Infection and Drug Resistance

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ORIGINAL RESEARCH

Clinical Efficacy and Cost-Effectiveness of β-Lactam/β-Lactamase Inhibitor Combinations and Carbapenems in Liver Cirrhosis Patients with Gram-Negative Bacteria Bloodstream Infection

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Background: Gram-negative bacteria bloodstream infection (GNB-BSI) results in considerable mortality and hospitality costs in cirrhotic patients. β-lactam/β-lactamase inhibitor combinations (BLBLIs) and carbapenems (CARs) are widely recommended for treating GNB-BSI in cirrhotic patients, while the efficacy and cost-effectiveness of two strategies have never been evaluated. Therefore, we conducted a retrospective cohort study to evaluate the efficacy and the cost-effectiveness of BLBLIs and CARs.

Patients and Methods: Cirrhotic patients with GNB-BSI treated by BLBLIs or CARs were included. A propensity score-matching analysis was performed to compare the efficacy between BLBLIs and CARs. A decision tree was used to estimate the clinical outcomes and direct costs of treating BSI using two strategies from the patients' perspective.

Results: No statistically significant difference was found between the BLBLIs (n = 41) group and the CARs (n = 43) group regarding the time to defervescence (2.4 ± 0.2 vs 2.5 ± 0.3, P = 0.94). Thirty-seven patients from each group were matched in propensity-score-matched cohort, and there was no significant difference between two groups in terms of the time to defervescence (2.4 ± 0.3 vs 2.4 ± 0.3, P = 0.75) and success rate (86.5% vs 78.4%; OR = 0.57; P = 0.36). Based on the drug and hospital costs in China, cefoperazone/sulbactam was cost-effective in the present analysis under the willingness-to-pay threshold (¥64,644).

Conclusion: The efficacy of BLBLIs is similar to CARs. Cefoperazone/sulbactam could be a cost-effective therapy in cirrhotic patients with GNB-BSI. Carbapenems-sparing regimens should be encouraged in regions with a low prevalence of MDR bacteria.

Keywords: liver cirrhosis, gram-negative bacteria, bloodstream infection, efficacy, cost-effectiveness

Introduction

Liver cirrhosis is a widespread disease and a leading cause of mortality worldwide.[1] Bacterial infection is one of the most important and serious complications in patients with cirrhosis,[2] which is associated with a higher morbidity and mortality.[3,4] The most common infections are spontaneous bacterial peritonitis, followed by urinary tract infection, pneumonia and bloodstream infection (BSI).[5] The incidence of BSI varies in patients with cirrhosis from 4% to 21%.[6] Gram-negative bacteria (GNB) were the leading cause of BSI episodes in 53–64% of cases.[7,8] This is because dysregulated intestinal bacterial translocation is the predominant pathophysiological mechanism of

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BSI in cirrhotic patients.[9] Moreover, the thirty-day mortality rate in cirrhotic patients who developed BSI was 2.4 to 6.3 times higher than that in non-cirrhotic patients.[10]

According to the European Association for the Study of the Liver and other recommendations based on experts' opinion,[11–13] β-lactam/β-lactamase inhibitor combinations (BLBLIs) and carbapenems (CARs) are widely recommended for the treatment of gram-negative bacteria bloodstream infection (GNB-BSI) in liver cirrhosis patients. With the increasing spread of multidrug-resistant (MDR) bacteria worldwide,[2] MDR-GNB account for an increasing proportion of BSI in cirrhotic patients,[8] which makes antibacterial strategies more complicated than they used to be. Therefore, these recommendations also emphasize that empirical antibiotic strategies need to be tailored according to local microbiological epidemiology. Notably, a previous study showed that the use of carbapenems was the only strong independent predictor for the emergence of MDR bacteria, including carbapenem-resistant MDR bacteria,[14] which represents a substantial global health and economic threat, and simultaneously increase the risk of death and the length of stay in patients with BSI.[15] Hence, it should be noted that carbapenems-sparing therapy options are urgently necessary to reduce the continuing prevalence of MDR bacteria[16] and consequent economic threat.

Several studies have indicated that appropriate non-CARs such as BLBLIs are not inferior to CARs as initial empirical therapy for GNB-BSI.[17–19] However, conflicting results have shown that BLBLIs therapy attributes to lower success and higher 14-day mortality in adult patients.[20,21] However, these results are of limited reference value for patients with cirrhosis. The efficacy of BLBLIs in comparison with CARs has never been evaluated in liver cirrhosis patients with GNB-BSI up to now. In addition, it has been reported that BSI results in a considerable increase in in-hospital costs.[22,23] Given the economic burden of BSI and the economic threat of using CARs, therapeutic decisions should be based on an evaluation of the costs and effectiveness of available alternatives. Therefore, we conducted a retrospective cohort study to compare the therapeutic efficacy of BLBLIs and CARs, and to evaluate the cost-effectiveness of two strategies in the treatment of GNB-BSI in cirrhotic patients from the perspective of patients using a decision tree model.

Methods

Patients

This retrospective cohort study included patients with GNB-BSI, who hospitalized in the First Affiliated Hospital of Xi'an Jiaotong University from January 2013 to December 2018. The inclusion criteria were the following: 1) diagnosis of cirrhosis according to standard criteria; 2) patients with polymicrobial or monomicrobial BSI at admission or during hospitalization; 3) parenteral therapy with BLBLIs or CARs for more than 72 h; 4) all patients received appropriate antibiotic therapy based on package inserts; 5) age >18 years old. Exclusion criteria were: 1) those were treated by combined therapy or antibiotics other than BLBLIs and CARs; 2) patients with polymicrobial infections due to gram-positive bacteria.

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of the study. Because all patient data were analyzed in anonymity, no additional informed consent was required. This study was conducted in accordance with the Declaration of Helsinki. Patients were ensured about the confidentiality of their information.

Data Collection

We retrospectively reviewed patients' medical records and the following demographic and clinical data were collected: age, sex, weight, creatinine clearance, comorbidities, and etiology of cirrhosis. Liver function was assessed using the Child-Turcotte-Pugh (CTP) score, Model of End Liver Disease (MELD) score, Chronic Liver Failure-Sequential Organ Failure Assessment (CLIF–SOFA) score and baseline Albumin-Bilirubin (ALBI) score. The severity of BSI was assessed using the Pitt bacteremia score (PBS)[24] and the Systemic Inflammatory Response Syndrome (SIRS) on the day of BSI onset. The sites of BSI onset, BSI source and major causative microorganisms and susceptibility results were recorded. We also recorded inflammatory markers of infection (eg C-reaction protein (CRP), procalcitonin (PCT), white blood cell (WBC) count and neutrophil percentage). Blood culture results, maximum body temperature during infection, the time to defervescence, antibiotic duration and the length of hospitalization, and concomitant medications including diuretics and human albumin were also collected.

Study Design

Identified patients who received BLBLIs as empirical therapy and subsequently as definitive therapy were classified into BLBLIs group (n = 41). Similarly, patients in CARs

group (n = 43) treated by CARs as empirical and subsequently definitive antibiotic therapy. In addition, patients empirically treated by BLBLIs and subsequently definitively treated by CARs according to the antimicrobial susceptibility tests were classified into the escalation group (n = 16).

