Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.7170-21
Intern Med 60: 3435-3440, 2021
http://internmed.jp

【 CASE REPORT 】

Liver Cirrhosis Complicated by Spontaneous Bacterial Peritonitis Caused by the *Burkholderia cepacia* Complex

Arisa Hamahata, Seiya Mitsusada, Tomoyuki Iwata, Ken Nakajima, Yuki Ogawa, Akira Miyazaki, Marina Kobayashi, Yushi Fujiwara, Yu Asano, Kazuhisa Mabuchi, Miki Yoshida and Ayako Misawa

Abstract:
A 79-year-old man with underlying alcoholic liver cirrhosis presented with complaints of a fever, abdominal pain, and difficulty walking. A diagnostic work-up revealed liver atrophy and chylous ascites, and spontaneous bacterial peritonitis (SBP) was diagnosed based on the cell and neutrophil counts. The *Burkholderia cepacia* complex (Bcc) was detected on blood and ascitic fluid cultures. Although broad-spectrum antibiotic therapy was initiated, the infection was difficult to control, and the patient died of multiple organ failure. Bcc is often multidrug-resistant and difficult to treat. SBP caused by Bcc has been rarely reported and may have a serious course, thus necessitating caution.

Key words: *Burkholderia cepacia* complex, multidrug-resistant bacteria, spontaneous bacterial peritonitis (SBP), liver cirrhosis

(Intern Med 60: 3435-3440, 2021)
(DOI: 10.2169/internalmedicine.7170-21)

Introduction

The *Burkholderia cepacia* complex (Bcc) is a collective term for a group of ≥20 Gram-negative bacilli found in the natural environment. This bacterial group causes fatal respiratory infections particularly in patients with cystic fibrosis (CF) and is often implicated in opportunistic infections (1). It has rarely been detected as a pathogen for spontaneous bacterial peritonitis (SBP) complicating liver cirrhosis (2). Of note, Bcc is intrinsically resistant to many antibiotics, and its infection follows a serious course characterized by septic shock and renal failure (3).

We herein report a case of SBP caused by a bacterial species requiring attention.

Case Report

Patient: A 79-year-old man.

Chief complaint: A fever, abdominal pain, and difficulty walking

Medical history: Alcoholic liver cirrhosis, diabetes mellitus, hypertension, and atrial fibrillation

Life history: Alcohol drinker (43 g/day)

History of present illness: In addition to the above complaints, the patient had also developed anorexia, abdominal pain, and generalized pain five days before admission. The patient had a fever and gradually became unable to take food orally, with walking also proving difficult. He was subsequently transferred to our hospital by ambulance.

State of illness at admission: The patient's height and body weight were 159 cm and 51.7 kg, respectively. The level of consciousness was Japan Coma Scale-0. His blood pressure was 125/67 mmHg. The pulse rate was 146 beats/min and regular. His body temperature was 38.5℃. There was no pallor in the palpebral conjunctiva, although icterus was detected in the bulbar conjunctiva. The cardiac and respiratory sounds were normal. Superficial lymph nodes were not palpable. The abdomen was flat and hard, and there was tenderness throughout the abdomen from the upper right abdomen to the midline as the strongest point. The liver was not palpable. No pedal edema was noted.

Department of Gastroenterology, Tokyo-Kita Medical Center, Japan
Received: January 26, 2021; Accepted: March 23, 2021; Advance Publication by J-STAGE: May 14, 2021
Correspondence to Dr. Seiya Mitsusada, seiyami@jadecom.com

Regarding the hematological findings on admission (Table 1), although there was no clear elevation in the white blood cell count, the C-reactive protein (CRP) level was 22.3 mg/dL, revealing an elevated inflammatory response. Renal dysfunction was noted with a creatinine level of 2.76 mg/dL, urea nitrogen level of 60.3 mg/dL, and estimated glomerular filtration rate of 18.2 mL/min/1.73 m^2. The albumin level was 2.2 g/dL. The total bilirubin level was 4.4 mg/dL. The prothrombin time was 34% (international normalized ratio: 1.67). The platelet count was 57,000/μL.

Table 1. Blood Test Results on Admission.

