

## Prevalence of Small Intestinal Bacterial Overgrowth in Patients with Liver Cirrhosis

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### INTRODUCTION

Patients with liver cirrhosis (LC) have an increased risk of infections due to bacterial translocation (BT)<sup>[1]</sup>. Over 70% of the cases are caused by intestinal bacteria and can be prevented by selective bacterial decontamination with non-absorbed or absorbed antibiotics, which confirms that the gut is the main source of microorganisms<sup>[2]</sup>. The gut microflora not only takes part in the pathogenesis of overt infective episodes and of the clinical consequences of sepsis, but it also contributes to the pro-inflammatory state of cirrhosis even in the absence of overt infection<sup>[1]</sup>. Although accurate mechanisms of BT are unknown, small intestinal bacterial overgrowth (SIBO), gut dysmotility, increased intestinal permeability and impaired defense mechanisms are regarded as major risk factors for BT<sup>[1,2]</sup>. SIBO is common in LC due to various causes<sup>[3,4]</sup> and is an independent risk factor for systemic endotoxemia, implicated in various pathophysiological sequelae of cirrhotic patients<sup>[5]</sup>.

Data on SIBO frequency in patients with LC and its association with the etiology and degree of liver damage are scanty and contradictory. Some authors suggested that SIBO might be related to the degree of liver dysfunction<sup>[3,6,7]</sup>, whereas others suggested that it was related to the portal hypertension<sup>[8]</sup>. The later may cause small bowel motility disturbances, which might be a predisposing factor for the SIBO.

The aim of this study was to assess the prevalence of SIBO using the lactulose hydrogen breath test (LHBT) and to analyze its relationship with the etiology of the disease and the severity of liver dysfunction in patients with LC.

### METHODS

The study included 43 patients with LC (33 males and 10 females; mean age 48 years, range 37-60), recruited from January 2008 to June 2009. The LC was diagnosed and staged by means of clinical presentation, laboratory results and abdominal ultrasound examination. The Child-Pugh (CP) score was used for an evaluation

### ABSTRACT

**AIM:** To assess the prevalence of small intestinal bacterial overgrowth (SIBO) and to analyze its relationship with the etiology of the disease and the severity of liver dysfunction in patients with liver cirrhosis (LC).

**METHODS:** Forty-three patients with LC (25 alcohol- and 18 viral-induced) and ten healthy subjects consented to participate in the study. According to Child-Pugh classification, 7 of the patients were with class A, 14 - class B and 22 - class C. SIBO was estimated indirectly by the lactulose hydrogen (H<sub>2</sub>) breath test.

**RESULTS:** In 4 of the patients no peak of H<sub>2</sub> was recorded. In comparison to the control group of healthy subjects, LC patients had significantly higher basal breathed H<sub>2</sub> (15.54±10.56 vs 6.24±3.39 ppm, *p*<0.05). The mean basal breathed H<sub>2</sub> in cirrhotic patients with evidence of SIBO was 29.33±6.69 ppm (range 21-42). Of the 39 patients with LC, 12 (31%) had SIBO compared to none of the healthy controls. No differences in SIBO regarding Child-Pugh score were found. SIBO was demonstrated in 45.5% of the alcohol- and only in 11.8% of the viral-induced LC (*p*<0.05).

**CONCLUSION:** SIBO is common in patients with LC and more frequent in the cases with alcoholic etiology, but it is not related to the severity of liver dysfunction. Future larger trials are needed to establish the exact role of these alterations in patients with LC.

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**Key words:** Small intestinal bacterial overgrowth; Lactulose hydrogen breath test; Liver cirrhosis; Alcohol

of the disease severity. Upper gastrointestinal endoscopy was performed to assess further complications of portal hypertension. The ascitic fluid was localized by ultrasonography and paracentesis was performed where possible. The presence of spontaneous bacterial peritonitis (SBP) was assessed by the number of polymorphonuclear leucocytes in the ascitic fluid over 250 cells/mm<sup>3</sup>.

Patients with anatomical predispositions for intestinal stasis, such as small intestinal diverticula on the small bowel series, were not included. In addition, the patients with diseases associated with impaired motility (diabetes mellitus, scleroderma), renal failure or previous abdominal surgery, as well as those who had received antibiotics, probiotics, lactulose, prokinetic or acid-suppressive drugs in the two weeks preceding the study were not included. Ten healthy persons (6 males and 4 females, mean age 46 years, range 32-60) were recruited as controls.