Definition and Outcomes

BSI was defined as the finding of an organism in a blood culture specimen. Empirical therapy was defined as antibiotic administered before the results of blood culture were available or within 48 h after the positive blood culture sample had been obtained. Definitive therapy was defined as the adjusted antibiotic regime based on the results of antimicrobial susceptibility tests. Polymicrobial infection was defined as the isolation of more than one causative microorganism from an episode. Antibiotic therapy was considered to be appropriate if isolates were sensitive to antibiotics, according to subsequent results of antimicrobial susceptibility tests, and patients received standard dosing regimen (or adjusted for renal function). Defervescence was defined as body temperature remained at less than 37.5°C for at least 24 h, and the time to defervescence was defined as the period between BSI onset and defervescence.[25] Sources of BSI were determined clinically according to the isolation of a microorganism from other clinical specimens before bacteremia onset. If the BSI source could not be attributed to a specific site, it was classified as primary BSI.

Microbiological outcome was classified as eradication, presumed eradication, persistence, and presumed persistence.[26] Both the eradication and presumed eradication were accessed as eradication, while persistence and presumed persistence were rated as persistence.

Antibiotic response was defined as a success if three of the following four criteria were met: (i) defervescence; (ii) there was a marked drop in levels of inflammatory markers such as CRP, PCT, WBC count or neutrophil percentage, or these markers' levels returned to normal range; (iii) resolution or partial resolution of infection symptoms or signs; (iv) a negative culture occurred on follow-up. Antibiotic responses were assessed on day 10 after initial treatment. Or they were assessed when patients discharged from hospital if antibiotic treatment duration less than 10 days.

The primary endpoint was the time to defervescence, and secondary endpoints were success rate and defervescence within 3 days after antibacterial therapy.

Statistical Analyses

All these analyses were performed using SPSS version 22.0 and R version 3.5.3. Continuous variables were expressed as mean ± SD or median (interquartile range [IQR]). We used the Student's *t*-test when data presented a normal distribution and the Mann–Whitney test was used when data present an abnormal distribution. Categorical variables were expressed as the counts (or percentage) and compared with the chi-square test or Fisher's exact test as appropriate.

A propensity score-matched analysis was performed using 1:1 or 2:1 and nearest-neighbour matching with a caliper length of 0.2 to control the confounding variables in the choice of antimicrobial agents between patients received BLBLIs antibiotics and those with CARs therapy. The propensity scores were calculated from variables with significant differences between two groups, including age, creatinine clearance and neutrophil percentage. Univariate and multivariate logistic regression analysis was performed in the matched cohort to identify potential predictors of therapy success. Variables found to have a *P* value of less than 0.2 in a univariate analysis were included in the multivariate logistic analysis.

Based on an existing analysis, which showed that the success rate of BLBLIs was 70.6% and of CARs was 94.1%.[21] We used G power 3.1 to determine that for assessing this difference with $\alpha = 0.05$, a sample size of 82 patients (41 patients in each group) was required to achieve a statistical power of 80%.

Cost-Effectiveness Analysis

Model Structure

Cefoperazone/sulbactam and meropenem are the most frequently used antibiotics in patients with cirrhosis in China. A decision tree model (Figure S1) was adopted to evaluate the cost-effectiveness of treating GNB-BSI by cefoperazone/sulbactam or meropenem from the perspective of patients, using the software of TreeAge Pro 2011. Possible treatment outcomes of therapy were clinical success rate, treatment failure due to lack of efficacy among survivors, and treatment failure due to death. When the initial empirical treatment of cefoperazone/sulbactam fails in the first 3 days, a subsequent modification of antibacterial therapy (meropenem) is required.

Model Inputs

Cefoperazone/sulbactam was considered as a comparator in the decision tree model. Data corresponding to the probability

of clinical success associated with cefoperazone/sulbactam and meropenem, and antibiotic duration, as well as the length of hospitalization, were extracted from the results of the present cohort study. The data of other variables and costs were obtained from published articles or government data. The incremental cost-effectiveness ratio (ICER) per clinical success rate saved was calculated, which was used to compare the performance of two treatment strategies. As the total time is shorter than 1 year, no discounting of costs and effects was adopted. We considered each treatment strategy with an ICER of less than the willingness-to-pay (WTP) threshold (¥64,644) (Chinese gross domestic product [GDP] per capita in 2018) to be acceptable.

Sensitivity Analyses

Deterministic sensitivity analyses were performed to examine the effects of varying parameters on the ICERs and to determine which variables were most sensitive to the results. Probabilistic sensitivity analysis was carried out with 10,000 times of Monte Carlo simulations to evaluate the impact of all variables simultaneously. The model and associated deterministic sensitivity analyses were developed from the patients perspective, with all costs are given in China Yuan.

Results

Common Pathogens and Susceptibility

A total of 194 causative microorganisms from 180 liver cirrhosis patients were collected, and 180 episodes of BSI, including 14 episodes of polymicrobial bacteremia were detected. *Escherichia coli* (110, 56.7%), *Klebsiella pneumoniae* (53, 27.3%), *Pseudomonas aeruginosa* (9, 4.6%), *Aeromonas aeruginosa* (7, 3.6%) and *Enterobacteriaceae* (6, 3.1%) constituted the major causative microorganisms. The susceptibility rates of common pathogens to piperacillin/tazobactam, cefoperazone/sulbactam, imipenem, meropenem, ciprofloxacin and ceftriaxone are listed in Table 1. Piperacillin/tazobactam and cefoperazone/sulbactam were, respectively, active against 92.7% and 85.4% of *Escherichia coli* and 96.2% and 93.3% of *Klebsiella pneumoniae*, respectively. Additionally, 109 (100%) *Escherichia coli* and 53 (100%) *Klebsiella pneumoniae* were susceptible to imipenem and meropenem. The susceptibility rates of *Pseudomonas aeruginosa* to these four antibiotics were 88.9%, 77.8%, 55.6% and 55.6%. By contrast, nearly and more than half of the *Escherichia coli* isolates were resistant to ciprofloxacin (49.1%) and ceftriaxone (56.9%). The susceptibility rates of *Klebsiella pneumoniae* to ciprofloxacin and ceftriaxone were 90.4% and 86.8%. Table S1also details the distribution of MIC_{50}s (MIC for 50% of the isolates), MIC_{90}s (MIC for 90% of the isolates) and MICs of piperacillin/tazobactam, imipenem, meropenem, ciprofloxacin and ceftriaxone for *Escherichia coli* and *Klebsiella pneumonia*.