WBC	3,090 /μL	BUN	60.3 mg/dL
Lymph	2.0 %	Cre	2.76 mg/dL
Stab	26.0 %	CRP	22.5 mg/dL
Seg	48.0 %	FBS	29 mg/dL
Myelo	2.0 %	HbA1c	7.6 %
Meta	9.0 %		
Atypi-Ly	2.0 %	Na	137 mmol/L
Hb	7.7 g/dL	K	3.8 mmol/L
Plt	5.7×10^4 /μL	Cl	99 mmol/L
		Ca	8.6 mmol/L
Alb	2.2 g/dL		
LDH	237 U/L	PT-sec	18.9 Sec
AST	105 U/L	PT%	34 %
ALT	127 U/L	PT-INR	1.67
ALP	138 U/L	APTT	46.6 sec
γGTP	168 U/L	Fib	291 mg/dL
T-Bil	4.4 mg/dL	Ddimer	10,4 μg/mL

The hemoglobin level and platelet counts were decreased. The hepatobiliary deviation enzyme levels were elevated. Renal dysfunction was detected. Elevated inflammatory responses, abnormal coagulation test values, and an elevated lactate level were also noted.

WBC: white blood cell, lymph: lymphocyte, stab: stab cell, seg: segmented cell, Myelo: myelocyte, Meta: metamyelocyte, Atypi-Ly: atypical, lymphocyte, Hb: hemoglobin, Plt: platelet, Alb: albumin, LDH: lactate, dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, γGTP: γ-Glutamyl TransPeptidase, T-Bil: total bilirubin, BUN: blood urea nitrogen, Cre: creatine, CRP: C-reactive protein, FBS: fasting blood sugar, HbA1c: hemoglobin A1c, PT-sec: prothrombin time-second, PT%: prothrombin time %, PT-INR: prothrombin time-international normalized ratio, APTT: activated partial thromboplastin time, Fib: Fibrinogen

On abdominal plain computed tomography, the liver was found to be cirrhotic and atrophied with an irregular surface. Ascites and mild splenomegaly were noted. Neither abscess formation nor free air was noted (Fig. 1). The hepatic reserve was classified as Child-Pugh category C (13 points). The Model for End-Stage Liver Disease (MELD) score was 22.

Paracentesis was performed for ascites, and the ascitic fluid was found to be yellow and purulent with a cell count of 68,195/μL, comprising 80.9% neutrophils (Table 2), and the serum to ascites albumin gradient was 1.26, suggesting leaky ascites. Furthermore, bacterial bodies were confirmed by Gram staining (Fig. 2).

Clinical course after admission: Based on the above results, SBP was diagnosed, and ceftriaxone (CTRX 2 g once daily) and human serum albumin 25% were initiated. However, the fever persisted, and the white blood cell count increased. On hospital day 3, Bcc was detected by blood culture. The antibiotic was switched to meropenem (MEPM 0.5 g twice daily) (Table 3). However, the white blood cell count remained elevated. On hospital day 6, because the drug sensitivity test of the ascitic fluid suggested that the bacteria might be resistant to MEPM, trimethoprim-sulfamethoxazole (ST 160 mg every 8 h) combination was added (Table 4). The patient still poorly responded to treatment; thus, MEPM was switched to levofloxacin (250 mg once daily) on hospital day 8.

Although the fever and abdominal pain started to improve, abdominal distension owing to ascites worsened, and while the CRP levels decreased, the white blood cell count remained elevated (Fig. 3). During progress, the blood sugar passed in 200-300 mg/dL. Since renal dysfunction also progressed with time, dialysis was considered on hospital day 11. However, the patient was placed on observation without dialysis because of his poor general condition and at the request of his family. He ultimately died on hospital day 12. MEPM, ST, Levofloxacin, and albumin were continued until

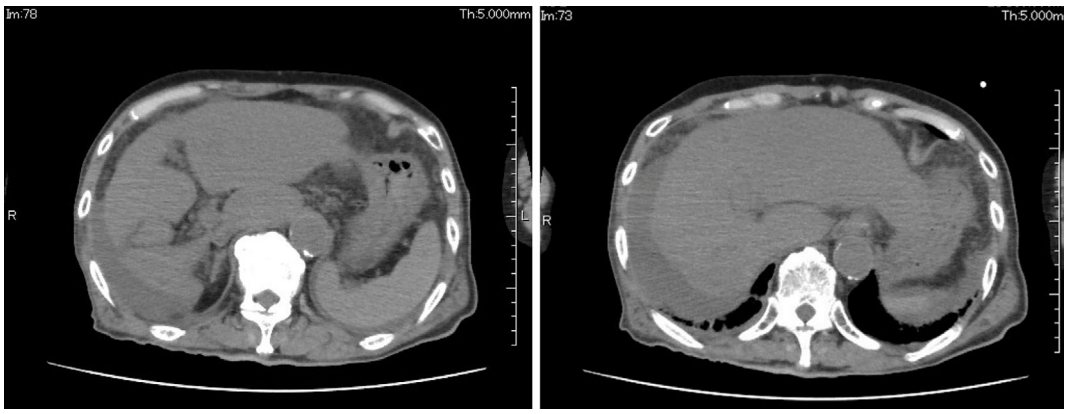

Figure 1. CT findings at the time of admission. There was fluid around the liver and spleen (ascites), and liver atrophy was noted. Neither free air nor abscess formation was noted.

