Microbiological Characteristics and Antibiotic Susceptibility in Liver Cirrhosis Patients With Nosocomial Spontaneous Bacterial Peritonitis Caused by *Escherichia coli*: A Multicenter Study

Bo Tu[1#], Yuening Zhang[2#], Jingfeng Bi[3#], Zhe Xu[1], Lei Shi[1], Xin Zhang[1], Peng Zhao[1], Dawei Zhang[1], Guang Yang[1], Enqiang Qin[1,✉]

Abstract

Escherichia coli is a prevalent causative pathogen of spontaneous bacterial peritonitis (SBP). In this retrospective study, we investigated the microbiological characteristics and antibiotic susceptibility of *E. coli* clinical isolates obtained from liver cirrhosis patients suffering from nosocomial SBP. Our results showed that extended-spectrum β-lactamase (ESBL)-producing *E. coli* accounted for 47% of the cases, while 62% of the isolates were multi-drug resistant (MDR) pathogens. ESBL-producing and MDR isolates showed high incidences of resistance to third-generation cephalosporins, but they displayed susceptibility to carbapenems, β-lactamase inhibitors, and aminoglycosides. Importantly, liver cirrhosis patients with MDR *E. coli* SBP showed a significantly higher death rate than patients with non-MDR infections ($P = 0.021$). The 30-day mortality of nosocomial SBP was independently correlated with female gender [odds ratio (OR) = 5.200, 95% confidence interval (CI) = 1.194–22.642], liver failure (OR = 9.609, 95% CI = 1.914–48.225), hepatocellular carcinoma (OR = 8.176, 95% CI = 2.065–32.364), hepatic encephalopathy (OR = 8.176, 95% CI = 2.065–32.364), model of end-stage liver disease score (OR = 1.191, 95% CI = 1.053–1.346), white blood cell count (OR = 0.847, 95% CI = 0.737–0.973), and ascites polymorphonuclear (OR = 95.903, 95% CI = 3.410–2697.356). In conclusion, third-generation cephalosporins may be inappropriate for empiric treatment of nosocomial SBP caused by *E. coli*, due to the widespread presence of ESBLs and high incidence of MDR pathogens.

Keywords: spontaneous bacterial peritonitis; *Escherichia coli*; liver cirrhosis; extended spectrum beta-lactamases; multidrug resistance

Introduction

Liver cirrhosis is characterized by diffuse fibrosis and the formation of regenerative nodules, leading to irreversible liver damages.[1,2] A variety of risk factors have been confirmed for liver cirrhosis, including chronic hepatitis virus infections, alcohol abuse, accumulation of fat in liver cells, alterations in inflammation, and other metabolic disorders.[3,4] Liver cirrhosis may lead to several fatal complications, such as hepatocellular carcinoma (HCC), hepatopulmonary syndrome, coagulation disorders, and bacterial infections.[5] Bacterial infections are a major cause for liver cirrhosis-related death, increasing the mortality by four-fold.[6] Unfortunately, liver cirrhosis patients show a high susceptibility to bacterial infections due to their immune dysregulation.[7]

Spontaneous bacterial peritonitis (SBP) is a serious complication and common cause of death in liver cirrhosis patients with ascites, and its prevalence ranges between 10% and 30% in hospitalized cirrhotic patients.[8] SBP can contribute to aggressive disease progression and severe complications in liver cirrhosis patients, consequently leading to long hospital stays, high costs, and poor prognosis.[9,10] Antimicrobial treatment should be timely and empirically performed for SBP cases without knowledge of the pathogens and drug sensitivity.[11] Gram-negative enteric bacteria such as *Escherichia coli* are considered as the leading group of pathogens involved in SBP, and third-generation cephalosporins are the first-line recommended treatment.[12,13] However, treatment failure with empiric antimicrobials is increasing, leading to high mortality in SBP cases.[14] The wide prevalence of multidrug-resistant (MDR) pathogens represents a leading cause for

therapeutic failure.[15,16] Extended-spectrum β-lactamase (ESBL) production is the most important antimicrobial resistance mechanism leading to treatment failure of *E. coli*,[17] because the ESBLs are able to hydrolyze broad-spectrum cephalosporins.[18] Most of the SBP patients are diagnosed during hospitalization and confirmed as nosocomial SBP. Patients diagnosed with nosocomial SBP show a high incidence of drug-resistant infections, leading to high mortality.[16,19] Therapeutic failure of third-generation cephalosporins is observed in 33%–75% of the nosocomial SBP cases.[20,21] Therefore, microbiological characterization of nosocomial SBP in cirrhosis patients is urgently required to improve empiric treatment. In this study, we investigated the microbiological characteristics and antibiotic management in nosocomial SBP caused by *E. coli* among liver cirrhosis patients.