Demographics and Clinical Characteristics

During the study period, 180 liver cirrhosis patients with GNB-BSI were identified. After the exclusion of 80 patients, 100 patients were involved in the present study (Figure 1). Forty-one patients (5 treated by piperacillin/tazobactam, 36 treated by cefoperazone/sulbactam) were classified into BLBLIs group, 43 patients (6 treated by Imipenem/cilastatin, 37 treated by meropenem) in CARs group, and 16 patients in escalation group. In the BLBLIs

Table 1 Susceptibility of the Major Causative Microorganisms in Liver Cirrhosis Patients

Microorganism (No. of Strains, %)	Susceptibility Rate (%, Sensitive Isolates/Total Isolates)					
	Piperacillin/ Tazobactam	Cefoperazone/ Sulbactam	Imipenem	Meropenem	Ciprofloxacin	Ceftriaxone
Escherichia coli (110, 56.7%)	92.7 (102/110)	85.4 (88/103)[b]	100 (109/109)[c]	100 (109/109)[d]	50.9 (56/110)	43.1 (47/109)[f]
Klebsiella pneumoniae (53, 27.3%)	96.2 (51/53)	93.3 (42/45)[b]	100 (53/53)	100 (53/53)	90.4 (47/52)[e]	86.8 (46/53)
Pseudomonas aeruginosa (9, 4.6%)	88.9 (8/9)	77.8 (7/9)	55.6 (5/9)	55.6 (5/9)	77.8 (7/9)	14.3 (1/7)[f]
Aeromonas (7, 3.6%)	100 (7/7)	100 (7/7)	85.7 (6/7)	85.7 (6/7)	100 (7/7)	100 (7/7)
Enterobacteriaceae (6, 3.1%)	100 (6/6)	66.7 (4/6)	100 (6/6)	100 (6/6)	100 (6/6)	83.3 (5/6)
Acinetobacter baumannii (4, 2.1%)	50 (2/4)	50 (1/2)[b]	50 (2/4)	50 (2/4)	50 (2/4)	0 (0/3)[f]
Klebsiella acidophilus (3, 1.5%)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)	100 (3/3)
Citrobacter youngae (2, 1.0%)	100 (1/1)[a]	50 (1/2)	100 (2/2)	100 (2/2)	100 (2/2)	50 (1/2)

Notes: [a]Values were calculated based on eligible isolates and excluded isolates which were not tested for susceptibility to piperacillin-tazobactam. [b]Values were calculated based on eligible isolates and excluded isolates which were not tested for susceptibility to cefoperazone-sulbactam. [c]Values were calculated based on eligible isolates and excluded isolates that were not tested for susceptibility to imipenem-cilastatin. [d]Values were calculated based on eligible isolates and excluded isolates which were not tested for susceptibility to meropenem. [e]Values were calculated based on eligible isolates and excluded isolates which were not tested for susceptibility to ciprofloxacin. [f]Values were calculated based on eligible isolates and excluded isolates which were not tested for susceptibility to ceftriaxone.

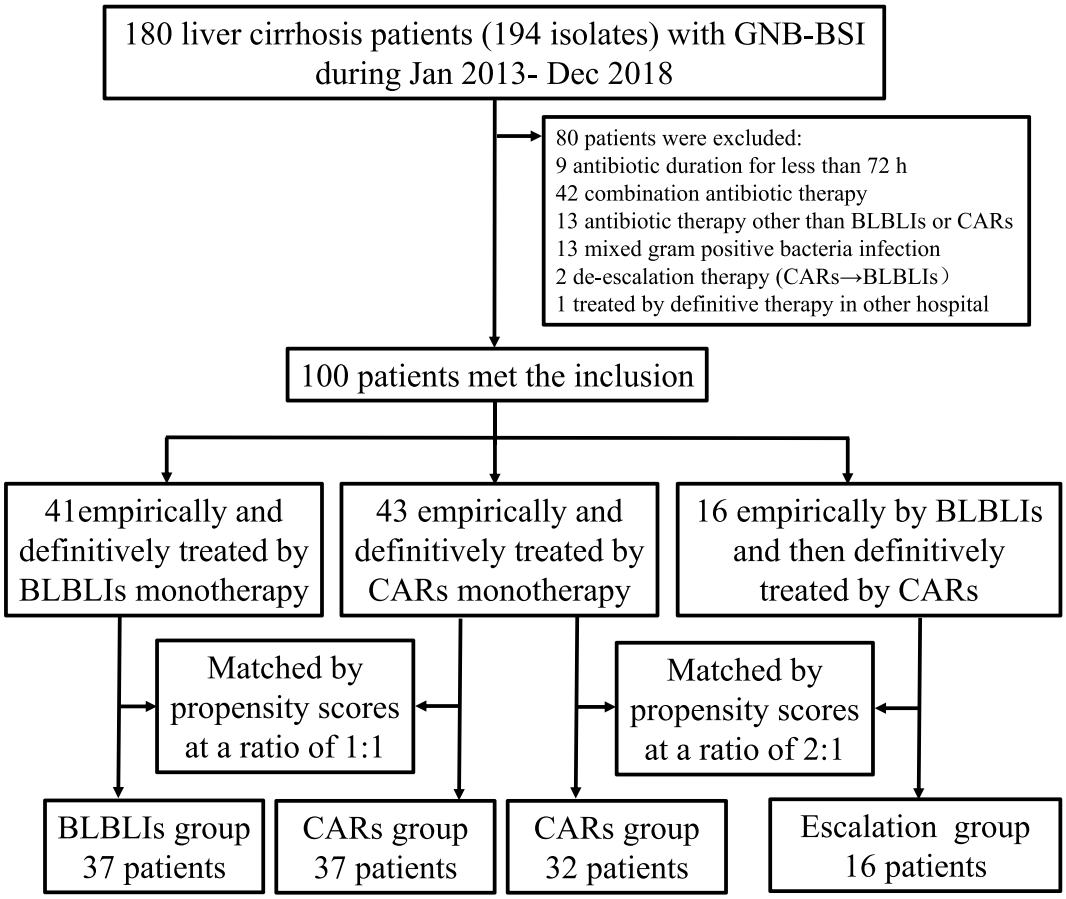


Figure 1 Patients inclusion flowchart.
Abbreviations: GNB, Gram-negative Bacteria; BSI, Bloodstream infection; BLBLIs: β-lactam/β-lactamase inhibitor combinations; CARs, Carbapenems.

group, the empirical treatment lasted for 3.5 ± 1.8 days, while the definitive treatment lasted for 6.9 ± 4.8 days. The empirical and definitive treatment duration was, respectively, 2.8 ± 1.1 days and 8.0 ± 4.0 days in CARs group. Meanwhile, 16 patients from the escalation group were empirically treated by BLBLIs (4 treated by piperacillin/tazobactam, 12 treated by cefoperazone/sulbactam) and subsequently definitively treated by CARs (5 treated by Imipenem/cilastatin, 11 treated by meropenem) according to the antimicrobial susceptibility tests. In the escalation group, the duration of empirical and definitive treatment was 3.1 ± 1.7 days and 9.6 ± 3.9 days. The dosage regimens of each antibiotic are summarized in Table S2. The comparisons of patient's baseline characteristics and outcomes between the BLBLIs group and CARs group are presented in Table 2. Patients treated by CARs were older (P = 0.04) and they had a lower creatinine clearance (P = 0.02) and higher neutrophil percentage (P = 0.03). Other variables such as body weight, maximum body temperature, antibiotic duration and the length of hospitalization were comparable between the two groups. No statistically differences were found between the BLBLIs group and the CARs group regarding the primary endpoint and secondary endpoints, including the time to defervescence (2.4 ± 0.2 vs 2.5 ± 0.3, P = 0.94), success rate (80.5% vs 79.1%; OR = 1.10; P = 0.87) and defervescence within 3 days after antibacterial therapy (81.6% vs 76.9%; OR = 1.33; P = 0.62) (Figure 2). The time to defervescence of piperacillin/tazobactam and cefoperazone/sulbactam were 2.5 ± 1.7 days and 3.8 ± 2.1 days (P = 0.32), respectively. The time to defervescence of imipenem/cilastatin and meropenem were 2.6 ± 1.6 days and 2.4 ± 1.9 days (P = 0.52), respectively.