Table 2. Ascites Test Results.

Albmin	0.94 g/dL	Cell count	68,195 μL
LDH	1,769 IU/L	Neut	80.9 %
Total cholesterol	33 mg/dL	Lymph	2.0 %
Sugar determination	49 mg/dL	Mono	13.8 %
Protein quantification	1.95 g/dL	Eos	3.3 %
Specific gravity	1.025	pH	7.2
Rivalta	(+)		

White blood cells in the ascites were increased. This result suggests SBP.
LDH: lactate dehydrogenase, Neut: neutrophil, Lymph: lymphocyte, Mono: monocyte, Eos: eosinophil

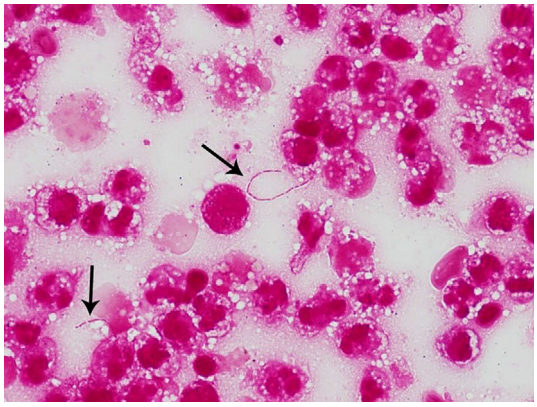

Figure 2. Hematoxylin and Eosin staining of ascites sample. The arrows indicate the *Burkholderia cepacia* complex.

death (Fig. 3).

Informed consent was obtained by allowing opt-out on our website.

Discussion

Bcc was first reported in 1950 by Burkholde as a phytopathogenic bacterium causing onion to rot and was referred to as *Pseudomonas cepacia* (4). In 1992, it was classified under the *Burkholderia* genus based on 16S ribosomal RNA sequencing, DNA-DNA homology values, composition of cytoplasmic lipid and fatty acid, and phenotypic characteristics (5). In recent years, further genetic analyses have divided Bcc into at least 21 species (6). Because the applications of Bcc in the agricultural field are numerous, research on its pathogenicity and safety is continuously being conducted for each class and species based on genetic information.

Bcc is a group of glucose-nonfermenting aerobic Gram-negative bacilli that exist in moist natural environments, such as water, sewage, vegetables, and fruits. In the medical field, Bcc is an important pathogen in patients with CF, bronchiectasis, and a history of lung transplantation; it is also responsible for nosocomial infections through contaminated medical devices, such as catheters and disinfectant solutions (1, 7, 8). Generally, this bacterial group is rarely reported except in immunocompromised patients and those with CF (9). The present patient had diabetes mellitus, but a blood test by a previous doctor 2 months before admission showed an HbA1c of 7.0% and occasional glycemic level of 150 mg/dL, so his glycemic control was not bad.

A previous study reported that Bcc was detected by positive ascitic fluid culture in 11 of 252 patients with SBP (4.3%) (3). However, commonly identified pathogens for SBP are Gram-negative bacilli (i.e. *Escherichia coli* and *Klebsiella*) and Gram-positive cocci (mainly streptococci and enterococci) (10). Bcc is often drug-resistant and intrinsically resistant to antibiotics, including aminoglycosides, first- and second-generation cephalosporins, synthetic penicillin, and polymyxins (11), as Bcc bacteria have a gene inducing β-lactamase that confers resistance to β-lactam antibiotics by altering penicillin-binding proteins and efflux pumps (3). The sensitivity and treatment of Bcc have been reported in immunocompromised patients and others in real-world clinical practice. In a report of patients infected with Bcc during the treatment of hematologic conditions, Bcc was found to be sensitive to imipenem in all patients, and their blood culture results became negative within 3 days of treatment with cefoperazone-sulbactam or piperacillin-tazobactam (12). In a cohort study that followed up non-CF patients positive for Bcc for 17 years, 94% and 88% of Bcc isolates were sensitive to trimethoprim-sulfamethoxazole and fluoroquinolones, respectively, whereas approximately 70% of the isolates were sensitive to ceftazidime and MEPM. The most frequently used antimicrobial agents in that cohort study were quinolone antimicrobial agents, followed by carbapenem antibiotics, ST combination, and ceftazidime. The study concluded that there was no marked difference in the prognosis, regardless of the antimicrobial agents, as long as an effective antimicrobial agent was selected (*in vitro*) (9).