Results

Patient baseline information

According to inclusion criteria, 211 *E. coli* nosocomial SBP cases in liver cirrhosis patients were included in our study. The mean age of patients was 50 years and the majority of cases were male (n = 176, 83%) (Table 1). The main cause for liver cirrhosis was a hepatitis B virus infection (n = 135, 64%) and most patients were confirmed at Child-Pugh stage C (n = 185, 88%), with a mean model of end-stage liver disease (MELD) score of 20.7 and a mean onset temperature of 38.8°C. The most common complications included liver failure (n = 99, 47%), hepatic encephalopathy (HE; n = 59, 28%), and renal dysregulation (n = 54, 26%). Laboratory examinations showed that white blood cell (WBC) counts were in the normal range (6.95 ± 4.42 × 10^9/L) and further analysis of ascites specimens showed average WBC counts and percentage of neutrophils were 6290.93 ± 12531.58/mm³ and 0.67 ± 0.26, respectively. The majority of patients displayed high polymorphonuclear leukocyte count values (≥250/mm³; n = 151, 72%). Microbiological tests showed that 99 (47%) patients were infected by ESBL-producing *E. coli*, while 130 (62%) isolates were confirmed as MDR *E. coli*. Finally, 58 patients died within 30 days after hospital admission, indicating a mortality rate of 27%.

Effects of ESBLs and MDR status on drug susceptibility

In vitro antibiotic susceptibility analysis showed that ESBL-producing *E. coli* displayed high incidences of resistance to penicillins (ampicillin: 100%; piperacillin: 98%) and quinolones (gatifloxacin: 75.0%; levofloxacin: 66%) (Table 2). Moreover, besides cefmetazole, their resistant rate to cephalosporins was higher than 50%. Importantly, ESBL-producing isolates were largely susceptible to minocycline, carbapenems, β-lactamase inhibitors, aminoglycosides, furadantin, and fosfomycin (Table 2). MDR-status was also a key factor for antibiotic susceptibility. In our study, over 40% of the MDR pathogens showed resistance to major cephalosporins, except for cefmetazole (Table 2). Furthermore, MDR *E. coli* displayed high incidences of resistance to penicillins (ampicillin: 100%; piperacillin: 83%) and quinolones (gatifloxacin: 78%; levofloxacin: 69%). The MDR pathogens displayed low incidences of resistance to minocycline, carbapenems, β-lactamase inhibitors, aminoglycosides, furadantin, and fosfomycin. In addition, it is noteworthy that one ESBL-producing isolate showed resistance to all tested antibiotics. This pathogen was carried by a 24-year-old male, who was diagnosed at Child stage C and a MELD score of 52. Unfortunately, without effective antibiotics this patient finally died.

Baseline and clinical characteristics of nosocomial spontaneous bacterial peritonitis (SBP) caused by *Escherichia coli* in liver cirrhosis patients

Parameters	Patients (n = 211, %)
Demographic data	
Age (years)	50.69 ± 12.45
Gender	
Males	176 (83.41)
Females	35 (16.59)
Clinical characteristics	
Etiology of cirrhosis	
Hepatitis C viral	14 (6.63)
Hepatitis B viral	135 (63.98)
Autoimmune	10 (4.74)
Alcohol	31 (14.69)
Others	21 (9.95)
Child-Pugh stage	
B	26 (12.32)
C	185 (87.68)
MELD	20.72 ± 8.27
onset temperature (°C)	38.79 ± 0.86
Complications	
Liver failure	99 (46.92)
HCC	36 (17.06)
HE	59 (27.96)
Diabetes mellitus	18 (8.53)
Renal dysregulation	54 (25.59)
Pneumonia	10 (4.74)
UGB	20 (9.48)
Hematological factors	
WBC (×10^9/L)	6.95 ± 4.42
Neutrophil (100%)	0.80 ± 0.096
Ascites examinations	
Leukocyte (/mm³)	6290.93 ± 12531.58
Polymorphonuclear (100%)	0.67 ± 0.26
PMN (/mm³)	5317.48 ± 11264.13
PMN stage	
≥250/mm³	150 (71.09)
<250/mm³	61 (28.91)
Microbiological examinations	
ESBL	
Negative	112 (53.08)
Positive	99 (46.92)
MDR	
Yes	130 (61.61)
No	81 (38.39)
Clinical outcomes	
Non-survivors	58 (27.49)
Improved	144 (68.25)
Invalid	9 (4.26)