Characteristics and Outcomes of Propensity-Score-Matched Cohort

In the propensity-matched cohort, 37 patients from each group were matched (Figure 1). After matching, the distribution of the baseline patient characteristics was comparable between the two groups (Table 2). The time to defervescence

Table 2 Clinical Characteristics and Outcomes of 84 Patients with GNB-BSI Treated by BLBLIs or CARs

Clinical Characteristics and Outcomes	Unmatched Data			Matched Data		
	BLBLIs (n=41)	CARs (n=43)	*P*-value[a]	BLBLIs (n=37)	CARs (n=37)	*P*-value[b]
Males, n (%)	29 (70.7)	27 (62.8)	0.44	27 (73.0)	25 (67.6)	0.61
Age (years), mean ± SD	53.2 ± 17.5	57.0 ± 11.5	0.04	53.8 ± 11.01	58.5 ± 11.2	0.23
Weight (kg), median (IQR)	62.0 (58.5–68.9)	62.6 (57.0–70.0)	0.90	62.0 (56.0–68.4)	62.6 (56–70.5)	0.88
Creatinine clearance (mL/min) median (IQR)	109.6 (89.9–152.5)	94.4 (61–118.5)	0.02	108.4 (83.8–133.5)	62.6 (56.0–70.5)	0.37
CTP grade, n (%)						
A	9 (22.0)	10 (23.3)	0.35	9 (24.3)	7 (18.9)	0.29
B	9 (22.0)	15 (34.9)		7 (18.9)	13 (35.1)	
C	23 (56.1)	18 (41.9)		21 (56.8)	17 (45.9)	
ΔMELD score, median (IQR)	0.0 (−2.0–0.0)	0.0 (−1.1–0.0)	0.53	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.71
ALBI, median (IQR)	−1.21 (−1.6- −0.9)	−1.42 (−2.0- −0.8)	0.65	−1.2 (−1.6- −0.9)	−1.4 (−1.9- −0.8)	0.74
CLIF-SOFA0[c], median (IQR)	6.0 (4.0–7.5)	7.0 (5.0–7.0)	0.22	6.0 (4.0–8.0)	7.0 (5.0–7.0)	0.35
CLIF-SOFA1[d], median (IQR)	6.0 (3.0–8.0)	6.0 (5.0–8.0)	0.51	6.0 (3.0–8.0)	6.0 (5.0–7.0)	0.49
SIRS, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–4.0)	0.44	3.0 (1.0–3.5)	2.0 (1.5–4.0)	0.69
Maximum body temperature, median (IQR)	38.8 (38.5–39.3)	39.0 (38.3–39.5)	0.67	38.9 (38.5–39.4)	39 (38.2–39.7)	0.85
WBC (10^{-9}), median (IQR)	4.2 (3.4–7.9)	6.5 (2.9–10.4)	0.18	4.1 (3.2–7.5)	6.5 (2.8–10.0)	0.28
Neutrophil percentage, median (IQR)	72.1 (31–82.9)	77.3 (64.7–89.1)	0.03	74.7 (53.3–83.0)	75.1 (63.0–86.5)	0.28
Platelet count, median (IQR)	57 (36–118)	69 (35–144)	0.60	56 (33–103)	69 (35–163)	0.43
Length of hospitalization, median (IQR)	13 (9–22)	17 (11–28)	0.18	14 (9.5–22.5)	18 (11.5–29)	0.23
Comorbidities, n (%)			0.17			0.60
Diabetes	8 (20.5)	5 (10.4)		7 (18.4)	5 (12.5)	
Hypertension	1 (2.6)	7 (14.6)		1 (2.6)	4 (10.0)	
Cancers	11 (28.2)	15 (31.2)		11 (28.9)	12 (30.0)	
Virus hepatitis	19 (48.7)	21 (43.8)		19 (50.0)	19 (47.5)	
Etiology of cirrhosis, n (%)			0.82			0.92
Hepatitis B virus	21 (51.2)	24 (55.8)		20 (54.1)	23 (62.2)	
Hepatitis C virus	7 (17.1)	6 (14.0)		6 (16.2)	4 (10.8)	
Alcoholic hepatitis	4 (9.8)	2 (4.7)		2 (5.4)	2 (5.4)	
Others	9 (22.0)	11 (25.6)		9 (24.3)	8 (21.6)	
Source of BSI, n (%)			0.05			0.15
SBP	13 (31.7)	3 (7.3)		10 (27.0)	3 (8.1)	
Primary BSI	13 (31.7)	10 (24.4)		12 (32.4)	7 (18.9)	
Pneumonia	4 (9.8)	6 (14.6)		4 (10.8)	6 (16.2)	
Biliary tract infection	4 (9.8)	12 (29.3)		4 (10.8)	11 (29.7)	
Intestinal infection	3 (7.3)	3 (7.3)		3 (8.1)	2 (5.4)	
Abdominal infection	2 (4.9)	4 (9.8)		2 (5.4)	3 (8.1)	
Urinary tract infection	2 (4.9)	3 (7.3)		2 (5.4)	3 (8.1)	
Site of infection, n (%)			0.54			0.13
Nosocomial infections	27 (65.9)	31 (72.1)		23 (62.6)	29 (78.4)	
Community acquired infections	14 (34.1)	12 (27.9)		14 (37.8)	8 (21.6)	
Bacteria, n (%)			0.93			0.96
Escherichia coli	21 (51.2)	23 (53.5)		19 (51.4)	18 (48.6)	
Klebsiella pneumoniae	11 (26.8)	12 (27.9)		10 (27.0)	11 (29.7)	
Others	9 (22.0)	8 (18.6)		8 (21.6)	8 (21.6)	
Drug-resistance bacteria, n (%)						
FQ-resistant gram-negative bacteria	11 (26.8)	12 (27.9)	0.91	10 (27)	11 (29.7)	0.80
G3-resistant gram-negative bacteria	1 (2.4)	7 (16.3)	0.07	1 (2.7)	7 (18.9)	0.06
Antibiotics duration, median (IQR)	10 (6–14)	11 (8–14)	0.27	10 (6–14)	11 (8–13.5)	0.27

(*Continued*)

Table 2 (Continued).

