Predictive Factors of Spontaneous Bacterial Peritonitis Caused by Gram-Positive Bacteria in Patients With Cirrhosis

Jung Ho Kim, Yong Duk Jeon, In Young Jung, Mi Young Ahn, Hea Won Ahn, Jin Young Ahn, Nam Su Ku, Sang Hoon Han, Jun Yong Choi, Sang Hoon Ahn, Young Goo Song, Kwang Hyub Han, and June Myung Kim

Abstract: Spontaneous bacterial peritonitis (SBP) in patients with cirrhosis is typically caused by gram-negative bacteria. However, the number of SBP cases due to gram-positive bacteria is steadily increasing. To date, little is known about the predictive factors involved in SBP infections.

We performed a retrospective cohort study of patients (>18 years) with SBP due to gram-positive and -negative bacteria who were enrolled from January 2006 to December 2013 at Severance Hospital in Seoul, Korea where the incidences of hepatitis B virus associated chronic liver disease, cirrhosis, and hepatocellular carcinoma are high. Only the 1st SBP episode for each patient within the study period was included in our analysis.

We identified 77 patients with cirrhosis and SBP. Of these, 27 patients (35%) had gram-positive bacterial infections and 50 patients (65%) had gram-negative bacterial infections. Our univariate analysis revealed that an early stage of cirrhosis (P = 0.004), lower creatinine level (P = 0.011), lower Sequential Organ Failure Assessment (SOFA) score (P = 0.001), lower Model for End-Stage Liver Disease score (P = 0.005), and use of systemic antibiotics within 30 days before SBP diagnosis (P = 0.03) were significantly associated with gram-positive bacterial infections. Our multivariate analysis indicated that the use of systemic antibiotics within 30 days before SBP diagnosis (odds ratio, 3.94; 95% CI, 1.11–13.96; P = 0.033) and a lower SOFA score (odds ratio, 0.56; 95% CI, 0.37–0.86; P = 0.007) were independent predictive factors of SBP caused by gram-positive bacterial infections in patients with cirrhosis. However, we did not observe a statistically significant difference in the 28-day mortality between the gram-positive and -negative bacterial infection groups (40.7% vs 46.0%, respectively; P = 0.407).

In this study, the incidence rate of SBP caused by gram-positive bacteria in patients with cirrhosis was similar to the rates reported in recently published studies. Furthermore, the use of systemic antibiotics within 30 days before SBP diagnosis and a lower SOFA score were significantly associated with SBP caused by gram-positive bacteria in patients with cirrhosis.

Introduction

Spontaneous bacterial peritonitis (SBP) is one of the most frequent bacterial infections in patients with cirrhosis and ascites, occurring in 10% to 25% of these patients. In addition, SBP is associated with high mortality rates (20%–40%) in these patients. SBP in patients with cirrhosis is typically caused by gram-negative bacteria that are part of the intestinal microbial flora (mainly species in the family Enterobacteriaceae). As a result of the recent changes in the epidemiology of bacteria that cause SBP, the choice of antibiotics for SBP has become a topic of discussion. It is thus important to understand the predictive factors for SBP caused by gram-positive bacteria in patients with cirrhosis. However, to our knowledge, no published studies have focused on this topic.

We performed the present retrospective cohort study to identify the predictive factors for and outcomes of SBP due to gram-positive versus -negative bacterial infections.

Materials and Methods

Study Design and Population

A retrospective cohort study was conducted to investigate the predictive factors for SBP caused by gram-positive bacteria in patients with cirrhosis. We enrolled 77 patients with cirrhosis and SBP (>18 years) who were hospitalized at the Severance Hospital in Seoul, Korea from 1 January 2006 to 31 December 2013. We only included the 1st episode of SBP for each patient within the study period in our analysis. Patients with a positive culture for highly suspicious skin contaminants (i.e., coagulase-negative Staphylococci, Corynebacterium, Propionibacterium, or Bacillus spp) and those with secondary peritonitis were excluded from this study. Secondary peritonitis was considered in patients with the following cases: polymicrobial infection, peritoneal dialysis, indwelling abdominal catheters, and a recent history of abdominal surgery. We reviewed the medical records of the patients and collected the following information: age, sex, cause of cirrhosis, ChildPugh score, concomitant hepatocellular...
cancer (HCC), history of undergoing transcatheter arterial chemoembolization, initial presenting symptoms, type of isolated bacteria, gastrointestinal bleeding, presentation of septic shock, laboratory results, history of SBP, and use of systemic antibiotics within 30 days before SBP diagnosis.

