



# Clinical impact of healthcare-associated acquisition in cirrhotic patients with community-onset spontaneous bacterial peritonitis

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**Background/Aims:** Healthcare-associated (HCA) infection is a recently suggested new category of community-onset infections. The implications of HCA infections in terms of diagnosis, treatment, and outcomes of spontaneous bacterial peritonitis (SBP) are not well understood. We sought to delineate the differences between community-acquired (CA) SBP and HCA SBP with specific interest in the antimicrobial resistance of causative microorganisms and outcomes.

**Methods:** We conducted a retrospective cohort study of all SBP episodes with positive ascitic culture and/or blood culture from June 2000 to August 2011. Community-onset SBP episodes were included when they occurred within 48 hours after admission and were classified as CA SBP and HCA SBP based on the predefined criteria.

**Results:** A total of 188 episodes of community-onset SBP were analyzed (65.4% HCA SBP and 34.6% CA SBP). HCA SBP had a higher resistance rate to third-generation cephalosporin (6.8% vs. 1.6%,  $p = 0.168$ ). The overall 30-day mortality was similar between both groups (37.4% vs. 41.5%,  $p = 0.638$ ). The independent risk factors for 30-day all-cause mortality in community-onset SBP included high Child-Pugh score, acute kidney injury, and resistance to third-generation cephalosporins; HCA infection was not associated.

**Conclusions:** Hepatic functional status, renal dysfunction, and third-generation cephalosporin resistant pathogens more adversely affected the outcome of cirrhotic patients with community-onset SBP rather than HCA infection. The higher rate of third-generation cephalosporin resistance was notable in HCA SBP, which will require a novel approach to empirical antibiotic treatment selection in this population.

**Keywords:** Spontaneous bacterial peritonitis; Liver cirrhosis; Mortality

## INTRODUCTION

The epidemiology of bacterial infections in cirrhosis has changed over the past two decades [1]. The prevalence of resistant bacterial infections has increased, and resistant bacteria are frequently observed in patients with

nosocomial infections, leading to poor outcomes [2,3]. Healthcare-associated (HCA) infections, a new category of community-onset infections, have similarities to nosocomial infections, with clinical characteristics that can be distinguished from community-acquired (CA) infections [4,5]. An understanding of the healthcare-related

population is needed for proper management of bacterial infections because most patients with advanced liver cirrhosis are commonly in contact with healthcare systems and require hospitalization due to complications. However, the clinical impacts of HCA infection are not well understood in patients with spontaneous bacterial peritonitis (SBP), a common bacterial infection in advanced cirrhosis [6,7].

The aim of our study was to evaluate the clinical implications of HCA SBP compared to CA SBP in cirrhosis. We sought to identify differences in the antimicrobial resistance of causative microorganisms and outcomes.

## METHODS

### Study design and population

A retrospective, observational cohort study was conducted to determine the differences between CA SBP and HCA SBP. Microbiology laboratory data for community-onset SBP episodes in cirrhotic patients were collected at the Samsung Medical Center, a 1,950-bed tertiary-care university hospital in South Korea, from June 2000 to August 2011. Patients aged > 18 years with positive ascites and/or blood results were enrolled in the study. We excluded patients with culture-negative SBP, secondary bacterial peritonitis, polymicrobial infections, bacterascites, and/or fungal peritonitis. A diagnosis of cirrhosis was established by clinical, histological, and/or radiological findings. Patient medical records were reviewed to collect data on age, sex, etiology of liver cirrhosis, Child-Pugh score and class, concomitant hepatocellular carcinoma (HCC), septic shock, acute kidney injury (AKI), laboratory ascites and serum profiles, empirical antibiotic regimen, previous history of SBP, antibiotic exposure within the 90 days prior to the SBP episode, and all-cause mortality at 30 days. This study was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB No. 2010-08-146). Written informed consent was waived because of the retrospective observational nature of the study.