SIBO was estimated indirectly by the LHBT, using a breath gas analyzer (Gastrolyzer Breath Hydrogen Bedford Scientific, UK). All participants were asked to avoid slowly absorbed carbohydrates in the day preceding the test. Basal breath specimens were obtained after an fasting overnight. Smoking and physical exercise were not permitted for 2 h before and during the test for a prevention of hyperventilation and consequent changes in breath hydrogen (H<sub>2</sub>) content. The H<sub>2</sub> exhalation was measured for 3 h (in 15-minute intervals) following the ingestion of 10 g lactulose dissolved in 100 mL tap water. The results were expressed in parts per million (ppm).

The LHBT was considered as positive for SIBO on the basis of the following criteria: the baseline value of H<sub>2</sub> above 20 ppm or/and early H<sub>2</sub> peak (12 ppm increasing of breath H<sub>2</sub> above the baseline value between 30 to 60 min after the lactulose ingestion) followed by a second peak or plateau<sup>[9,10]</sup>.

### Statistical analysis

All values were expressed as mean±standard deviation (SD) or proportions. Nonparametric Mann-Whitney U test for overall testing the difference between subject groups and Chi-square for comparing proportions were used. Each hypothesis was tested at a level of significance of 0.05.

### Ethics approval

The study was approved by the Ethics Committee at the University Hospital Queen Joanna in Sofia, Bulgaria. Written informed consent was obtained from all patients and control subjects.

## RESULTS

The baseline characteristics of the investigated subjects are shown in table 1.

**Table 1** Clinical parameters of two groups.

Parameter	N
Male: female, n	33:10
Mean age, years, range	54,0 (36-70)
Aetiology	
Alcohol	25
HBV or HCV	18
Child-Pugh class	
A	7
B	14
C	22
Ascites	
Present	32
Absent	11

In twenty-five patients the alcohol was identified as a cause, assessed by a history of drinking at least 80 g of alcohol daily for more

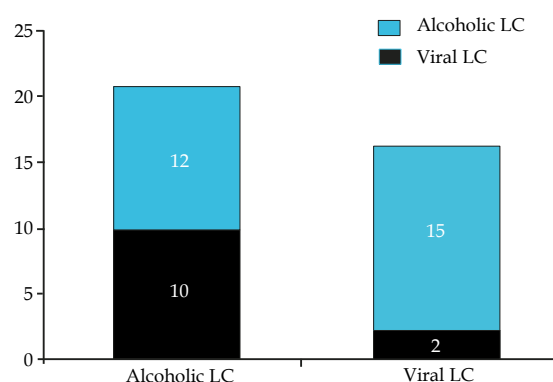
than five years. All were HBs antigen negative and HCV antibody negative. In the remaining 18 patients LC was virus-related (Hepatitis B or Hepatitis C virus). Ascites was present in 32 of the cirrhotic patients (22 with CP C and 10 with CP B). Paracentesis was performed in 27 of the patients, because of small amount of ascitic fluid in the remaining 5 patients.

In 4/43 (9.3%) of the patients (one with CP class B, 3 with class C; 3 with alcoholic and 1 with viral LC; all with evidences of ascites) no peak of H<sub>2</sub> was recorded (non-producers) and they were excluded from the final analysis.

The mean basal value of the H<sub>2</sub> concentration in exhaled air was found to be higher in the cirrhotic patients compared to that of healthy individuals (15.54±10.56 vs 6.24±3.39 ppm, *p*<0.05). The evidence of SIBO was found in a third (31%) of the LC patients, but in none of the controls (*p*<0.05). The mean basal breathed H<sub>2</sub> in cirrhotic patients with evidence of SIBO was 29.33±6.69 ppm (range 21-42).

Data of SIBO were found in 34.4% (11/32) of patients with decompensated cirrhosis (CP class B/C) and in 14.3% (1/7) of patients with compensated cirrhosis (CP class A) (*p*=0.36). No differences in SIBO regarding CP score were found. There was not a significant difference in the incidence of SIBO between cirrhotic patients with and without ascites (31.3% vs 18.2%, respectively, *p*=0.46). The frequency of SIBO was significantly higher in the patients with alcohol-induced liver disease compared to that with viral-related LC (45.5% vs 11.8%, respectively, *p*<0.05) (Figure 1).

SBP was diagnosed in 2/27 of ascitic patients. Both patients met the criteria for SIBO.



**Figure 1** Distribution of patients with SIBO according to the etiology of liver cirrhosis.

## DISCUSSION

In normal individuals, intestinal peristalsis, gastric acid, and mucosal immunity prevent the development of SIBO. Abnormalities in one or more of these factors facilitate the manifestation of SIBO.