ESBL: extended-spectrum β-lactamase; HCC: hepatocellular carcinoma; HE: hepatic encephalopathy; MDR: multidrug-resistant; MELD: model for end-stage liver diseases; PMN: ascites polymorphonuclear leukocyte count; UGB: upper gastrointestinal bleeding; WBC: white blood cell count.

Impact of ESBL-producing and MDR E. coli infections on clinical and laboratory characteristics of SBP in liver cirrhosis patients

To analyze the impact of ESBL and MDR on clinical and laboratory characteristics and outcome, we compared the clinical and laboratory information of the SBP cases according to the presence of ESBL and MDR status. Our results demonstrated that MDR status was significantly correlated with the ESBL production (P < 0.001) (Table 3). Furthermore, while basic patient and laboratory characteristics were not significantly

Table 2

Effects of extended-spectrum β-lactamase (ESBL)-producing and multidrug resistant (MDR) *E. coli* infections on antibiotic resistance

Antibiotics	ESBL-producing *E. coli*		ESBL-negative *E. coli*			MDR *E. coli*		Non-MDR *E. coli*		
	Total number	Resistant rate (n, %)	Total number	Resistant rate (n, %)	P value	Total number	Resistant rate (n, %)	Total number	Resistant rate (n, %)	P value
Cephalosporins										
Cefepime	97	53.61%	112	0.89%	<0.001	128	40.63%	81	1.23%	<0.001
Cefoperazone	37	97.30%	27	3.70%	<0.001	49	73.47%	15	6.67%	<0.001
Cefotaxime	16	100.00%	25	0.00%	<0.001	18	88.89%	23	0.00%	<0.001
Ceftazidime	99	62.63%	112	0.89%	<0.001	130	48.46%	81	0.00%	<0.001
Ceftriaxone	99	100.00%	112	0.00%	<0.001	130	75.38%	81	1.23%	<0.001
Cefmetazole	64	10.94%	59	0.00%	0.009	82	8.54%	41	0.00%	0.054
Cefazolin	47	100.00%	75	5.33%	<0.001	62	82.26%	60	0.00%	<0.001
Aztreonam	99	70.71%	112	0.00%	<0.001	130	53.85%	81	0.00%	<0.001
Penicillins										
Ampicillin	96	100.00%	111	65.775	<0.001	127	100%	80	42.50%	<0.001
Piperacillin	64	98.44%	76	26.32%	<0.001	88	86.36%	52	13.46%	<0.001
Quinolones										
Gatifloxacin	16	75.00%	25	8.00%	<0.001	18	77.78%	23	0.00%	<0.001
Levofloxacin	99	65.66%	112	29.46%	<0.001	130	69.23%	81	9.88%	<0.001
Tetracyclines										
Minocycline	16	18.75%	25	8.00%	0.305	18	16.67%	23	8.70%	0.439
Carbapenems										
Imipenem	99	1.01%	112	0.00%	0.286	130	0.77%	81	0.00%	0.429
Meropenem	92	1.09%	104	0.00%	0.286	123	0.81%	73	0.00%	0.440
β-lactamase inhibitors										
Piperacillin/tazobactam	99	9.09%	111	0.90%	0.005	130	7.69%	80	0.00%	0.011
Cefperazone/sulbactam	63	6.35%	63	0.00%	0.042	81	4.94%	45	0.00%	0.130
Ticarcillin/Clavulanate	64	71.87%	59	23.73%	<0.001	82	70.73%	41	4.88%	<0.001
Aminoglycoside										
Amikacin	99	6.06%	112	0.00%	0.080	130	4.61%	81	0.00%	0.050
Tobramycin	30	20.00%	61	1.96%	0.005	43	16.28%	38	0.00%	0.009
Sulfonamide antibacterial										
SMZCO	98	78.57%	112	58.03%	0.002	129	82.17%	81	44.44%	<0.001
Others										
Furadantin	83	4.82%	87	2.30%	0.373	112	4.46%	58	1.72%	0.359
Fosfomycin	52	9.61%	35	0.00%	0.059	68	7.35%	19	0.00%	0.223

ESBL: extended-spectrum β-lactamase; MDR: multidrug-resistant.

correlated with ESBL producing or MDR *E. coli*, patients suffering from SBP caused by MDR *E. coli* showed a significantly higher death rate than non-MDR infections ($P = 0.021$) (Table 3). Therefore, it appears that multidrug resistance had a significant impact on the clinical outcome of SBP in liver cirrhosis patients.