Clinical Characteristics and Outcomes	Unmatched Data			Matched Data		
	BLBLIs (n=41)	CARs (n=43)	*P*-value[a]	BLBLIs (n=37)	CARs (n=37)	*P*-value[b]
Hydrothorax (%)	11 (26.8)	13 (30.2)	0.73	10 (27.0)	11 (29.7)	0.80
Parenteral nutrition (%)	8 (19.5)	16 (37.2)	0.07	7 (18.9)	14 (37.8)	0.07
Diuretics (%)	31 (75.6)	32 (74.4)	0.90	30 (81.1)	27 (73.0)	0.41
Human albumin (%)	35 (85.4)	37 (86.0)	0.93	31 (83.8)	31 (83.8)	1.00
Clinical outcome						
Time to defervescence, mean ± SD	2.4 ± 0.2	2.5 ± 0.3	0.94	2.4 ± 0.3	2.4 ± 0.3	0.75
Defervescence within 3 days after antibacterial therapy[e], n (%)	31 (81.6)	30 (76.9)	0.62	28 (82.4)	26 (78.8)	0.71
Success rate (%)	33 (80.5)	34 (79.1)	0.87	32 (86.5)	29 (78.4)	0.36
Microbiological efficacy (%)	34 (82.9)	34(79.1)	0.65	30 (81.1%)	29 (78.4%)	0.77
In hospital mortality	1 (2.4)	3 (7.0)	0.62	1 (2.7)	3 (8.1)	0.62

Notes: [a]*P*-values provided based on a comparison between BLBLIs and CARs group (unmatched data). [b]*P*-values provided based on a comparison between BLBLIs and CAR groups (matched data). [c]CLIF-SOFA evaluated before the appearance of BSI. [d]CLIF-SOFA evaluated at the onset of BSI. [e]A total of seven afebrile patients (3 patients in BLBLI group and 4 patients in CAR group) were excluded.

Abbreviations: GNB-BSI, Gram-negative bacteria bloodstream infection; SBP, Spontaneous bacterial peritonitis; CTP, Child-Turcotte-Pugh; MELD, Model for End-Stage Liver Disease; ALBI, Albumin-Bilirubin; CLIF-SOFA, Chronic Liver Failure-Sequential Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome; FQ, Fluoroquinolones; G3, The third generations of cephalosporins.

(2.4 ± 0.3 vs 2.4 ± 0.3, P = 0.75), success rate (86.5% vs 78.4%; OR = 0.57; P = 0.36) and defervescence within 3 days after antibacterial therapy (82.4% vs 78.8%; OR = 1.26; P = 0.71) (Figure 2) between two groups were not significantly different. The in-hospital mortality was 2.7% in the BLBLIs group and 8.1% in the CARs group (P = 0.62) (Table 2). No difference was found between patients who were both empirically and definitively treated by cefoperazone/sulbactam and those treated by meropenem regarding the time to defervescence (2.5 ± 1.6 vs 2.4 ± 1.9, P = 0.58).

Empirically Treated by BLBLIs or CARs

An escalation group analysis was conducted to compare the genuine effect of initial empirical antibiotics and excluded confounding effects of definitive antibiotics. Patients in escalation group (n = 16) were compared to those from CARs group (n = 43). In the propensity-matched cohort, 16 patients empirically treated by BLBLIs and 32 patients (5 treated by imipenem/cilastatin, 27 treated by meropenem) empirically treated by CARs were included (Figure 1). Patients empirically treated by BLBLIs had significantly prolonged time to defervescence both in the unmatched cohort (3.5 ± 2.1 vs 2.5 ± 1.8, P = 0.049) and matched cohort (3.5 ± 2.1 vs 2.2 ± 1.5, P = 0.03). Conversely, the success rate of escalation group and CARs group are similar both before (68.8% vs 79.1%, OR = 1.72, P = 0.41) and after matching (68.8% vs 81.3%, OR = 1.97, P = 0.54). Furthermore, the time to defervescence of cefoperazone/sulbactam and meropenem, the most frequently used antibiotics in these patients, were compared (Figure S2). The time to defervescence of patients treated by cefoperazone/sulbactam was significantly longer than that when treated by meropenem both before (3.8 ± 2.1 vs 2.4 ± 1.9, P = 0.02) and after matching (3.8 ± 2.1 vs 2.3 ± 1.6, P = 0.015).

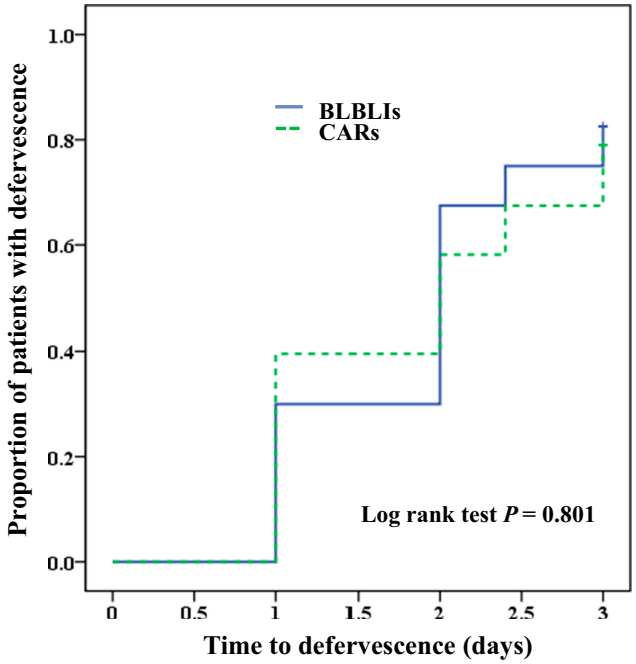


Figure 2 Kaplan–Meier curves of the time to defervescence within 3 days after BSI onset in 84 liver cirrhosis patients.

Abbreviations: BLBLIs, β-lactam/β-lactamase inhibitor combinations; CARs, Carbapenems.

Predictors Associated with Efficacy

In the current study, we assessed antibiotic responses according to established evaluation criteria in 10 days after antimicrobial treatment. The result of multivariate logistic regression analysis showed that only the time to defervescence was inversely associated with therapy success (OR 0.699, 95% CI 0.506–0.965, $P = 0.03$) (Table 3).

Cost-Effectiveness Analysis

Base Case Analysis

Outcomes and total costs of the two treatment strategies are summarized in Table S3: The ICER was calculated relative to cefoperazone/sulbactam, which was considered the baseline drug. In the present cohort, meropenem was dominated by cefoperazone/sulbactam. The efficacy of meropenem was similar to cefoperazone/sulbactam and which was comparatively more costly than cefoperazone/sulbactam. Hence, cefoperazone/sulbactam was cost-effective in the present analysis under the WTP threshold (Table 4).

Sensitivity Analyses

Deterministic sensitivity analyses revealed that the results were most sensitive to the success rate of BSI associated with cefoperazone/sulbactam or meropenem. When the WTP threshold was set at ¥64,644, the clinical success rate of BSI associated with cefoperazone/sulbactam less than 78.32% or meropenem higher than 83.93% made the use of meropenem becomes acceptable. Results of probabilistic sensitivity analyses suggested that cefoperazone/sulbactam was cost-effective with a probability of 91.30% under the threshold currently accepted in China (¥64,644) (Figure 3).