### Definitions

SBP was defined as an elevated absolute polymorphonuclear neutrophil count  $\geq 250$  cells/mm<sup>3</sup> in ascitic fluid [8]. Bacterascites was defined as a positive ascitic fluid

culture in the setting of an ascitic fluid polymorphonuclear neutrophil count < 250 cells/mm<sup>3</sup> [9]. Community-onset SBP was defined as a SBP that occurred within 48 hours of admission to the hospital. Community-onset SBP was classified as CA SBP or HCA SBP based on the predefined criteria [4,5,7]. HCA SBP was defined by the following criteria: attended a hemodialysis clinic or received hemodialysis or intravenous chemotherapy in the 30 days before the episode, hospitalized in an acute care hospital or an emergency department for 2 or more days within the previous 90 days, or resided in a nursing home or long-term care facility. Patients who did not meet the criteria for a HCA SBP were defined as having CA SBP. The severity of hepatic dysfunction was assessed at the time of SBP diagnosis using the Child-Pugh classification. Septic shock was defined as a persistent arterial hypotension with a systolic arterial pressure below 90 mmHg or a decrease in systolic blood pressure of > 40 mmHg from baseline despite adequate volume resuscitation [10]. AKI was defined by an absolute increase in serum creatinine concentration of  $\geq 0.3$  mg/dL from the baseline, a  $\geq 50\%$  increase in serum creatinine concentration (1.5-fold from the baseline), or a reduction in urine output of less than 0.5 cc/kg/hr for more than 6 hours [11]. The definition of appropriate antibiotic treatment included initiation of antibiotic treatment within 24 hours, which included at least one antibiotic with *in vitro* activity against the isolated pathogen.

### Laboratory tests

Ascitic fluid was drawn by paracentesis using an aseptic technique and inoculated into blood culture bottles placed beside the bed. The ascitic fluid specimens obtained were also sent to the laboratory for biochemical profiles. Ascitic fluid and blood were incubated in the BacT/Alert 3D automated blood culture system (bioMérieux, Marcy l'Etoile, France). Microbiological identification was performed using a standard identification card. Antimicrobial susceptibility was tested using the modified broth microdilution method on the VITEK II automated system (bioMérieux). Minimum inhibitory concentration breakpoints and quality-control protocols were used according to the standards established by the Clinical and Laboratory Standard Institute [12].

### Statistical analysis

The Student *t* test and the Mann-Whitney test were used to compare continuous variables. The chi-square test and the Fisher exact test were performed to determine

the categorical variables. A stepwise logistic regression analysis was used to control the confounding variables of the independent risk factors for 30-day all-cause mortality. Variables with a *p* < 0.05 in the univariate analysis

**Table 1. Clinical characteristics of patients with community-onset spontaneous bacterial peritonitis**

Variable	CA SBP (n = 65)	HCA SBP (n = 123)	Total (n = 188)	<i>p</i> value
Age, yr	58.4 ± 10.9	57.0 ± 10.4	57.5 ± 10.6	0.382
Male sex	46 (70.8)	92 (74.8)	138 (73.4)	0.604
Cause of liver cirrhosis				
HBV	33 (50.8)	88 (71.5)	121 (64.4)	0.006
HCV	15 (23.1)	18 (14.6)	33 (17.6)	0.162
Alcohol	12 (18.5)	12 (9.8)	24 (12.8)	0.109
Other	8 (12.3)	7 (5.7)	15 (8.0)	0.155
Child-Pugh classification				
Score	10.9 ± 1.5	11.2 ± 1.5	11.1 ± 1.5	0.183
Class B	9 (13.8)	16 (13.0)	25 (13.3)	1.000
Class C	56 (86.2)	107 (87.0)	163 (86.7)	1.000
Concomitant hepatocellular carcinoma	29 (44.6)	80 (65.0)	109 (58.0)	0.008
Septic shock	20 (30.8)	36 (29.3)	56 (29.8)	0.868
Acute kidney injury	30 (46.2)	61 (49.6)	91 (48.4)	0.759
Gastrointestinal bleeding ≤ 7 days	7 (10.8)	9 (7.3)	16 (8.5)	0.584
Hepatic encephalopathy	15 (23.1)	29 (23.6)	44 (23.4)	1.000
Laboratory finding				
Serum Na, mmol/L	128.8 ± 6.7	128.5 ± 6.1	128.6 ± 6.3	0.830
Serum creatinine, mg/dL	1.66 ± 1.07	1.69 ± 1.07	1.68 ± 1.07	0.997 <sup>a</sup>
Ascites PMN, 10 <sup>3</sup> cells/μL	8,015 ± 12,864	15,112 ± 79,359	12,658 ± 64,629	0.425 <sup>a</sup>
Ascites protein, g/L	832.1 ± 628.7	1,003.0 ± 831.9	945.0 ± 771.2	0.095 <sup>a</sup>
Previous SBP episodes	8 (12.3)	43 (35.0)	51 (27.1)	0.001
Previous antibiotic uses ≤ 90 days <sup>b</sup>	1 (1.5)	49 (39.8)	50 (26.6)	< 0.001
Bacteremia	52 (80.0)	92 (74.8)	114 (76.6)	0.473
Empirical antibiotic regimen				
Third-generation cephalosporin <sup>c</sup>	62 (95.4)	103 (83.7)	165 (87.8)	0.033
Piperacillin/tazobactam or carbapenem	2 (3.1)	14 (11.4)	16 (8.5)	0.058
Appropriate antibiotics ≤ 24 hr <sup>d</sup>	60 (100)	112 (95.7)	173 (97.2)	0.167 <sup>e</sup>
All cause of 30-day mortality	27 (41.5)	46 (37.4)	73 (38.8)	0.638