The study was approved by the Institutional Review Board (IRB) of Yonsei University Health System Clinical Trial Center. Since the study was retrospective and the study subjects were anonymized, the IRB waived the requirement for written consent from the patients.

**Definitions**

SBP was defined by the presence of ascitic fluid with a polymorphonuclear leukocyte (PMN) count of >250 cells/mm³, and culture-positive SBP implied a positive culture result in ascitic fluid among SBP. During the study period, 204 patients with cirrhosis and SBP were observed, including 127 culture-negative SBP cases. Cirrhosis in all patients was confirmed by clinical, hematological, and biochemical laboratory findings and ultrasound. Chronic kidney disease (CKD) was defined as a glomerular filtration rate of <60 mL/min/1.73 m² for ≥3 months irrespective of other signs of kidney damage.14 Nosocomial infection was defined as an infection that occurred >48 hours after admission to the hospital. Infections diagnosed within the 1st 48 hours of hospitalization were classified as community-acquired infections.15 Hepatic encephalopathy was defined as an episode of mental confusion, disorientation, excitation, abnormal behavior, or asterixis.15 Gastrointestinal variceal bleeding was confirmed by endoscopy.16 Antibiotic prophylaxis therapy was defined as the use of rifaximin (Norvasc) for the use of a vasopressor to maintain blood pressure.2 Clinical manifestations included the presence of the following initial symptoms: fever (temperature of >38°C), abdominal pain, and diarrhea (defined as ≥3 loose stools per day).

**Laboratory Tests**

Ascitic fluid specimens were obtained aseptically by paracentesis and inoculated into blood culture bottles at the bedside. Ascitic fluid samples were also sent to the microbiology laboratory for PMN counting and Gram staining. We injected 10 mL of ascitic fluid samples into blood bottles (bioMerieux) and cultured using BacT/ALERT 3D system (bioMerieux). Remaining ascitic fluid from each sample was cultured using conventional methods (i.e., MacConkey agar, inoculating blood agar, thioglycollate broth, and phenylethanol agar). After day 3 of incubation and a lack of growth, conventional agar was considered negative and discarded.

**Statistical Analysis**

Independent t tests were used to compare continuous variables, and Chi-square or Fisher exact tests were used to compare categorical variables. Predictive factors for gram-positive bacterial infections were determined by a multivariate binary logistic regression analysis including significant univariate predictors (P < 0.05) using a stepwise backward elimination from the total cohort of culture-positive cases of SBP. P-values of <0.05 were considered statistically significant. PASW ver. 18 for Windows (SPSS Inc., Chicago, IL) was used for analyses.

**RESULTS**

### Demographic Characteristics

In total, 77 patients with cirrhosis and SBP were identified (61 male and 16 female). Table 1 shows the demographic and clinical characteristics of the patients. The most frequent causes of cirrhosis were hepatitis B virus (55.8%), hepatitis C virus (20.8%), and excessive alcohol ingestion (14.3%). There were 3 patients (3.9%) in Child–Pugh class A, 23 patients (29.9%) in class B, and 51 (66.2%) in class C.