Multivariate analysis for 30-day mortality

Logistic regression analysis was performed to identify independent indicators for 30-day mortality in liver cirrhosis patients with nosocomial SBP. Our results demonstrated that mortality of the study population was independently correlated with female gender ($P = 0.028$), liver failure ($P = 0.006$), HCC ($P = 0.029$), HE ($P = 0.003$), high MELD score ($P = 0.005$), low WBC ($P = 0.019$), and high ascites polymorphonuclear ($P = 0.007$) (Table 4).

Discussion

Nosocomial SBP is one of the commonly observed bacterial infections in hospitalized patients, posing a great threat to human life.[22] Timely antibiotic treatment is an effective way to reduce the mortality of patients with SBP. However, therapeutic failures may occur. In order to improve the efficacy of empirical treatments, we investigated the microbiological characteristics

and antibiotic sensitivity of *E. coli* isolates obtained from nosocomial SBP cases in liver cirrhosis patients.

In our study, 88% of the cases were diagnosed at Child-Pugh stage C, which is consistent with a previous study that reported 87% of the *E. coli* SBP cases at Child-Pugh stage C.[23] ESBL-producing *E. coli* was isolated from 47% of the cultures, while the rate of MDR infections was 62% in our study. We investigated the clinical characteristics of SBP in liver cirrhosis patients, caused by ESBL-producing and MDR infections. Our analysis demonstrated that ESBL-producing and MDR infections were not associated with clinical symptoms of SBP, but MDR infections might result in higher mortality.

ESBL-producing and MDR are two major reasons for treatment failure in *E. coli* SBP. In our study, we found that ESBL-producing and MDR *E. coli* showed significantly higher resistance to cephalosporins, penicillins, quinolones, tobramycin, and SMZCO. Importantly, over 40% of the isolated pathogens showed resistance to third-generation cephalosporins, which is similar to a previous study that reported a resistance rate to the third-generation cephalosporins of 48% in *E. coli* isolated from SBP specimens.[24] Chon et al. indicated that antibiotic switching and mortality were higher in patients with nosocomial SBP during hospitalization, thereby revealing high therapeutic failure of third-generation cephalosporin.[25] Therefore, third-generation cephalosporins might be inappropriate for empiric treatment of

Table 3

Comparison of clinical and laboratory data of the study subjects according to their microbiological examinations