Values are presented as mean ± SD or number (%) of patients.

CA, community-acquired; SBP, spontaneous bacterial peritonitis; HCA, healthcare-associated; HBV, hepatitis B virus; HCV, hepatitis C virus; PMN, polymorphonuclear neutrophil.

<sup>a</sup>Mann-Whitney test.

<sup>b</sup>Prior antibiotics are defined as antibiotics used for more than 2 days.

<sup>c</sup>Third-generation cephalosporins included ceftriaxone or cefotaxime.

<sup>d</sup>Both gram-positive and gram-negative organisms were analyzed except for 10 anaerobic isolates.

<sup>e</sup>Fisher exact test.

were included in the multivariate analysis. All *p* values were two-tailed, and a *p* < 0.05 was considered statistically significant. Data were analyzed with SPSS version 21.0 (IBM Co., Armonk, NY, USA).

## RESULTS

### Clinical characteristics of patients with community-acquired vs. healthcare-associated SBP

A total of 573 community-onset SBP cases were identified during the study period. Culture-positive SBP cases

included 164 patients with 188 episodes (32.8%); of these, 65.4% (123/188) were characterized as HCA SBP. The clinical characteristics of patients with community-onset SBP are shown in Table 1. The mean age of the study population was 57 years (standard deviation [SD], ± 10.6) with male predominance (73%). The majority of patients were Child-Pugh class C (86.7%), and almost half of the cases (48.4%) had AKI. The clinical characteristics were similar between CA SBP and HCA SBP; however, the patients with HCA SBP had significantly more concomitant HCC, previous SBP episodes, and prior antibiotic exposure within 90 days. The overall 30-day mortality of

**Table 2. Comparison of isolated microorganisms in patients with community-onset spontaneous bacterial peritonitis**

Microorganisms	CA SBP (n = 65)	HCA SBP (n = 123)	Total (n = 188)	<i>p</i> value
Gram negative bacteria	44 (67.7)	101 (82.1)	145 (77.1)	0.029
<i>Escherichia coli</i>	24 (36.9)	53 (43.1)	77 (41.0)	0.439
<i>Klebsiella pneumoniae</i>	12 (18.5)	28 (22.8)	40 (21.3)	0.576
<i>Aeromonas</i> spp.	5 (7.7)	6 (4.9)	11 (5.9)	0.517 <sup>a</sup>
Other <sup>b</sup>	3 (4.6)	14 (11.4)	17 (9.0)	0.181
Gram positive bacteria	21 (32.3)	22 (17.9)	43 (22.9)	0.029
<i>Streptococcus</i> spp.	8 (12.3)	9 (7.3)	17 (9.0)	0.290
<i>Streptococcus pneumoniae</i>	7 (10.8)	4 (3.3)	11 (5.9)	0.050 <sup>a</sup>
<i>Staphylococcus aureus</i> <sup>c</sup>	2 (3.1)	3 (2.4)	5 (2.7)	1.000 <sup>a</sup>
Anaerobic bacteria	4 (6.2)	6 (4.9)	10 (5.3)	0.740 <sup>a</sup>

Values are presented as number (%) of patients.

CA, community-acquired; SBP, spontaneous bacterial peritonitis; HCA, healthcare-associated.

<sup>a</sup>Fisher exact test.

<sup>b</sup>*Achromobacter xylosoxidans* (1), *Acinetobacter baumannii* (4), *Citrobacter freundii* (1), *Enterobacter cloacae* (1), *Klebsiella oxytoca* (4), *Klebsiella ozaenae* (1), *Pseudomonas aeruginosa* (1), *Salmonella* spp. (1), *Serratia marcescens* (1), *Shewanella putrefaciens* (1), and *Stenotrophomonas maltophilia* (1).

<sup>c</sup>One methicillin-resistant *S. aureus* case was detected in HCA SBP.