Data from our study clearly indicate that nearly one third of the patients with LC have evidence of SIBO compared to healthy subjects.

The microbiological analysis of the jejunal aspirate is regarded as a "gold" standard in diagnosis of SIBO. However, this method requires intubation and does not detect unculturable species. Moreover, it is cumbersome, time-consuming and generally not well tolerated. In the recent decades, breath tests are widely used in clinical practice to assess SIBO. They are simple, inexpensive, non-invasive, easily applicable, and without risk of contamination<sup>[11,12]</sup>. The LHBT has been used as an indirect indicator of SIBO in several settings such as Published studies are quite heterogenic showing prevalence of

SIBO in 20%-60% in the cirrhotic patients<sup>[5,15]</sup>. Several alterations in defensive mechanisms in LC could be responsible for its occurrence, including prolonged small intestinal transit, achylia and hypochlorhydria, a decreasing of the Ig A secretion, abnormalities in bile secretion, and malnutrition caused by liver dysfunction and alcoholism<sup>[16]</sup>.

Although we did not find significant differences in prevalence of SIBO in regards to the severity of the LC, such relationship was previously reported as existing. SIBO is present in 30-61% of decompensated cirrhotics, and its prevalence is more frequent in advanced disease<sup>[3,6,7]</sup>. More advanced liver disease with impaired liver function, ascites, portal enteropathy, hypoalbuminemia are all factors facilitating SIBO. Despite the fact that all except for one of the cirrhotics with SIBO had ascites, we, like some authors did not find any association between prevalence of SIBO and the presence or absence of ascites<sup>[6]</sup>.

We found significant differences in the prevalence of SIBO between cirrhotic patients depending on the etiology of liver disease. In the present study, we have demonstrated that SIBO occurs significantly more frequently in patients with alcoholic LC (45.5%) compared to those with viral etiology of the disease (11.8%). Similar findings are also published even in the absence of decompensated disease, thus proving the leading role of chronic alcohol exposure per se.

A few studies are available in the literature investigating the relationship between alcohol consumption and intestinal bacterial growth. These studies suggest that chronic alcohol abuse can promote SIBO. Excessive alcohol consumption leads to quantitative and qualitative changes in the jejunal flora. The incidence of SIBO in alcoholic liver disease was three times higher than in healthy controls<sup>[14]</sup>.

The studies, performed in “real life”, also demonstrated recent evidences of influence of alcohol on the dysregulation of intestinal antimicrobial molecules. This leads to enteric microbiome changes and induces alcoholic steatohepatitis<sup>[17]</sup>. Overgrowth of Gramnegative bacteria can result in increased production of endotoxin that can escape into portal circulation leading to increased plasma levels of endotoxin<sup>[18]</sup>. Alcohol consumption can affect the colonic microbiome composition and can suggest that dysbiosis may be an important mechanism of alcohol-induced endotoxemia. Futuremore, clinical and animal data indicate that gut-derived endotoxin and other luminal bacterial products are necessary cofactors for development of alcoholic liver disease<sup>[19]</sup>. On the other hand, SIBO could worsen liver function in alcohol-induced liver diseases by triggering and maintaining the necro-inflammatory liver alterations both through the metabolism of ethanol and through the activation of key hepatic innate immune cell populations<sup>[20]</sup>.

In conclusion, the data from our study indicate that SIBO is present in nearly one third of patients with LC. SIBO is more frequent in the cases with alcoholic etiology, but is not related to the severity of liver dysfunction.

Ongoing research is needed to reveal mechanisms of the gut flora derangement in the patients with alcoholic liver disease. This could further facilitate the rationale of therapeutic usage of different antibiotics and probiotics in patients of alcoholic LC.