Parameters	ESBL-producing E. coli (n = 99)	ESBL-negative E. coli (n = 112)	P	MDR E. coli (n = 130)	Non-MDR E. coli (n = 81)	P
Demographic data						
Age (years)	49.93 ± 12.18	51.13 ± 12.07	0.484	50.47 ± 12.30	50.73 ± 12.75	0.883
Gender			0.339			0.868
Males	80 (80.81)	96 (85.71)		108 (83.08)	68 (83.95)	
Females	19 (19.19)	16 (14.29)		22 (16.92)	13 (16.05)	
Clinical characteristics						
Etiology of cirrhosis			0.906			0.988
Hepatitis C viral	5 (5.05)	9 (8.04)		9 (6.92)	5 (6.17)	
Hepatitis B viral	63 (63.64)	72 (64.29)		82 (63.08)	53 (65.43)	
Autoimmune	5 (5.05)	5 (4.46)		6 (4.61)	4 (4.94)	
Alcohol	16 (16.16)	15 (13.39)		19 (14.61)	12 (14.81)	
Others	10 (10.10)	11 (9.82)		14 (10.77)	7 (8.64)	
Child-Pugh stage			0.933			0.661
B	12 (12.12)	14 (12.50)		15 (11.54)	11 (13.58)	
C	87 (87.87)	98 (87.50)		115 (88.46)	70 (86.42)	
MELD	20.82 ± 8.64	20.63 ± 7.97	0.872	20.04 ± 7.80	21.15 ± 8.56	0.345
onset temperature (°C)	38.83 ± 0.85	38.76 ± 0.88	0.570	38.89 ± 0.84	38.72 ± 0.88	0.192
Complications						
Liver failure	46 (46.46)	53 (47.32)	0.901	61 (46.92)	38 (46.91)	0.999
HCC	18 (18.18)	18 (16.07)	0.684	26 (20.00)	10 (12.35)	0.151
HE	32 (32.32)	27 (24.11)	0.184	41 (31.54)	18 (22.22)	0.143
Diabetes mellitus	9 (9.09)	9 (8.04)	0.784	11 (8.46)	7 (8.64)	0.964
Renal dysregulation	24 (24.24)	30 (26.79)	0.673	36 (27.69)	18 (22.22)	0.376
Pneumonia	5 (5.05)	5 (4.46)	0.841	8 (6.15)	2 (2.47)	0.221
UGB	10 (10.10)	10 (8.93)	0.772	14 (10.77)	6 (7.41)	0.417
Hematological factors						
WBC (×10^9/L)	7.31 ± 4.66	6.62 ± 4.18	0.284	7.27 ± 4.90	6.43 ± 3.49	0.207
Neutrophil (100%)	0.81 ± 0.098	0.79 ± 0.095	0.322	0.81 ± 0.095	0.79 ± 0.099	0.221
Ascites examinations						
Leukocyte (/mm^3)	5971.96 ± 7961.63	6572.88 ± 15523.17	0.729	7207.60 ± 14955.53	4819.74 ± 6928.91	0.179
Polymorphonuclear (100%)	0.70 ± 0.25	0.65 ± 0.27	0.114	0.70 ± 0.25	0.63 ± 0.27	0.074
PMN (/mm^3)	5057.76 ± 7132.32	5547.05 ± 13964.92	0.754	6177.57 ± 13531.69	3937.07 ± 5888.20	0.160
PMN stage			0.850			0.621
≥250/mm^3	71 (71.71)	79 (70.54)		94 (72.37)	56 (69.14)	
<250/mm^3	28 (28.28)	33 (29.46)		36 (27.69)	25 (30.86)	
Microbiological examinations						
ESBL			–			<0.001
ESBL-producing E. coli	–	–		98 (75.38)	1 (1.23)	
ESBL-negative E. coli	–	–		32 (24.62)	80 (98.76)	
MDR			<0.001			–
MDR-E. coli	98 (98.99)	32 (28.57)		–	–	
MDR-negative E. coli	1 (1.01)	80 (71.43)		–	–	
Clinical outcomes						
Survival status			0.139			0.021
Non-survivors	32 (32.32)	26 (23.21)		43 (33.08)	15 (18.52)	
Survivors	67 (67.68)	86 (76.79)		87 (66.92)	66 (81.48)	

HCC: hepatocellular carcinoma; ESBL: extended-spectrum β-lactamase; HE: hepatic encephalopathy; MDR: multidrug-resistant; MELD: model for end-stage liver diseases; PMN: ascites polymorphonuclear leukocyte count; UGB: upper gastrointestinal bleeding; WBC: white blood cell count.

nosocomial SBP. The isolated pathogens in our study showed high sensitivity to carbapenems, β-lactamase inhibitors, and aminoglycoside antibiotics. Carbapenems, such as imipenem and meropenem, are effective antibiotics for liver cirrhosis patients presenting infections, particularly for those cephalosporins-resistant cases.[26] However, wide application of carbapenems may stimulate the bacteria develop carbapenemase-producing ability, leading to poor therapeutic efficacy based on the current antibiotics.[27,28] β-lactamase inhibitors and aminoglycoside antibiotics might be excellent substitutes for third-generation cephalosporins as empirical treatments. However, one of our isolates showed resistance to all tested antibiotics in our current study, and therefore this isolate might be identified as a "pan-drug-resistant" (PDR) bacterium. PDR infections represent a leading cause for empiric treatment failure and high mortality.[15] Moreover, due to the abuse of broad-spectrum antibiotics in clinics and transfection of antibiotic resistance genes, the prevalence of PDR appears to be increasing.[29,30] PDR infections pose a great challenge to the current antibiotic management. Therefore, it is urgent to explore new antibiotics for PDR infections. In addition, rapid pathogen identification and targeted therapy may decrease the occurrence of PDR infections.