**Table 3. Antimicrobial resistance patterns of isolated microorganisms**

Antimicrobial resistance <sup>a</sup>	CA SBP (n = 61)	HCA SBP (n = 117)	Total (n = 178)	<i>p</i> value
Trimethoprim-sulfamethoxazole	7 (11.5)	26 (22.2)	33 (18.5)	0.104
Fluoroquinolones	6 (9.8)	19 (16.2)	25 (14.0)	0.267
Third-generation cephalosporins <sup>b</sup>	1 (1.6)	8 (6.8)	9 (5.1)	0.168 <sup>c</sup>
ESBL-producer	1 (1.6)	4 (3.4)	5 (3.2)	0.662 <sup>c</sup>

Values are presented as number (%) of patients.

CA, community-acquired; SBP, spontaneous bacterial peritonitis; HCA, healthcare-associated; ESBL, extended-spectrum β-lactamase.

<sup>a</sup>Both gram-positive and gram-negative organisms were included except for 10 anaerobic isolates.

<sup>b</sup>Third-generation cephalosporins included ceftriaxone or cefotaxime.

<sup>c</sup>Fisher exact test.

**Table 4. Risk factors for 30-day mortality in patients with community-onset spontaneous bacterial peritonitis**

Variable	Alive (n = 115)	Dead (n = 73)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Age, yr	55.5 ± 10.7	60.5 ± 9.7	1.05 (1.02–1.08)	0.002		
Child-Pugh score	10.7 ± 1.4	11.7 ± 1.4	1.79 (1.40–2.28)	< 0.001	1.73 (1.32–2.28)	< 0.001
Concomitant hepatocellular carcinoma	60 (52.2)	49 (67.1)	1.87 (1.02–3.45)	0.044		
Hepatic encephalopathy	21 (18.3)	23 (31.5)	2.06 (1.02–4.08)	0.038		
Bacteremia	82 (71.3)	62 (84.9)	2.29 (1.06–4.84)	0.035		
Septic shock	18 (15.7)	38 (52.1)	5.85 (2.96–11.56)	< 0.001		
Acute kidney injury	36 (31.3)	55 (75.3)	6.71 (3.46–13.00)	< 0.001	7.04 (3.29–15.09)	< 0.001
Third-generation cephalosporin resistance	2 (1.8)	7 (10.4)	6.36 (1.28–31.58)	0.024	9.49 (1.20–74.89)	0.033
Inappropriate antibiotics ≤ 24 hr	2 (1.8)	3 (4.5)	2.56 (0.42–15.70)	0.311		
HCA SBP	77 (67.0)	46 (63.0)	0.84 (0.46–1.55)	0.580		

Values are presented as mean ± SD or number (%) of patients.  $p < 0.05$  were included in the multivariate analysis. OR, odds ratio; CI, confidence interval; HCA, healthcare-associated; SBP, spontaneous bacterial peritonitis.

community-onset SBP was 38.8% regardless of the site of acquisition (37.4% for HCA SBP vs. 41.5% for CA SBP,  $p = 0.638$ ).

### Causative microorganisms and patterns of antibiotic resistance

The most common community-onset SBP isolate was *Escherichia coli* (77 isolates [41.0%]), followed by *Klebsiella pneumoniae* (40 isolates [21.3%]) (Table 2). HCA SBP had a higher proportion of gram-negative bacteria, while gram-positive bacteria were more frequent in CA SBP. According to *in vitro* antimicrobial susceptibility testing, 5.1% (9/178, except 10 anaerobic cases) were resistant to third-generation cephalosporins as follows: 6 *E. coli*, 1 *Achromobacter xylosoxidans*, 1 *Acinetobacter baumannii*, and 1 methicillin-resistant *Staphylococcus aureus* (Table 3). Among the resistant *E. coli*, five isolates were extended-spectrum  $\beta$ -lactamase producers, one case of which was a CA SBP. The rate of third-generation cephalosporin resistance was higher in HCA SBP (6.8% for HCA SBP vs. 1.6% for CA SBP,  $p = 0.168$ ), in which all cases were isolated in 2007 or later. In the majority of cases (97.2% [173/178]), patients received appropriate antibiotics within 24 hours, including carbapenems in the four cases of patients with third-generation cephalosporin resistance.

### Risk factors for 30-day all-cause mortality

A total of 73 deaths (38.8%) occurred during the study period. Variables associated with 30-day all-cause mortality by univariate analysis were analyzed using a logistic regression model. The independent risk factors for 30-day all-cause mortality in community-onset SBP were high Child-Pugh score, AKI, and third-generation cephalosporin resistant pathogens; however, HCA infection was not identified as a predictor (Table 4).