Although there have been a few reports of Bcc isolated from patients with SBP, a report of 11 cases indicated that Bcc was sensitive to cotrimoxazole and MEPM and resistant to CTRX, ceftazidime, cefepime, cefotaxime, and colistin (3). Another case report showed that patients survived after two weeks of treatment with MEPM (13). In general, the early use of antibiotics is recommended because the SBP prognosis is poor even with culture results being unknown. Third-generation cephalosporins are the first choice (14). In recent years, however, the spread of multidrug-resistant bacterial infections has reduced the efficacy of commonly used antibiotics, including third-generation cephalosporins (15). The selection of initial antibiotics should be adjusted according to the presence of risk factors for multidrug-resistant bacterial infection and the severity of infection, and regional epidemiology should also be considered. In a population at high risk for multidrug-resistant bacterial infections, empirical treatment requires the use of broad-spectrum antibiotics (carbapenem or tigecycline) and drugs with known activity against resistant bacteria. An early de-escalation strategy is recommended (16). Based on the above findings, infection with Bcc should be treated with carbapenem, ST combina-

Table 3. **Results of the Sensitivity Test of *Burkholderia Cepacia* (Blood Culture).**

Drug	MIC* (μg/mL)	Result	Drug	MIC* (μg/mL)	Result
ampicillin	4	R	meropenem	≤0.25	S
piperacillin	64	R	aztreonam	16	I
SBT/ABPC**	≤2	R	gentamaicin	8	I
TAZ/PIPC***	≤4	R	amikacin	16	S
cefazolin	≥64	R	minomaicin	≤1	S
cefmetazole	≥64	R	levofloxacin	1	S
ceftriaxone	≤1	R	ciprofloxacin	1	S
ceftazidime	≤1	R	ST****		S
cefepine	≤1	R			

*MIC: minimum inhibitory concentration. **SBT/ABPC: sulbactam/ampicillin.
***TAZ/PIPC: poperacillin/tazobactam. ****ST: sulfamethoxazole/trimethoprim.

Table 4. **Results of the Sensitivity Test of *Burkholderia Cepacia* (Ascitic Fluid).**

Drug	MIC* (μg/mL)	Result	Drug	MIC* (μg/mL)	Result
ampicillin	≥32	R	meropenem	8	I
piperacillin	≥128	R	aztreonam	≥64	R
SBT/ABPC**	≥32	R	gentamaicin	8	I
TAZ/PIPC***	≥128	R	amikacin	16	S
cefazolin	≥64	R	minomaicin	≤1	S
cefmetazole	≥64	R	levofloxacin	1	S
ceftriaxone	≥64	R	ciprofloxacin	1	S
ceftazidime	16	I	ST****		S
cefepine	32	R			

*MIC: minimum inhibitory concentration. **SBT/ABPC: sulbactam/ampicillin.
***TAZ/PIPC: poperacillin/tazobactam. ****ST: sulfamethoxazole/trimethoprim.