### Microbiological Characteristics

The organisms isolated from the ascitic fluid of patients with SBP are listed in Table 2. There were 50 patients (64.9%) with gram-negative infections and 27 patients (35.1%) with gram-positive infections. *Escherichia coli* was the most common isolate (32.5%), followed by *Klebsiella pneumoniae* (19.5%). Eleven of the gram-negative bacteria (22%) were extended spectrum beta-lactamase (ESBL) positive (+). For patients with gram-positive bacterial infections, *Enterococcus* spp and *Staphylococcus aureus* were the most common isolates (13.0%), followed by *Streptococcus* spp (9.1%). *Enterococci* species included 7 *Enterococcus faecium, 2 E raffinosus*, and 1 *E faecalis*. Two of the *E faecium* isolates were vancomycin resistant. *Staphylococcus aureus* comprised 6 methicillin-resistant *S aureus* (MRSA) and 4 methicillin-susceptible *S aureus* (MSSA). Antibiotics used for the definitive treatment of SBP were listed in Table 3. We did not observe a statistically significant difference in the proportion of patients who received appropriate definitive antimicrobial therapy considering their susceptibility testing results between the gram-positive and -negative bacterial infection groups (84.6% vs 92%, respectively; P = 0.264).

### Predictive Factors of Gram-Positive Bacterial Infections

There were no statistically significant differences in age, sex, cause of cirrhosis, concomitant HCC, history of undergoing transcatheter arterial chemoembolization, underlying diabetes mellitus, CKD, or history of SBP between patients with gram-positive and -negative bacterial infections. However, the results of our univariate analysis indicated that the following factors were significantly associated with gram-positive bacterial infections: early stage of cirrhosis (P = 0.004), a low creatinine level (P = 0.011), a low Sequential Organ Failure Assessment (SOFA) score (P = 0.001), a low Model for End-Stage Liver Disease score (P = 0.005), and use of systemic antibiotics within 30 days before SBP diagnosis (P = 0.03). The results of the multivariate analysis revealed that the use of systemic antibiotics within 30 days before SBP diagnosis (odds ratio, 3.94; 95% confidence interval, 1.11–13.96; P = 0.033) and a lower SOFA score (odds ratio, 0.56; 95% confidence interval, 0.37–0.86; P = 0.007) were independent predictive factors for SBP caused by gram-positive bacterial infections in patients with cirrhosis. However, we did not observe a statistically significant difference in 28-day mortality between the gram-positive and -negative bacterial infection groups (40.7% vs 46.0%, respectively; P = 0.407) (Table 4).

**DISCUSSION**

SBP is a common complication in patients with cirrhosis and ascites despite recent improvements in therapeutic...
TABLE 1. Clinical Characteristics and Laboratory Findings of Patients With Spontaneous Bacterial Peritonitis