## DISCUSSION

In our study, the clinical characteristics and outcomes were similar between CA and HCA SBP. The prevalence of third-generation cephalosporin resistance was quite low in both gram-negative and gram-positive pathogens. However, the rate of resistant microorganisms tended to be higher in HCA SBP than in CA SBP. All of the resistant pathogens have been isolated since 2007, which reflects the tendency of increasing resistance rates. Interestingly, instead of third-generation cephalosporins, broad-spectrum antibiotics were frequently selected by the treating physicians as an initial regimen in HCA SBP due to concerns about resistant pathogens. Consequently, the majority of patients received appropriate antibiotics within 24 hours, which might influ-

ence the mortality in both groups. The current clinical practice guideline recommends third-generation cephalosporins as the gold-standard empirical antibiotic treatment for bacterial infections in cirrhotic patients [8]. Nevertheless, empirical antibiotics are often ineffective in the treatment of nosocomial SBP, which leads to unfavorable outcome [13]. Therefore, medical researchers suggest the use of broader-spectrum antibiotics for nosocomial SBP as empiric therapeutic regimens [2]. Since antibiotic resistance in HCA SBP is as frequent as that in nosocomial SBP, different antibiotic strategies are required for these populations according to the local epidemiology [7].

Our data demonstrated that HCA SBP exhibited a high frequency of prior SBP episodes, previous antibiotic use, and concomitant HCC compared to CA SBP. As expected from the criteria of HCA infection, the variables indicated that cirrhotic patients had been repeatedly exposed to healthcare environments in which their normal flora may change to resistant pathogens during hospitalization. Indeed, a comprehensive approach is warranted in the HCA population with resistance patterns similar to the nosocomial acquisition population [2,3]. Since the HCA infection criteria are based on patients with bacteremia, further reassessment is needed to determine whether the previous criteria are suitable in SBP.

In the present study, the 30-day all-cause mortality of community-onset SBP was 38.8% regardless of the site of acquisition. Consistent with previous studies, the independent risk factors for mortality were Child-Pugh score, AKI, and resistance to third-generation cephalosporins [13-15]. In decompensated cirrhosis, SBP naturally develops via spontaneous bacterial translocation in connection with impairment of the immune system. Bacterial infection provokes an inflammatory response with increasing cytokines and vasodilator factors, which results in arterial vasodilatation. Consequently, circulatory dysfunction compromises renal failure that eventually deteriorates hepatic failure in advanced cirrhosis, even after rapid resolution of the infection [16]. Indeed, renal failure is markedly severe in patients with SBP, which is the most important predictor of poor outcome [17,18]. In our study, acute renal failure occurred in 50% of patients in both groups, and was also confirmed as a poor prognostic factor.

This study has a number of limitations. Patients with nosocomial SBP were not included during the study period; thus, antimicrobial resistance patterns and clinical characteristics were not directly investigated between nosocomial SBP and community-onset SBP. Second, because this was a retrospective study, unknown confounding factors could be biased in both groups. For example, we included SBPs with one or more episodes that might influence clinical outcome. Lastly, our results were derived from only one clinical center; therefore, the results might not be generalized to other hospitals having different epidemiological data. However, several studies have already noted the increasing rate of resistant pathogens in the HCA population [3,7]. Unfortunately, we were not able to determine the risk factors for resistance because of the relatively low rate of resistance in community-onset SBP.

In conclusion, the severities of underlying hepatic function, renal dysfunction, and resistance to third-generation cephalosporins were associated with 30-day all-cause mortality, while HCA infection did not affect the prognosis in community-onset SBP. Nonetheless, the rate of third-generation cephalosporin resistance was predominant in HCA SBP. Understanding the characteristics of the HCA population is crucial to optimizing the use of broad-spectrum antibiotics as well as to improving survival in cirrhotic patients.

## KEY MESSAGE

1. The clinical implication of healthcare-associated (HCA) acquisition is not well understood in cirrhotic patients with spontaneous bacterial peritonitis (SBP).
2. Compared to community-acquired SBP, the rate of third-generation cephalosporin resistance was predominant in HCA SBP.
3. The severity of underlying hepatic function, renal dysfunction, and resistance to third-generation cephalosporins were associated with 30-day mortality, while HCA acquisition did not affect the prognosis in community-onset SBP.

## Conflict of interest

No potential conflict of interest relevant to this article was reported.

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