In the current study, we also analyzed the risk factors for mortality among the study population. Multivariate analysis

Table 4

Logistic regression for independent factors related to 30-day mortality among the study population

Factors	30-day mortality	
	OR (95% CI)	P
Gender	**5.200 (1.194–22.642)**	**0.028**
Age	0.999 (0.954–1.045)	0.956
Hepatitis B viral	1.677 (0.094–29.796)	0.725
Autoimmune	6.333 (0.212–189.057)	0.287
Alcohol	1.194 (0.047–30.529)	0.915
Others	1.679 (0.086–32.758)	0.732
Liver failure	**9.609 (1.914–48.225)**	**0.006**
HCC	**12.644 (1.299–123.065)**	**0.029**
HE	**8.176 (2.065–32.364)**	**0.003**
Diabetes mellitus	2.651 (0.164–42.932)	0.493
Renal dysregulation	3.233 (0.838–12.476)	0.089
Pneumonia	0.463 (0.059–3.625)	0.463
UGB	3.026 (0.553–16.559)	0.202
Child-Pugh stage	0.121 (0.007–2.183)	0.152
MELD	**1.191 (1.053–1.346)**	**0.005**
Onset temperature	0.670 (0.350–1.283)	0.227
WBC	**0.847 (0.737–0.973)**	**0.019**
Neutrophil	54.467 (0.107–29891.047)	0.207
Leukocyte	0.999 (0.999–1.000)	0.166
Polymorphonuclear	**95.903 (3.410–2697.356)**	**0.007**
PMN	1.001 (1.000–1.001)	0.262
ESBL	1.070 (0.238–4.803)	0.930
MDR	1.664 (0.345–8.024)	0.526

HCC: hepatocellular carcinoma; ESBL: extended-spectrum β-lactamase; HE: hepatic encephalopathy; MDR: multidrug-resistant; MELD: model for end-stage liver diseases; PMN: ascites polymorpho-nuclear leukocyte count; UGB: upper gastrointestinal bleeding; WBC: white blood cell count.

indicated that female gender, presentation of liver failure, HCC and HE, high MELD score, WBC, and polymorphonuclear were independent risk factors for mortality in liver cirrhosis patients suffering from *E. coli* SBP. The effects of gender on mechanisms of liver cirrhosis have rarely been reported. Tommaso et al. reported that the interaction between hepatitis virus infection and alcohol might contribute to greater liver damage in females than that in males.[31] Their study might explain the results obtained in our study. Besides, the presentation of liver failure, HCC and HE, as well as high MELD score contributed to high mortality in nosocomial SBP. These results might reveal that not only the disease itself, but also the related complications could influence the clinical outcomes in SBP patients. In addition, we also found that polymorphonuclear in ascitic fluid was independently associated with mortality of SBP. In our SBP cases, the function of neutrophils in ascites was severely impaired, which might explain their high susceptibility to infections and high levels of polymorphonuclear.[32,33] Polymorphonuclear in ascitic fluid might be an effective biomarker for disease progression and clinical outcomes in SBP patients.

Our study has several limitations. Firstly, the study was retrospective in design and the sample size was relatively small, which reduces its statistical power. Secondly, the analysis results might be affected by the ascitic fluid culturing technique. Therefore, further well-designed prospective studies with extended sample size are required to improve our analysis.

Conclusions

Due to the widespread nature of ESBL-producing and MDR *E. coli*, β-lactamase inhibitors and carbapenem antibiotics may be appropriate alternatives for third-generation cephalosporins for empirical treatment of nosocomial SBP in liver cirrhosis patients. The mortality of nosocomial SBP appeared to be independently correlated with female gender, liver failure, HCC and HE, high MELD score, as well as WBC, and ascites polymorphonuclear. These results may be helpful for improvement of empirical treatment guidelines for nosocomial SBP caused by *E. coli*, and for improvement of therapeutic efficacy and clinical outcomes.

Material and methods

Study population and inclusion criteria

The present study was a multicenter retrospective study of *E. coli* SBP in liver cirrhosis patients at the Beijing 302 Hospital and Beijing You'an Hospital from January 2015 to December 2018. The patients came from several provinces and cities in China. The patients included in our study were recruited based on the following criteria: (1) adult population; (2) diagnosed with liver cirrhosis combined with nosocomial SBP; (3) aerobic and anaerobic cultures of bedside inoculation were both positive; (4) *E. coli* was the only pathogen isolated from their ascitic cultures; (5) patients had available medical records. In addition, all the participants were primarily diagnosed with SBP, and those with evidences for a secondary peritonitis were excluded from our observational study.