Discussion

To the best of our knowledge, this retrospective study represented the first comparison of efficacy between BLBLIs and CARs in cirrhotic patients with GNB-BSI. The study included 100 liver cirrhosis patients with GNB-BSI and a propensity score-matched analysis was performed to control variables that had an impact on therapy choices. A decision tree was also used to estimate the clinical outcomes and direct costs of treating GNB-BSI using two strategies. The results indicated that there was no significant difference between two groups in terms of the time to defervescence, the success rate and defervescence within 3 days after antibacterial therapy. Moreover, cefoperazone/sulbactam is a cost-effective therapy.

The third-generation cephalosporins, as the frontline used antibiotics for empirical coverage of GNB, were active against 63.2% to 73.3% of GNB in liver cirrhosis patients with BSI,[27] and were adequate in only 60% of BSI episodes.[9] Even in regions with a low prevalence of extended spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, cephalosporins showed a poor antibiotic coverage.[28] Conversely, the previous study revealed that the isolated gram-negative bacterial strains exhibited high sensitivity to cefoperazone/sulbactam (89.9%), piperacillin/tazobactam (91.7%), imipenem (95.7%) and meropenem (96.4%), whether these strains produce ESBLs or not.[27] In this study center, ceftriaxone was against as low as 43.1% of *Escherichia coli* and 86.8% of

Table 3 Univariate and Multivariate Logistic Regression Analysis of Antibiotic Responses at 10 Days After Antibacterial Treatment

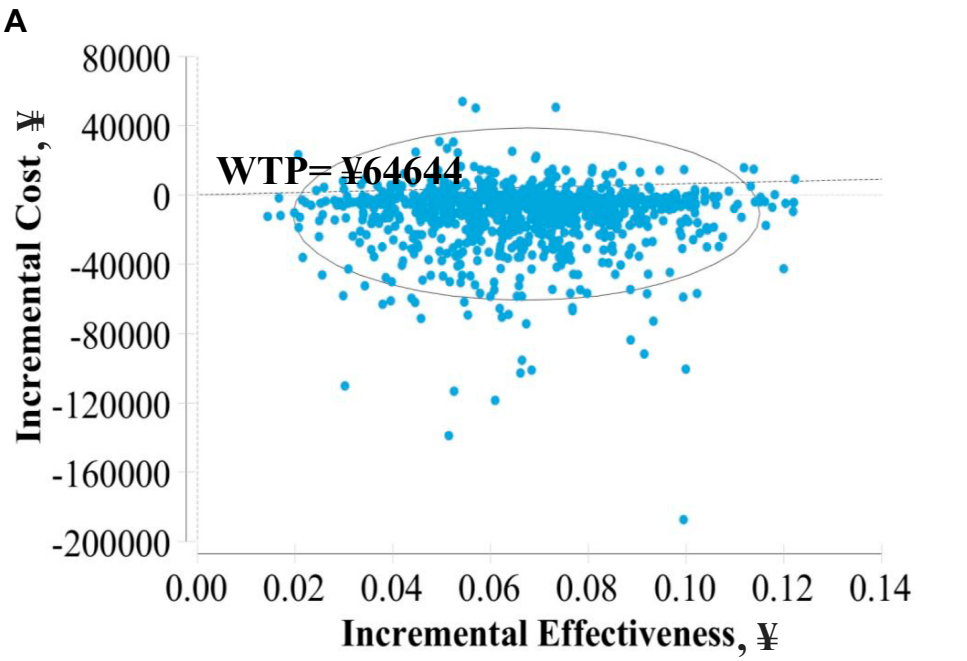
Clinical Characteristics	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Platelet count	1.01 (0.997–1.02)	0.15		
ALBI	0.421 (0.149–1.195)	0.10		
CLIF-SOFA0*	0.819 (0.602–1.116)	0.21		
Time to defervescence	0.695 (0.506–0.948)	0.02	0.699 (0.506–0.965)	0.03

Note: *CLIF-SOFA evaluated before the appearance of BSI.
Abbreviation: ALBI, Albumin-Bilirubin

Table 4 Cost-Effectiveness of Cefoperazone/Sulbactam and Meropenem for Treatment of Cirrhotic Patients with GNB-BSI

	Total Cost (CNY)	Total Effectiveness (%)	ΔC	ΔE	ICER
CPZ/SBT	57153.36	0.7070280			
MEM	68389.85	0.6394420	11,236.49	−0.06759	Dominated

Abbreviations: GNB-BSI, Gram-negative bacteria bloodstream infection; CPZ/SBT, Cefoperazone/sulbactam; MEM, Meropenem; CNY, China yuan; ΔC, Incremental cost; ΔE, Incremental effectiveness; ICER, Incremental cost-effectiveness ratio per clinical success rate saved.



Quadrant	Incr. Cost (CNY)	Incr. Effect (%)	Incr. Cost-Effect	Frequency	Probability
IV	IC<0	IE>0	Superior	8240	82.4%
I	IC>0	IE>0	ICER<64644	886	8.9%
III	IC<0	IE<0	ICER>64644	3	0.03%
I	IC>0	IE>0	ICER>64644	870	8.7%
III	IC>0	IE<0	ICER<64644	0	0
II	IC>0	IE<0	Inferior	0	0

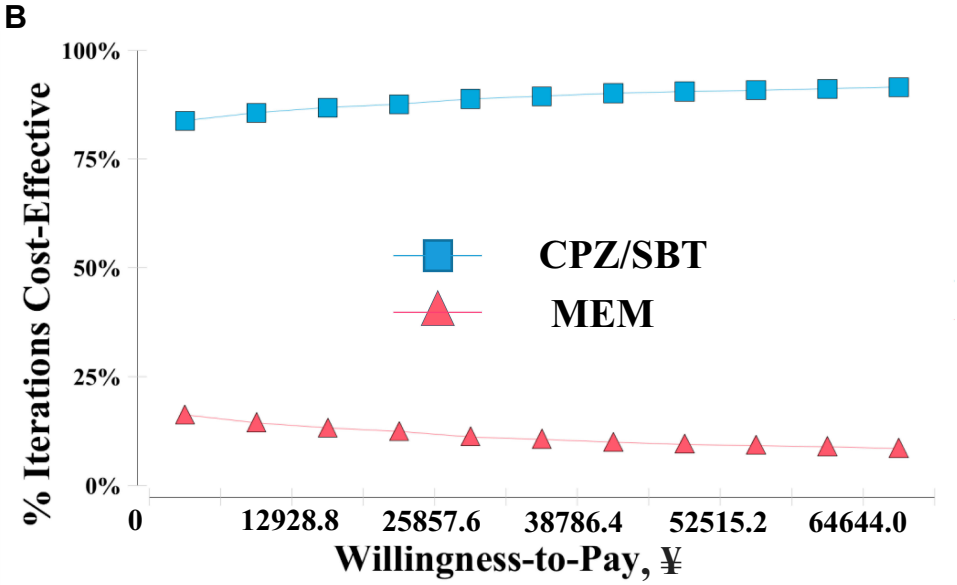


Figure 3 Incremental cost-effectiveness plane and table, with cost-effectiveness acceptability curves (CEAC). (**A**) Monte Carlo simulation. Each blue spot represents one of the 10,000 iterations. (**B**) Cost-effectiveness acceptability curves.