|                          | Total (n = 77) | Gram (+) Infection (n = 27) | Gram (-) Infection (n = 50) | P-Value |
|--------------------------|---------------|-----------------------------|-----------------------------|---------|
| Age                      | 58.6 ± 10.2   | 59.5 ± 9.4                  | 58.1 ± 10.7                 | 0.565   |
| Sex                      |               |                             |                             | 0.430   |
| Male                     | 61 (79.2)     | 21 (77.8)                   | 40 (80)                     |         |
| Female                   | 16 (20.8)     | 6 (22.2)                    | 10 (20)                     |         |
| Cause of liver cirrhosis |               |                             |                             | 0.424   |
| HBV                      | 43 (55.8)     | 15 (55.6)                   | 28 (56)                     |         |
| HCV                      | 16 (20.8)     | 8 (29.6)                    | 8 (16)                      |         |
| Alcohol                  | 11 (14.3)     | 2 (7.4)                     | 9 (18)                      |         |
| NBNC                     | 7 (9.1)       | 2 (7.4)                     | 5 (10)                      |         |
| Child–Pugh classification|               |                             |                             | 0.004   |
| A                        | 3 (3.9)       | 3 (11.1)                    | 0                           |         |
| B                        | 23 (29.9)     | 11 (40.7)                   | 12 (24)                     |         |
| C                        | 51 (66.2)     | 13 (48.2)                   | 38 (76)                     |         |
| MELD score               | 20.87 ± 6.57  | 18.07 ± 7.01                | 22.38 ± 5.86                | 0.005   |
| HCC                      | 43 (55.8)     | 15 (55.6)                   | 28 (56)                     | 0.686   |
| TACE history             | 35 (45.5)     | 13 (48.2)                   | 22 (44)                     | 0.963   |
| DM                       | 21 (27.3)     | 7 (25.9)                    | 14 (28)                     | 0.890   |
| Type of DM therapy       |               |                             |                             |         |
| Insulin                  | 5 (6.49)      | 2 (7.4)                     | 3 (6)                       | 0.758   |
| Oral hypoglycemic agent  | 12 (15.58)    | 3 (11.1)                    | 9 (18)                      | 0.561   |
| CKD                      | 14 (18.2)     | 4 (14.8)                    | 10 (20)                     | 0.761   |
| Ulcer disease            | 32 (41.6)     | 12 (44.4)                   | 20 (40)                     | 0.654   |
| Malignant solid organ tumor | 50 (64.9) | 20 (74.1)                   | 30 (60)                     | 0.253   |
| Malignant lymphoma       | 2 (2.6)       | 2 (7.4)                     | 0                           | 0.117   |
| Previous variceal bleeding | 38 (49.4) | 11 (40.7)                   | 27 (54)                     | 0.317   |
| Previous HEP             | 28 (36.4)     | 8 (29.6)                    | 20 (40)                     | 0.409   |
| SBP history              | 6 (7.8)       | 1 (3.7)                     | 5 (10)                      | 0.659   |
| Rifaximim within 30 days before SBP diagnosis | 11 (14.3) | 4 (14.8) | 7 (14) | 1 |
| Use of systemic antibiotics within 30 days before SBP diagnosis | 27 (35.1) | 14 (19.1) | 13 (26) | 0.03 |
| Nosocomial infection (>48 hours) | 33 (42.9) | 15 (55.6) | 18 (36) | 0.16 |
| Combined UTI             | 8 (10.39)     | 1 (3.7)                     | 7 (14)                      | 0.248   |
| Mucositis                | 1 (1.3)       | 0 (0.0)                     | 1 (2)                       | 1       |
| PPI administration       | 22 (28.6)     | 9 (33.3)                    | 13 (26)                     | 0.497   |
| Soft tissue infection    | 0 (0.0)       | 0 (0.0)                     | 0 (0)                       | 1       |
| Steroid use              | 2 (2.6)       | 1 (3.7)                     | 1 (2)                       | 1       |
| NSBB use                 | 22 (28.6)     | 4 (14.8)                    | 18 (36)                     | 0.065   |
| BMI                      | 22.28 ± 2.8   | 22.52 ± 3.08                | 22.16 ± 2.67                | 0.614   |
| Bacteremia               | 32 (41.6)     | 7 (20.5)                    | 25 (50)                     | 0.295   |
| Septic shock             | 17 (22.1)     | 3 (11.1)                    | 14 (28)                     | 0.148   |
| Appropriate definitive antimicrobial therapy | 68 (89.5) | 22 (64.6) | 46 (92) | 0.264 |
| SOFA score               | 6.1 ± 2.26    | 4.74 ± 1.91                 | 6.84 ± 2.1                  | 0.001   |
| Charlson index           | 6.47 ± 2.77   | 6.81 ± 2.68                 | 6.28 ± 2.83                 | 0.409   |
| 28-day mortality         | 34 (44.2)     | 11 (40.7)                   | 23 (46)                     | 0.407   |
| Serum                    |               |                             |                             |         |
| WBC count, /mm$^3$       | 9250 ± 5797   | 9090 ± 4052                 | 9337 ± 6587                 | 0.840   |
| Platelet, 10$^9$/L       | 94 ± 50       | 108 ± 65                    | 86 ± 38                     | 0.131   |
| Creatinine, mg/dL        | 2.02 ± 1.83   | 1.43 ± 0.93                 | 2.34 ± 2.1                  | 0.011   |
| Albumin, g/dL            | 2.45 ± 0.42   | 2.55 ± 0.42                 | 2.39 ± 0.42                 | 0.114   |
| Total bilirubin, mg/dL   | 5.64 ± 8.57   | 6.03 ± 7.87                 | 5.43 ± 4.52                 | 0.721   |
| Prothrombin time (INR)   | 1.60 ± 0.55   | 1.48 ± 0.53                 | 1.66 ± 0.55                 | 0.155   |
| CRP, mg/dL               | 72.79 ± 30.34 | 66.83 ± 43.06 | 76.54 | 0.449 |
| HbA1c                    | 6.87 ± 1.46   | 6.68 ± 1.1                  | 6.93 ± 1.59                 | 0.77    |
| Peritoneal fluid         |               |                             |                             |         |
| WBC, /mm$^3$             | 6140 ± 6973   | 4487 ± 5023                 | 7033 ± 7727                 | 0.127   |
| PMN count, /mm$^3$       | 5201 ± 6490   | 3538 ± 4769                 | 6099 ± 7136                 | 0.099   |
| Protein, g/dL            | 1.28 ± 0.7    | 1.38 ± 0.85                 | 1.23 ± 0.61                 | 0.384   |
| Albumin, g/dL            | 0.6 ± 0.31    | 0.68 ± 0.4                  | 0.56 ± 0.24                 | 0.183   |