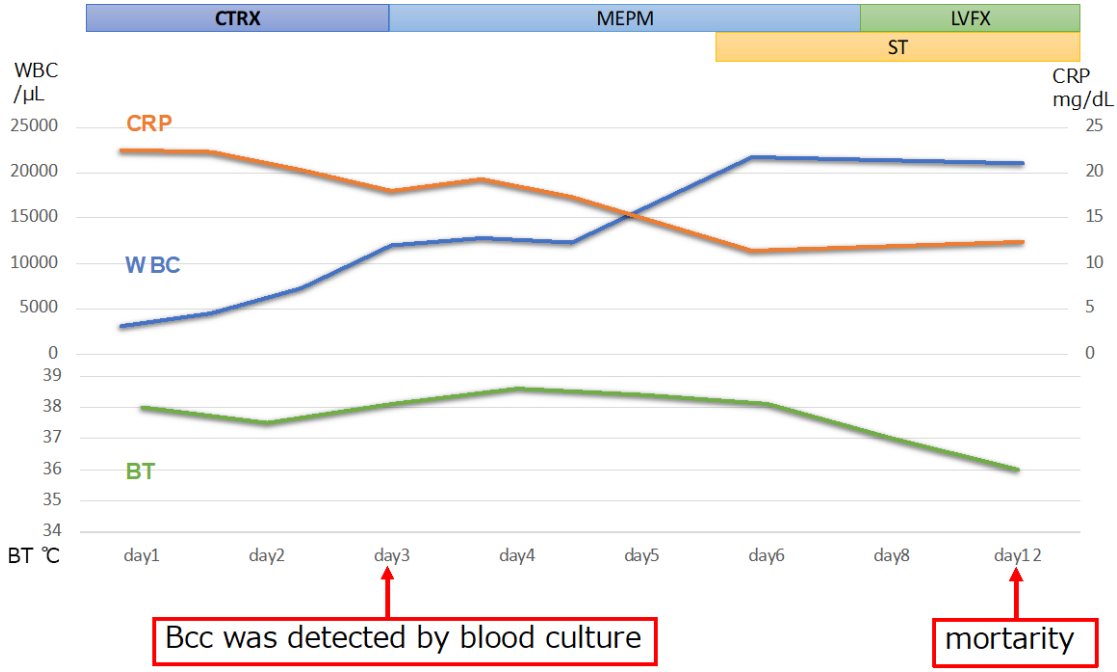

Figure 3. **Progress chart during hospitalization. Despite using broad-spectrum antibacterial drugs, although the CRP levels decreased, the white blood cell count remained elevated. CRP: C-reactive protein, WBC: white blood cell, BT: body temperature**

tion, quinolones, tetracycline, and chloramphenicol.

According to a systematic review, the mortality rate of SBP patients is 31.5% at 1 month and 66.2% at 12 months, and the mortality rate of patients with bacteremia is 42.2% (17). Factors determining the prognosis of patients with SBP include renal dysfunction, the MELD score, refractoriness to treatment, immunologic suppressor factors, and nosocomial SBP (18). Patients with liver cirrhosis who develop SBP are at risk of developing renal failure (19). However, renal failure, which occurs even after treatment with appropriate antibiotics, may be caused by excessive inflammatory responses of the host or hemodynamic changes associated with sepsis, instead of tissue damage directly caused by the bacteria (20). In a study including the largest number of patients with SBP caused by Bcc, 10 of 11 patients developed acute kidney injury, and 8 of 11 patients died of sepsis or multiple organ failure (3). This suggests that infection with Bcc is likely to be complicated by fatal conditions, such as renal failure, and multidrug resistance of Bcc is not the only issue to be considered. Thus, Bcc may be a bacterial group that is likely to cause sepsis associated with excessive inflammatory responses and hemodynamic changes in the host.

In the present case, the Cre value of 1.16 mg/dL (blood test at the previous doctor) increased sharply to 2.7 mg/dL within 2 months before admission. In addition, the patient was in septic shock at the time of admission. These findings suggest that the main cause of renal dysfunction at the time of admission in this patient was multiple organ failure associated with infectious disease. Furthermore, we cannot rule out the potential involvement of type 1 hepato-renal syndrome secondary to SBP in the exacerbation of the renal function after hospitalization.

In patients with liver cirrhosis, SBP is considered to be caused by enterobacterial proliferation and changes in the intestinal barrier owing to portal hypertension in addition to reticuloendothelial system dysfunction (21). Although many aspects of the association between intestinal microflora and Bcc in liver cirrhosis are unknown, they seem to be interrelated to an extent. Because Bcc cannot be killed by disinfectant solutions such as chlorhexidine (22), the possibility of infection from disinfectant solutions by multiple punctures has also been mentioned (13). In the present case, although the patient had been admitted to a previous hospital for treatment multiple times, we were unable to confirm whether or not ascites paracentesis had been performed at the previous hospital. In addition, this patient was unemployed at the time of admission (although he almost never went out), and we had no information on his previous occupation. Therefore, the route of infection was unknown.

Conclusion

Because Bcc is multidrug-resistant, its infection is likely to become serious and difficult to treat. Although reports of SBP caused by Bcc are rare, many describe SBP complicated by acute kidney injury. The first-choice drug for SBP is a third-generation cephem antibiotic. However, Bcc can be resistant to this drug, causing multiple organ failure and resulting in a high mortality rate. Our patient also had a serious clinical course. In clinical practice, caution should be exercised.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

We thank Miyuki Isonishi, Department of Clinical Laboratory, Tokyo-Kita Medical Center, for providing expertise in the diagnosis.