## REFERENCES

- 1 Almeida J, Galhenage S, Yu J, Galhenage S, Yu Jenifer, Kurtovic J, Riordan SM. Gut flora and bacterial translocation in chronic liver disease. *World J Gastroenterol* 2006; **12**(10): 1493-502
- 2 Rasaratnam B, Connelly N, Chin-Dusting J. Nitric oxide and the hyperdynamic circulation in cirrhosis: is there a role for selective intestinal decontamination? *Clin Sci (Lond)* 2004; **107**: 425-434
- 3 Morenos CF, De Las Castano G, Ramos Martin L, Lopez Arias MJ, Ledesma F, Pons Romero F. Small bowel bacterial overgrowth in patients with alcoholic cirrhosis. *Dig Dis Sci* 1995; **40**: 1252-1256
- 4 Lakshmi CP, Ghoshal Uday C, Kumar Sunil, Goel Amit, Misra Asha, Mohindra Samur, Choudhuri G. Frequency and Factors Associated with Small Intestinal Bacterial Overgrowth in Patients with Cirrhosis of the Liver and Extra Hepatic Portal Venous Obstruction. *Dig Dis Sci* 2010; **55**: 1142-1148
- 5 Bauer TM, Schwacha H, Steinbrückner B, Brinkmann FE, Ditzen AK, Aponte JJ, Pelz K, Berger D, Kist M, Blum HE. Small intestinal bacterial overgrowth in human cirrhosis is associated with systemic endotoxemia. *Am J Gastroenterol* 2002; **97**: 2364-2370
- 6 Yang CY, Chang CS, Chen GH. Small intestinal bacterial overgrowth in patients with liver cirrhosis, diagnosed with glucose H2 or CH4 breath tests. *Scand J Gastroenterol* 1998; **33**: 867-871
- 7 Pande C, Kumar A, Sarin S. Small-intestinal bacterial overgrowth in cirrhosis is related to the severity of liver disease. *Aliment Pharmacol Ther* 2009; **29**:1273-1281
- 8 Gunnarsdottir SA, Sadik R, Shev S, Simrén M, Sjövall H, Stotzer PO, Abrahamsson H, Olsson R, Björnsson ES. Small intestinal motility disturbances and bacterial overgrowth in patients with liver cirrhosis and portal hypertension. *Am J Gastroenterol*. 2003; **98**: 1362-1370
- 9 Stoinov S, Mendizova A, Nakov V, Penchev P, Savov G, Tsoleva N, Gerova V, Kadyan H. Evaluation of bowel motility in patients with chronic alcoholism by means of lactulose hydrogen breath test. *Comptes rendus de l'Academie bulgare des Sciences*. 2000; **53**: 119-121
- 10 Kerlin P, Wong L. Breath hydrogen testing in bacterial overgrowth of the small intestine. *Gastroenterology* 1988; **95**: 982-988
- 11 Ghoshal UC, Ghoshal U, Das K, Misra A. Utility of hydrogen breath tests in diagnosis of small intestinal bacterial overgrowth in malabsorption syndrome, and its relationship with oro-cecal transit time. *Indian J Gastroenterol* 2006; **25**: 6-10
- 12 Riordan SM, Duncombe VM, Thomas MC, Nagree A, Bolin TD, McIver CJ, Williams R. Small intestinal bacterial overgrowth, intestinal permeability and non-alcoholic steatohepatitis. *Gut* 2002; **50**: 136-138
- 13 Romagnuolo J, Schiller D, Bailey RJ. Using breath test wisely in a gastroenterology practice: an evidence-based review of indications and pitfalls in interpretation. *Am J Gastroenterol* 2002; **97**: 1113-1126
- 14 Bode C, Kolepke R, Schäfer K, Bode JC. Breath hydrogen excretion in patients with alcoholic liver disease-evidence of small intestinal bacterial overgrowth. *Z Gastroenterol* 1993; **31**: 3-7
- 15 Lata J, Stiburek O, Kopacova M. Spontaneous bacterial peritonitis: A severe complication of liver cirrhosis. *World J Gastroenterol* 2009; **15**: 5505-5510
- 16 Shindo K, Machida M, Miyakawa K, Fukumura M. A syndrome of cirrhosis, achlorhydria, small intestinal bacterial overgrowth and fat malabsorption. *Am J Gastroenterol* 1993; **88**: 2084-2091
- 17 Yan AW, Fouts DE, Brandl J, Starkel P, Torralba M, Schott E, Tsukamoto H, Nelson KE, Brenner DA, Schabl B. Enteric dysbiosis associated with a mouse model of alcoholic liver disease. *Hepatology* 2011; **53**: 96-105
- 18 Pivohit V, Bode JC, Bode C, Brenner D, Choudhry M,

Hamilton F, Kang Y, Keshavarzian A, Rao R, Sartor R, Swanson Ch, Turner J. Alcohol, intestinal bacterial overgrowth, intestinal permeability to endotoxin, and medical consequences: summary of a symposium. *Alcohol* 2008; **42**: 349-361

- 19 Mutlu E, Keshavarzian A, Engen P, Fotsyth CB, Sikaroodi M, Gillevet P. Intestinal dysbiosis: a possible mechanism of alcohol-induced endotoxemia and alcoholic steatohepatitis in rats. *Alcohol Clin Exp Res* 2009; **33**:1836-1846
- 20 Son G, Kremer M, Hines IN. Contribution of Gut Bacteria

to Liver Pathobiology Hindawi Publishing Corporation Gastroenterol Res Pract. 2010.

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