Data are number (%) of patients, unless otherwise indicated. BMI = body mass index, CKD = chronic kidney disease, CRP = C-reactive protein, DM = diabetes mellitus, HBV = hepatitis B virus, HCC = hepatocellular carcinoma, HCV = hepatitis C virus, HEP = hepatic encephalopathy, MELD = Model for End-Stage Liver Disease, NBNC = non-hepatitis B non-hepatitis C, NSBB = nonselective β-blocker, PMN = polymorphonuclear leukocyte, PPI = proton pump inhibitor, SBP = spontaneous bacterial peritonitis, SOFA = sequential organ failure assessment, TACE = transcatheter arterial chemoembolization, UTI = urinary tract infection, WBC = white blood cell.
Gram-negative bacteria (most frequently *E. coli*) through translocation from the intestinal lumen are responsible for the majority of SBP cases. However, the preponderance of infections caused by gram-negative bacteria due to epidemiological changes has shifted to a higher prevalence of infections being caused by gram-positive cocci. In a study by Alexopoulou et al., the majority of isolated pathogens from patients with SBP were gram-positive cocci (55%). Our findings are in agreement with several recent reports that showed a high frequency of gram-positive bacterial infections associated with SBP.

We observed that the use of systemic antibiotics within 30 days before SBP diagnosis and a lower SOFA score were independent predictors of SBP caused by gram-positive bacteria in patients with cirrhosis. However, the effects of proton pump inhibitor administration, taking nonselective β-blocker and taking rifaximin for prophylaxis within 30 days before SBP diagnosis on the predominance of gram-positive bacteria could not be proven in our study.

In this study, the use of systemic antibiotics within 30 days before SBP diagnosis was an independent predictive factor in patients with cirrhosis and SBP caused by gram-positive bacterial infections. Innate and adaptive immune dysfunction, also referred to as cirrhosis-associated immune dysfunction syndrome, is a major component of cirrhosis. Bacterial infections are common and represent important causes of liver-related disease.

### Table 2. Bacteria Isolated From Ascitic Fluid in Patients With Spontaneous Bacterial Peritonitis

| Microorganisms | Susceptibility | n (%) |
|----------------|---------------|------|
| **Gram-positive (n = 27, 35.1%)** | | |
| *Enterococcus spp* | VSE | 8 (10.39) |
| | VRE | 2 (2.60) |
| *Staphylococcus aureus* | MSSA | 4 (5.19) |
| | MRSA | 6 (7.79) |
| *Streptococcus spp* | ESBL (–) | 7 (9.09) |
| *Aeromonas spp* | ESBL (–) | 3 (3.90) |
| | ESBL (+) | 1 (1.30) |
| *Citrobacter freundii* | ESBL (–) | 2 (2.60) |
| | ESBL (+) | 0 |
| *Enterobacter spp* | ESBL (–) | 2 (2.60) |
| | ESBL (+) | 0 |
| **Gram-negative (n = 50, 64.9%)** | | |
| *Escherichia coli* | ESBL (–) | 21 (27.27) |
| | ESBL (+) | 4 (5.19) |
| *Klebsiella pneumoniae* | ESBL (–) | 9 (11.69) |
| | ESBL (+) | 6 (7.79) |
| *Providencia rettgeri* | ESBL (–) | 1 (1.30) |
| | ESBL (+) | 0 |
| *Pseudomonas aeruginosa* | ESBL (–) | 1 (1.30) |
| | ESBL (+) | 0 |