Diagnosis standards

Liver cirrhosis was defined according to clinical examinations, laboratory tests, and histological and imaging evidences, and the disease severity was evaluated by Child-Pugh stage and MELD scores.[34,35] Diagnosis of SBP was made according to the criteria defined by the American Association for the Study of Liver Diseases and European Association for the Study of the Liver,[36,37] as follows: (1) presence of the typical signs or symptoms: abdominal pain, fever, diarrhea, tenderness, and/or rebound pain; (2) positive ascitic fluid bacterial culture; (3) no signs for other infections. Nosocomial SBP was defined as an infection occurring later than 48 hours after hospital admission. Antibiotic susceptibility testing was performed by disk diffusion method, and the results were analyzed based on the Clinical Laboratories Standards Institute criteria.[38] *E. coli* ATCC 25922 was included in all tests as quality control. Isolated pathogens showing resistance to three or more antibiotics from different classes were confirmed as MDR.[39] The clinical outcome was analyzed by the 30-day mortality.

Statistical analysis

The continuous variables were expressed as mean ± standard deviation, and compared between two groups using Student *t*-test (normal distribution) or the rank sum test (abnormal distribution). The categorical variables were recorded as case number and percentages, and their comparisons were performed by Chi-square test. The baseline characteristics of the study subjects were compared according to the presence of ESBL and MDR status. In addition, logistic regression was performed to identify the independent indicators of the study population for 30-day mortality. All analyses were performed using SPSS 18.0 software (SPSS Inc., Chicago, IL, USA). P values ≤ 0.05 were considered as statistically significant.

References

[1] Lo RC, Kim H. Histopathological evaluation of liver fibrosis and cirrhosis regression. *Clin Mol Hepatol* 2017;23(4):302–307.

[2] McPhail MJW, Parrott F, Wendon JA, et al. Incidence and outcomes for patients with cirrhosis admitted to the United Kingdom critical care units. *Crit Care Med* 2018;46(5):705–712.

[3] González-Navajas JM. Inflammasome activation in decompensated liver cirrhosis. *World J Hepatol* 2016;8(4):207–210.

[4] Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet* 2014;383 (9930):1749–1761.

[5] Nusrat S, Khan MS, Fazili J, et al. Cirrhosis and its complications: evidence based treatment. *World J Gastroenterol* 2014;20(18): 5442–5460.

[6] 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* 2010;139(4):1246–1256.

[7] Bruns T, Zimmermann HW, Stallmach A. Risk factors and outcome of bacterial infections in cirrhosis. *World J Gastroenterol* 2014;20 (10):2542–2554.

[8] Dever JB, Sheikh MY. Review article: spontaneous bacterial peritonitis–bacteriology, diagnosis, treatment, risk factors and prevention. *Aliment Pharmacol Ther* 2015;41(11):1116–1131.

[9] Devani K, Charilaou P, Jaiswal P, et al. Trends in hospitalization, acute kidney injury, and mortality in patients with spontaneous bacterial peritonitis. *J Clin Gastroenterol* 2019;53(2):e68–e74.

[10] Wiest R, Krag A, Gerbes A. Spontaneous bacterial peritonitis: recent guidelines and beyond. *Gut* 2012;61(2):297–310.

[11] Strauss E. The impact of bacterial infections on survival of patients with decompensated cirrhosis. *Ann Hepatol* 2014;13(1):7–19.

[12] Fagiuoli S, Colli A, Bruno R, et al. Management of infections in cirrhotic patients: report of a consensus conference. *Dig Liver Dis* 2014;46 (3):204–212.

[13] Sberna AL, Bouillet B, Rouland A, et al. European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD) and European Association for the Study of Obesity (EASO) clinical practice recommendations for the management of non-alcoholic fatty liver disease: evaluation of their application in people with type 2 diabetes. *Diabet Med* 2018;35(3):368–375.

[14] Fernández J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol* 2012;56(Suppl 1):S1–S12.

[15] Merli M, Lucidi C, Di Gregorio V, et al. The spread of multi drug resistant infections is leading to an increase in the empirical antibiotic treatment failure in cirrhosis: a prospective survey. *PLoS One* 2015;10 (5):e0127448.