Abbreviations: CPZ/SBT, cefoperazone/sulbactam; MEM, meropenem; Incr. Cost, incremental cost; Incr. Eff, incremental effectiveness; Incr. Cost-Effect, Incremental cost-effectiveness.

Klebsiella pneumoniae. Whereas these isolates, *Escherichia coli* and *Klebsiella pneumoniae*, were highly sensitive to piperacillin/tazobactam, cefoperazone/sulbactam, and the susceptibility rates ranged from 85.4% to 96.2%. Imipenem and meropenem were active in vitro as high as 100% of major causative microorganisms. Accordingly, it is reasonable to not choose the third generation cephalosporins but BLBLIs and CARs as the initial antimicrobial therapy for GNB-BSI in this region.

There are no preferred therapeutic strategies of GNB-BSI in cirrhotic patients, according to guidelines or expert consensus documents. Up to now, several studies have tried to evaluate the effectiveness of BLBLIs and CARs on BSI due to ESBLs bacteria, and indicated controversial results.[17–21] It remains unknown whether these results are applicable to cirrhotic patients due to their unique pathophysiological characteristics. Compared with non-cirrhotic patients, antibiotics' pharmacokinetics variability and cirrhosis associated immune dysfunction are the main contributors to therapeutic failure for liver cirrhosis patients,[9] which can alter the pharmacokinetic/pharmacodynamic behavior of antimicrobial agents and eventually cause unpredictable antibiotic efficacy. Nevertheless, the present study was the first to demonstrate the similar therapeutic efficacy of BLBLIs and CARs for GNB-BSI in cirrhotic patients.

Optimal antimicrobial treatment duration for GNB-BSI remains unclear, but some study results demonstrated that the risk of treatment failure was significantly higher in patients receiving a short course (7–10 day) therapy than that when receiving a long course (>10 days) of antimicrobial therapy.[29] Thus, the efficacy was evaluated on day 10 after antibiotics treatment. In the present study, there was no significant difference in regard to the time to defervescence and the success rate between two groups, both in the unmatched and matched cohort (Table 2).

In the escalation group analysis, the success rate of the escalation group and CARs group are similar before and after the match. The same result was supposed to be drawn from the escalation cohort in terms of the time to defervescence. However, patients empirically treated by BLBLIs had significantly prolonged time to defervescence. Furthermore, patients empirically treated by cefoperazone/sulbactam had a significantly longer time to defervescence than those empirically treated by meropenem (Figure S2). These results were inconsistent with the results from BLBLIs and CARs groups. We also noticed that BLBLIs-resistant pathogens were isolated in 3 out of 16 patients in the escalation group, and thus we deduced that inappropriate empirical therapy with cefoperazone/sulbactam caused a longer time to defervescence. These results indicated that appropriate empirical antibiotics therapy must be administered as soon as possible in cirrhotic patients with GNB-BSI.

Additionally, we evaluated the potential predictors of efficacy at 10 days after initial antibiotics treatment, and found the only independent predictor was the time to defervescence. Thus, choosing a reasonable antibiotics therapy to make patients defervescence quickly will benefit to improve the clinical efficacy. Theoretically, using appropriate antibiotics and immune status associated with cirrhotic patients were key contributors to the clinical efficacy of antibiotics treatment. Therefore, the common use of empirical antibiotics should refer to local epidemiology and most importantly take patients' risk factors for MDR bacterial infection into consideration.

Cefoperazone/sulbactam is one of the commonly used BLBLIs in China. The resistance rates to cefoperazone/sulbactam were relatively low in ESBL-producing *Escherichia coli* (12.3%) and *Klebsiella pneumoniae* (16.1%) isolates.[30] In the hospital where this study is based, cefoperazone/sulbactam and meropenem are also of the most frequently used two antibiotics in patients with cirrhosis and are similar in clinical success rates (83.3% vs 78.4%, $P = 0.60$). However, thrombocytopenia associated with cefoperazone/sulbactam have been confirmed by several studies,[31,32] which may cause increased hospitalization costs for liver cirrhosis patients. In addition, the unit price of meropenem is more expensive than cefoperazone/sulbactam in China. Thus, we evaluated the cost-effectiveness of treating GNB-BSI using cefoperazone/sulbactam or meropenem and found that cefoperazone/sulbactam was dominant and more cost-effective compared with meropenem under the WTP threshold. This result was also confirmed by probabilistic sensitivity analyses using MCS with 10,000 times. Nevertheless, the results of the deterministic analyses suggested that the superiority of meropenem over cefoperazone/sulbactam for successful treatment of GNB-BSI was sensitive to the clinical success rate of both drugs. Only if the clinical success rate of BSI associated with cefoperazone/sulbactam less than 78.32% or over than 83.93% for meropenem would lead to evaluating meropenem as superior to cefoperazone/sulbactam.

The highlight of the present study lies in that appropriate BLBLIs might be a reasonable alternative to CARs in regions with relatively low drug-resistance prevalence for the treatment of patients with GNB-BSI. Nevertheless, there were several limitations to the present study. (1) This

retrospective study with relatively small samples did not investigate the mortality because of incomplete patients' information after patients' discharge. So, the prognostic benefit of BLBLIs and CARs remains unclear. (2) Variables (CRP and PCT) used to assess the severity of BSI, and variables (drug-resistant bacteria and liver function, as well as prior antibiotic exposure) that have been demonstrated to influence the choices of treatment regimens and clinical outcomes should be also included in the propensity match. Regrettably, we failed to include these variables into propensity score-matching analysis, in order to avoid large sample size loss. (3) The present study suggested that BLBLIs might be a reasonable alternative to CARs if BLBLIs are susceptible to major causative microorganisms isolated in BSI. However, the result should be cautiously interpreted to guide antibiotic regimens in regions with high BLBLIs resistance prevalence. (4) A drawback of the current cost-effectiveness analysis lies in that only the probability and cost associated with primary or severe adverse events (ie thrombocytopenia for cefoperazone/sulbactam) was taken into consideration in the decision tree model. Ignoring differences in the probability and cost of other adverse events may influence results.

In conclusion, the present study showed that no statistically significant difference was observed for the efficacy of BLBLIs and CARs treatment in cirrhotic patients with GNB-BSI. Economic evaluation demonstrated that cefoperazone/sulbactam might be a cost-effective therapy for the treatment of GNB-BSI in patients with cirrhosis. BLBLIs might be a reasonable alternative to CARs, and carbapenems-sparing regimens could be encouraged in regions with a low prevalence of MDR bacteria.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no conflicts of interest.