Data are the numbers (%) of patients. ESBL = extended spectrum beta-lactamase, MRSA = methicillin-resistant *S. aureus*, MSSA = methicillin-susceptible *S. aureus*, VRE = vancomycin-resistant Enterococci, VSE = vancomycin-susceptible Enterococci.

### Table 3. Antibiotics Used for the Definitive Treatment of Spontaneous Bacterial Peritonitis (SBP)

| Microorganisms | Quinolones | Cephalosporins | Piperacillin/Tazobactam | Carabapenem | Glycopeptide | Tigecycline |
|----------------|------------|----------------|------------------------|-------------|--------------|-------------|
| **Gram-positive (n = 27, 35.1%)** | | | | | | |
| *Enterococcus spp* | 2 (0) | 2 (2) | 5 (5) |
| *Staphylococcus aureus* | 3 (2) | | | | | |
| *Streptococcus spp* | 1 (1) | 6 (6) | | | | |
| *Aeromonas spp* | 2 (2) | 2 (2) | | | | |
| *Citrobacter freundii* | | 2 (2) | | | | |
| *Enterobacter spp* | | 2 (2) | | | | |
| *Escherichia coli* | 17 (14) | 3 (3) | 5 (5) | | | |
| **Gram-negative (n = 50, 64.9%)** | | | | | | |
| *Klebsiella pneumoniae* | 1 (1) | 6 (5) | 8 (8) | 1 (1) |
| *Providencia rettgeri* | | | | | | |
| *Pseudomonas aeruginosa* | | | | | | |
| **Total n** | 4 (4) | 40 (33) | 6 (6) | 15 (14) | 10 (10) | 1 (1) |

Data are the numbers of patients. Figures in parenthesis refer to the numbers of patients who treated with appropriate antibiotics considering susceptibility testing results.
complications, progression of liver failure, and mortality related to cirrhosis. Thus, early diagnosis and prompt initiation of adequate antibiotic therapy is essential in the management of patients with cirrhosis and bacterial infections. As a result, patients with cirrhosis consume more antibiotics than the general population. In our study, 27 patients (35.1%) had taken systemic antimicrobial therapy within the past 30 days, but in cases of gram-positive bacterial infections, the proportion increased to 51.9% (14 of 27). This result might be attributed to 2 factors. First, although there were no statistically significant differences between the 2 groups in the rate of nosocomial infections, gram-positive bacterial infections were reported more frequently in the hospital than gram-negative infections (55.6% vs 36.0%, respectively; \(P = 0.16\)). Second, the prevalence of infections caused by multiresistant bacteria (e.g., methicillin-resistant \(S\) aureus and \(E\) faecium) is increasing in cirrhosis patients.

In addition, this study showed that a lower SOFA score was associated with SBP caused by gram-positive bacterial infections in patients with cirrhosis. The SOFA score is a simple but effective method to describe organ dysfunction/failure in critically ill patients not only in the ICU but also in other places, such as emergency departments. As many patients with SBP were admitted via the emergency department, calculating the SOFA score is important for predicting the outcome along with other clinical information. Regular, repeated scoring enables a patient’s condition and disease development to be monitored and better understood.

In conclusion, our findings are in agreement with several recent studies that reported a high frequency of gram-positive SBP. In addition, the use of systemic antibiotics within 30 days before SBP diagnosis and a lower SOFA score were significantly associated with SBP caused by gram-positive bacteria in patients with cirrhosis. Therefore, it is important that physicians take all of these factors into account when diagnosing and treating patients with cirrhosis and SBP.

