial translocation in different experimental models of acute liver failure [27–29]. Other authors have failed to show changes in intestinal bacterial concentrations of enterobacteria or in the incidence of bacterial translocation in an experimental model of prehepatic portal hypertension in rats treated with a strain of *Lactobacillus acidophilus* [30]. It should be pointed out, however, that this experimental model is different from the model of experimental cirrhosis used in the present study. In addition, the probiotic used was not the same, and it has been observed that different strains of probiotics show different characteristics and effects [29].

La1 administration can also contribute to the decrease in bacterial translocation through the improvement in the immune defense mechanisms. Certainly, different strains of probiotics have shown immunostimulatory and immunomodulatory properties [25,33,34]. La1 in particular has been observed to enhance the phagocytic activity of peripheral leukocytes in volunteers [33]. Although we did not directly assess the possible immunomodulatory effect of La1 in this experimental situation, we determined the levels of endotoxemia. Endotoxemia has been shown to be increased in cirrhosis [43], and it has been related to bacterial translocation and to passage of bacterial products from the intestinal lumen to extraintestinal sites [44]. Besides, endotoxemia seems to play a role in the pathogenesis of bacterial infections (favoring bacterial translocation) [45] and ascites formation (favoring arteriolar vasodilation) [43] in cirrhosis. In the present study, endotoxemia significantly decreased in rats receiving antioxidants combined with La1 but not in rats receiving antioxidants alone, compared to rats treated with water. This cannot be due only to changes in the intestinal flora, because rats treated with antioxidants alone showed similar changes compared to rats treated with antioxidants combined with La1 but no variations in endotoxemia. The decrease in endotoxemia observed in rats treated with La1 may possibly be due to activation of the monocyte–macrophage system that would increase the capacity of endotoxin clearance from the internal milieu [46]. Indeed, a decrease in endotoxemia was recently observed in an experimental model of necrotizing enterocolitis in rats treated with *Bifidobacterium infantis* [47].

Another interesting finding in the present study was the absence of differences between groups in the lactobacilli count, as an increase in the counts of these bacteria in rats receiving La1 could have been expected. It is difficult to explain this finding, and the results of other studies using different experimental models of bacterial translocation treated with different probiotics are contradictory [27–30]. This lack of effect of La1 administration on the intestinal concentration of lactobacilli can be explained by the presence of large amounts of lactobacilli in the intestine of the rats (normal or cirrhotic), even in the absence of lactobacilli supplementation, that would make it difficult to demonstrate changes after probiotic administration.

In conclusion, antioxidants alone or in combination with La1 decrease the rate of bacterial translocation in ascitic cirrhotic rats and could be a promising strategy to prevent SBP in cirrhosis. Further studies are needed to determine the effect of La1 without antioxidants in this experimental model.

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