[16] Alexopoulou A, Vasilieva L, Agiasotelli D, et al. Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia. *World J Gastroenterol* 2016;22(15):4049–4056.

[17] Jain M, Varghese J, Michael T, et al. An insight into antibiotic resistance to bacterial infection in chronic liver disease. *J Clin Exp Hepatol* 2017;7 (4):305–309.

[18] Rodríguez-Baño J, Gutiérrez-Gutiérrez B, Machuca I, et al. Treatment of infections caused by extended-spectrum-beta-lactamase-, AmpC-, and carbapenemase-producing Enterobacteriaceae. *Clin Microbiol Rev* 2018;31(2):e00079-17.

[19] Shi L, Wu D, Wei L, et al. Nosocomial and community-acquired spontaneous bacterial peritonitis in patients with liver cirrhosis in China: comparative microbiology and therapeutic implications. *Sci Rep* 2017;7: 46025.

[20] Ariza X, Castellote J, Lora-Tamayo J, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. *J Hepatol* 2012;56(4): 825–832.

[21] Fernández J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. *Hepatology* 2012;55(5):1551–1561.

[22] 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(6):1310–1324.

[23] Bae S, Kim T, Kim MC, et al. Clinical characteristics and outcomes of spontaneous bacterial peritonitis caused by *Enterobacter* species versus *Escherichia coli*: a matched case-control study. *BMC Infect Dis* 2016;16:252.

[24] Balaraju G, Patil M, Krishnamurthy AC, et al. Comparative study of community acquired and nosocomial spontaneous bacterial peritonitis and its variants in 150 patients. *J Clin Exp Hepatol* 2017;7(3):215–221.

[25] Chon YE, Kim SU, Lee CK, et al. Community-acquired vs. nosocomial spontaneous bacterial peritonitis in patients with liver cirrhosis. *Hepatogastroenterology* 2014;61(136):2283–2290.

[26] Badawy AA, Zaher T, Sharaf SM, et al. Effect of alternative antibiotics in treatment of cefotaxime resistant spontaneous bacterial peritonitis. *World J Gastroenterol* 2013;19(8):1271–1277.

[27] Harris PN, Tambyah PA, Paterson DL. β-lactam and β-lactamase inhibitor combinations in the treatment of extended-spectrum β-lactamase producing Enterobacteriaceae: time for a reappraisal in the era of few antibiotic options? *Lancet Infect Dis* 2015;15:475–485.

[28] Rodríguez-Baño J, Navarro MD, Retamar P, et al. β-Lactam/β-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum β-lactamase-producing *Escherichia coli*: a post hoc analysis of prospective cohorts. *Clin Infect Dis* 2012;54:167–174.

[29] Carter D, Charlett A, Conti S, et al. A risk assessment of antibiotic pan-drug-resistance in the UK: Bayesian analysis of an expert elicitation study. *Antibiotics (Basel)* 2017;6(1):9.

[30] Potter RF, D'Souza AW, Dantas G. The rapid spread of carbapenem-resistant Enterobacteriaceae. *Drug Resist Updat* 2016;29:30–46.

[31] Stroffolini T, Sagnelli E, Andriulli A, et al. Sex difference in the interaction of alcohol intake, hepatitis B virus, and hepatitis C virus on the risk of cirrhosis. *PLoS One* 2017;12(11):e0185710.

[32] Engelmann C, Becker C, Boldt A, et al. Ascites neutrophil function is significantly impaired in patients with decompensated cirrhosis but can be restored by autologous plasma incubation. *Sci Rep* 2016;6: 37926.

[33] Na SH, Kim EJ, Nam EY, et al. Comparison of clinical characteristics and outcomes of spontaneous bacterial peritonitis and culture negative neutrocytic ascites. *Scand J Gastroenterol* 2017;52(2):199–203.

[34] Pugh RN, Murray-Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973;60(8):646–649.

[35] Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001;33(2):464–470.

[36] Runyon BA, AASLD Practice Guidelines Committee. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology* 2009;49(6):2087–2107.

[37] 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 (3):397–417.

[38] Jepsen P, Ott P, Andersen PK, et al. Clinical course of alcoholic liver cirrhosis: a Danish population-based cohort study. *Hepatology* 2010;51 (5):1675–1682.

[39] Magiorakos AP, Srinivasan A, Carey RB, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. *Clin Microbiol Infect* 2012;18(3):268–281.