**REFERENCES**

1. Lutz P, Nischalke HD, Strassburg CP, et al. Spontaneous bacterial peritonitis: the clinical challenge of a leaky gut and a cirrhotic liver. *World J Hepatol*. 2015;7:304–314.
2. Cheong HS, Kang CI, Lee JA, et al. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. *Clin Infect Dis*. 2009;48:1230–1236.
3. Tandon P, Garcia-Tsao G. Bacterial infections, sepsis, and multi-organ failure in cirrhosis. *Semin Liver Dis*. 2008;28:26–42.
4. Arroyo V, Jimenez W. Complications of cirrhosis. II. Renal and circulatory dysfunction. Lights and shadows in an important clinical problem. *J Hepatol*. 2000;32(1 Suppl):157–170.
5. Caruntu FA, Benea L. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, treatment. *J Gastrointest Liver Dis*. 2006;15:51–56.
6. Guarner C, Soriano G. Spontaneous bacterial peritonitis. *Semin Liver Dis*. 1997;17:203–217.
7. Guarner C, Runyon BA. Spontaneous bacterial peritonitis: pathogenesis, diagnosis, and management. *Gastroenterologist*. 1995;3:311–328.

8. Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology*. 2009;49:2087–2107.

9. European Association for the Study of the Liver. (EASL) clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. *J Hepatol*. 2010;53:397–417.

10. Fernandez J, Navasa M, Gomez J, et al. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. *Hepatology*. 2002;35:140–148.

11. Cholongitas E, Papatheodoridis GV, Lahanas A, et al. Increasing frequency of Gram-positive bacteria in spontaneous bacterial peritonitis. *Liver Int*. 2005;25:57–61.

12. Reuken PA, Pletz MW, Baier M, et al. Emergence of spontaneous bacterial peritonitis due to enterococci – risk factors and outcome in a 12-year retrospective study. *Aliment Pharmacol Ther*. 2012;35:1199–1208.

13. Alexopoulou A, Papadopoulos N, Eliopoulos DG, et al. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. *Liver Int*. 2013;33:975–981.

14. Korhonen PE. How to assess kidney function in outpatient clinics. *Int J Clin Pract*. 2015;69:156–161.

15. Mullen KD. Review of the final report of the 1998 Working Party on definition, nomenclature and diagnosis of hepatic encephalopathy. *Aliment Pharmacol Ther*. 2007;25(Suppl 1):11–16.

16. Augustin S, Muntaner L, Altamirano JT, et al. Predicting early mortality after acute variceal hemorrhage based on classification and regression tree analysis. *Clin Gastroenterol Hepatol*. 2009;7:1347–1354.

17. Vlachogiannakos J, Viazis N, Vasianopoulou P, et al. Long-term administration of rifaximin improves the prognosis of patients with decompensated alcoholic cirrhosis. *J Gastroenterol Hepatol*. 2013;28:450–455.

18. Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. *Gut*. 2012;61:297–310.

19. Fernandez J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology*. 2012;55:1551–1561.

20. Sipeki N, Antal-Szalmas P, Lakatos PL, et al. Immune dysfunction in cirrhosis. *World J Gastroenterol*. 2014;20:2564–2577.

21. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60:1310–1324.

22. Strauss E. The impact of bacterial infections on survival of patients with decompensated cirrhosis. *Ann Hepatol*. 2013;13:7–19.

23. Arabi YM, Dara SI, Memish Z, et al. Antimicrobial therapeutic determinants of outcomes from septic shock among patients with cirrhosis. *Hepatology (Baltimore, MD)*. 2012;56:2305–2315.

24. Jones AE, Trzeciak S, Kline JA. The Sequential Organ Failure Assessment score for predicting outcome in patients with severe sepsis and evidence of hypoperfusion at the time of emergency department presentation. *Crit Care Med*. 2009;37:1649–1654.

25. Hifumi T, Fujishima S, Abe T, et al. Prognostic factors of *Streptococcus pneumoniae* infection in adults. *Am J Emerg Med*. 2015.

26. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on ‘sepsis-related problems’ of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26:1793–1800.