References

1. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. *Lancet*. 2014;383:1749–1761. doi:10.1016/S0140-6736(14)60121-5
2. Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology*. 2019;156:1368–1380. doi:10.1053/j.gastro.2018.12.005
3. 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. doi:10.1002/hep.25532
4. Kang CI, Song JH, Chung DR, et al. Liver cirrhosis as a risk factor for mortality in a national cohort of patients with bacteremia. *J Infect*. 2011;63:336–343. doi:10.1016/j.jinf.2011.07.012
5. National Guideline C. *National Institute for Health and Care Excellence: Guidance Cirrhosis in Over 16s: Assessment and Management*. National Institute for Health and Care Excellence (UK); 2016.
6. Leber B, Spindelboeck W, Stadlbauer V. Infectious complications of acute and chronic liver disease. *Semin Respir Crit Care Med*. 2012;33:80–95. doi:10.1055/s-0032-1301737
7. Bartoletti M, Giannella M, Lewis R, et al. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. *Clin Microbiol Infect*. 2018;24:546.e1–546.e8. doi:10.1016/j.cmi.2017.08.001
8. Bartoletti M, Giannella M, Caraceni P, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. *J Hepatol*. 2014;61:51–58. doi:10.1016/j.jhep.2014.03.021
9. Bartoletti M, Giannella M, Lewis RE, Viale P. Bloodstream infections in patients with liver cirrhosis. *Virulence*. 2016;7:309–319. doi:10.1080/21505594.2016.1141162
10. Linderoth G, Jepsen P, Schonheyder HC, Johnsen SP, Sorensen HT. Short-term prognosis of community-acquired bacteremia in patients with liver cirrhosis or alcoholism: a population-based cohort study. *Alcohol Clin Exp Res*. 2006;30:636–641. doi:10.1111/j.1530-0277.2006.00074.x
11. Fernandez J, Acevedo J. New antibiotic strategies in patients with cirrhosis and bacterial infection. *Expert Rev Gastroenterol Hepatol*. 2015;9:1495–1500. doi:10.1586/17474124.2015.1100075
12. 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. doi:10.1016/j.jhep.2014.01.024
13. Fernandez J, Gustot T. Management of bacterial infections in cirrhosis. *J Hepatol*. 2012;56(Supp 1):S1–S12. doi:10.1016/S0168-8278(12)60002-6
14. Mucke MM, Mayer A, Kessel J, et al. Quinolone- and multidrug-resistance predict failure of antibiotic prophylaxis of spontaneous bacterial peritonitis. *Clin Infect Dis*. 2019. doi:10.1093/cid/ciz540
15. Stewardson AJ, Marimuthu K, Sengupta S, et al. Effect of carbapenem resistance on outcomes of bloodstream infection caused by Enterobacteriaceae in low-income and middle-income countries (PANORAMA): a multinational prospective cohort study. *Lancet Infect Dis*. 2019;19:601–610. doi:10.1016/S1473-3099(18)30792-8
16. Hayden MK, Won SY. Carbapenem-sparing therapy for extended-spectrum beta-Lactamase-producing E coli and Klebsiella pneumoniae Bloodstream Infection: the search continues. *JAMA*. 2018;320:979–981. doi:10.1001/jama.2018.12565
17. Ko JH, Lee NR, Joo EJ, et al. Appropriate non-carbapenems are not inferior to carbapenems as initial empirical therapy for bacteremia caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae: a propensity score weighted multicenter cohort study. *Eur J Clin Microbiol Infect Dis*. 2018;37:305–311. doi:10.1007/s10096-017-3133-2

18. Rodriguez-Bano J, Navarro MD, Retamar P, Picon E, Pascual A. Beta-Lactam/beta-lactam inhibitor combinations for the treatment of bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli: a post hoc analysis of prospective cohorts. *Clin Infect Dis*. 2012;54:167–174. doi:10.1093/cid/cir790
19. Perez F, Bonomo RA. Can we really use β-lactam/β-lactam inhibitor combinations for the treatment of infections caused by extended-spectrum β-lactamase-producing bacteria? *Clin Infect Dis*. 2012;54:175–177. doi:10.1093/cid/cir793
20. Su J, Guo Q, Li Y, et al. Comparison of empirical therapy with cefoperazone/sulbactam or a carbapenem for bloodstream infections due to ESBL-producing Enterobacteriaceae. *J Antimicrob Chemother*. 2018;73:3176–3180. doi:10.1093/jac/dky323
21. Bin C, Hui W, Renyuan Z, et al. Outcome of cephalosporin treatment of bacteremia due to CTX-M-type extended-spectrum beta-lactamase-producing Escherichia coli. *Diagn Microbiol Infect Dis*. 2006;56:351–357. doi:10.1016/j.diagmicrobio.2006.06.015
22. Kilgore M, Brossette S. Cost of bloodstream infections. *Am J Infect Control*. 2008;36:S172.e1–S172.e3. doi:10.1016/j.ajic.2008.10.004
23. Digiovine B, Chenoweth C, Watts C, Higgins M. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med*. 1999;3:976–981. doi:10.1164/ajrccm.160.3.9808145
24. Paterson DL, Ko WC, Von Gottberg A, et al. International prospective study of Klebsiella pneumoniae bacteremia: implications of extended-spectrum beta-lactamase production in nosocomial Infections. *Ann Intern Med*. 2004;140:26–32. doi:10.7326/0003-4819-140-1-200401060-00008
25. Lee CC, Wang JL, Lee CH, et al. Clinical benefit of appropriate em*pirical fluoroquinolone therapy for adults with community-onset bacteremia in comparison with third-generation-cephalosporin therapy. *Antimicrob Agents Chemother*. 2017;61:e02174–16. doi:10.1128/AAC.02174-16
26. Liang X, Fan Y, Yang M, et al. A prospective multicenter clinical observational study on vancomycin efficiency and safety with therapeutic drug monitoring. *Clin Infect Dis*. 2018;67:S249–S255. doi:10.1093/cid/ciy680
27. Xie Y, Tu B, Xu Z, et al. Bacterial distributions and prognosis of bloodstream infections in patients with liver cirrhosis. *Sci Rep*. 2017;7:11482. doi:10.1038/s41598-017-11587-1
28. Novovic S, Semb S, Olsen H, Moser C, Knudsen JD, Homann C. First-line treatment with cephalosporins in spontaneous bacterial peritonitis provides poor antibiotic coverage. *Scand J Gastroenterol*. 2012;47:212–216. doi:10.3109/00365521.2011.645502
29. Nelson AN, Justo JA, Bookstaver PB, Kohn J, Albrecht H, Al-Hasan MN. Optimal duration of antimicrobial therapy for uncomplicated Gram-negative bloodstream infections. *Infection*. 2017;45:613–620. doi:10.1007/s15010-017-1020-5
30. Yang Q, Zhang H, Cheng J, et al. In vitro activity of flomoxef and comparators against Escherichia coli, Klebsiella pneumoniae and Proteus mirabilis producing extended-spectrum beta-lactamases in China. *Int J Antimicrob Agents*. 2015;45:485–490. doi:10.1016/j.ijantimicag.2014.11.012
31. Loo AS, Gerzenshtein L, Ison MG. Antimicrobial drug-induced thrombocytopenia: a review of the literature. *Semin Thromb Hemost*. 2012;38:818–829. doi:10.1055/s-0032-1328882
32. Li Y, Hu YF, Peng FC. Evidence-based analysis of thrombocytopenia caused by cefoperazone/sulbactam. *Chin J Hosp Pharm*. 2009;44:1938–1941.