References

1. Devanga Ragupathi NK, Veeraraghavan B. Accurate identification and epidemiological characterization of Burkholderia cepacia complex: an update. Annals Clin Microbiol Antimicrob **18**: 7, 2019.
2. Fiore M, Maraolo AE, Gentile I, et al. Nosocomial spontaneous bacterial peritonitis antibiotic treatment in the era of multi-drug resistance pathogens: a systematic review. World J Gastroenterol **23**: 4654-4660, 2017.
3. Taneja S, Kumar P, Gautam V, et al. Spontaneous bacterial peritonitis by *Burkholderia cepacia* complex: a rare, difficult to treat infection in decompensated cirrhotic patients. J Clin Exp Hepatol **7**: 102-106, 2017.
4. WH B. Sour skin, a bacterial rot of onion bulbs. Phytopathology **40**: 115-117, 1950.
5. Yabuuchi E, Kosako Y, Oyaizu H, et al. Proposal of *Burkholderia* gen. nov. and transfer of seven species of the genus *Pseudomonas* homology group II to the new genus, with the type species *Burkholderia cepacia* (Palleroni and Holmes 1981) comb. nov. Microbiol Immunol **36**: 1251-1275, 1992.
6. Furlan JPR, Pitondo-Silva A, Braz VS, Gallo IFL, Stehling EG. Evaluation of different molecular and phenotypic methods for identification of environmental *Burkholderia cepacia* complex. World J Microbiol Biotechnol **35**: 39, 2019.
7. Lipuma JJ. Update on the *Burkholderia cepacia* complex. Curr Opin Pulm Med **11**: 528-533, 2005.
8. Vandamme P, Dawyndt P. Classification and identification of the *Burkholderia cepacia* complex: past, present and future. Syst Appl Microbiol **34**: 87-95, 2011.
9. El Chakhtoura NG, Saade E, Wilson BM, Perez F, Papp-Wallace KM, Bonomo RA. A 17-year nationwide study of *Burkholderia cepacia* complex bloodstream infections among patients in the United States Veterans Health Administration. Clin Infect Dis **65**: 1253-1259, 2017.
10. EASL clinical practice guidelines on the management of ascites, spontaneous bacterial peritonitis, and hepatorenal syndrome in cirrhosis. J Hepatol **53**: 397-417, 2010.
11. Sfeir MM. *Burkholderia cepacia* complex infections: More complex than the bacterium name suggest. J Infect **77**: 166-170, 2018.
12. Baul SN, De R, Mandal PK, Roy S, Dolai TK, Chakrabarti P. Outbreak of Burkholderia cepacia infection: a systematic study in a Hematolooncology unit of a tertiary care hospital from eastern India. Mediterr J Hematol Infectious Dis **10**: e2018051, 2018.
13. Mukhopadhyay C, Bhargava A, Ayyagari A. Two novel clinical presentations of *Burkholderia cepacia* infection. J Clin Microbiol **42**: 3904-3905, 2004.
14. Dever JB, Sheikh MY. Review article: spontaneous bacterial peritonitis-bacteriology, diagnosis, treatment, risk factors and prevention. Aliment Pharmacol Ther **41**: 1116-1131, 2015.
15. Piano S, Brocca A, Mareso S, Angeli P. Infections complicating cirrhosis. Liver Int 38 Suppl **1**: 126-133, 2018.
16. Fernández J, Acevedo J. New antibiotic strategies in patients with

cirrhosis and bacterial infection. Expert Rev Gastroenterol Hepatol **9**: 1495-1500, 2015.

17. Arvaniti V, D'Amico G, Fede G, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology **139**: 1246-1256, 1256.e1241, 2010.

18. Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol **9**: 260-265, 2011.

19. Navasa M, Follo A, Filella X, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. Hepatology **27**: 1227-1232, 1998.

20. Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med **341**: 403-409, 1999.

21. Ascione T, Di Flumeri G, Boccia G, De Caro F. Infections in patients affected by liver cirrhosis: an update. Infez Med **25**: 91-97, 2017.

22. Sobel JD, Hashman N, Reinherz G, Merzbach D. Nosocomial *Pseudomonas cepacia* infection associated with chlorhexidine contamination. Am J Med **73**: 183-186, 1982.