Clinical Infectious Diseases

MAJOR ARTICLE

Extended Infusion of β-Lactams for Bloodstream Infection in Patients With Liver Cirrhosis: An Observational Multicenter Study

Michele Bartoletti,[1] Maddalena Giannella,[1] Russell E. Lewis,[1] Paolo Caraceni,[2] Sara Tedeschi,[1] Mical Paul,[3] Christoph Schramm,[4] Tony Bruns,[5] Manuela Merli,[6] Nazaret Cobos-Trigueros,[7] Elena Seminari,[8] Pilar Retamar,[9] Patricia Muñoz,[10] Mario Tumbarello,[11] Patrizia Burra,[12] Maria Torrani Cerenzia,[13] Bruno Barsic,[14] Ester Calbo,[15] Alberto Enrico Maraolo,[16] Nicola Petrosillo,[17] Maria Angeles Galan-Ladero,[18] Gianpiero D'Offizi,[19] Yael Zak-Doron,[3] Jesus Rodriguez-Baño,[9] Maurizio Baldassarre,[2,20] Gabriella Verucchi,[1] Marco Domenicali,[2] Mauro Bernardi,[2] and Pierluigi Viale[1]; on behalf of ESGBIS/BICHROME study group

[1]Infectious Diseases Unit, Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, and [2]Department of Medical and Surgical Sciences, University of Bologna, Italy; [3]Unit of Infectious Diseases, Rambam Health Care Campus, HaAliya HaShniya, Israel; [4]Department of Gastroenterology and Hepatology, University Clinic of Cologne, and [5]Department of Internal Medicine IV, Jena University Hospital, Friedrich Schiller University, Germany; [6]Division of Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Viale, Italy; [7]Department of Infectious Diseases, Hospital Clínic, University of Barcelona, Spain; [8]Department of Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [9]Unidad Clínica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen Macarena–Instituto de Biomedicina de Sevilla (IBIS) and Departamento de Medicina, Universidad de Sevilla, and [10]Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain; [11]Fondazione Policlinico Universitario A. Gemelli IRCCS, Roma, Italy, [12]Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padova University Hospital, and [13]Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, University of Turin, Italy; [14]Infectious Diseases, University Hospital for Infectious Diseases "Dr Fran Mihaljevic," Zagreb, Croatia; [15]Infectious Disease Unit, Service of Internal Medicine, Hospital Universitari Mútua de Terrassa, Barcelona, Spain; and [16]Department of Clinical Medicine and Surgery, Section of Infectious Diseases, University of Naples Federico II, [17]2nd Infectious Diseases Division, National Institute for Infectious Diseases L. Spallanzani, Rome, [18]Clinical Microbiology, Nuestra Senora del Prado Hospital, [19]Hepatology and Infectious Diseases Unit, National Institute for Infectious Diseases L. Spallanzani, Rome, and [20]S.Orsola-Malpighi University Hospital, Center for Applied Biomedical Research, Bologna, Italy

Background. We analyzed the impact of continuous/extended infusion (C/EI) vs intermittent infusion of piperacillin-tazobactam (TZP) and carbapenems on 30-day mortality of patients with liver cirrhosis and bloodstream infection (BSI).

Methods. The BICRHOME study was a prospective, multicenter study that enrolled 312 cirrhotic patients with BSI. In this secondary analysis, we selected patients receiving TZP or carbapenems as adequate empirical treatment. The 30-day mortality of patients receiving C/EI or intermittent infusion of TZP or carbapenems was assessed with Kaplan-Meier curves, Cox-regression model, and estimation of the average treatment effect (ATE) using propensity score matching.

Results. Overall, 119 patients received TZP or carbapenems as empirical treatment. Patients who received C/EI had a significantly lower mortality rate (16% vs 36%, $P = .047$). In a Cox-regression model, the administration of C/EI was associated with a significantly lower mortality (hazard ratio [HR], 0.41; 95% confidence interval [CI], 0.11–0.936; $P = .04$) when adjusted for severity of illness and an ATE of 25.6% reduction in 30-day mortality risk (95% CI, 18.9–32.3; $P < .0001$) estimated with propensity score matching. A significant reduction in 30-day mortality was also observed in the subgroups of patients with sepsis (HR, 0.21; 95% CI, 0.06–0.74), acute-on-chronic liver failure (HR, 0.29; 95% CI, 0.03–0.99), and a model for end-stage liver disease score ≥25 (HR, 0.26; 95% CI, 0.08–0.92). At competing risk analysis, C/EI of beta-lactams was associated with significantly higher rates of hospital discharge (subdistribution hazard [95% CI], 1.62 [1.06–2.47]).

Conclusions. C/EI of beta-lactams in cirrhotic patients with BSI may improve outcomes and facilitate earlier discharge.

Keywords. liver cirrhosis; bloodstream infection; β-lactam antibiotics; continuous infusion.

Liver cirrhosis is a widespread disease and a leading cause of mortality in developed countries [1]. The natural history of liver cirrhosis is characterized by subsequent episodes of decompensation often triggered by infection [2–4].

Approximately 20% of all infections that require hospital admission in patients with liver cirrhosis are due to primary or secondary bacteremia with associated mortality rates between 25% and 58% [5, 6], which is significantly higher than that in noncirrhotic patients with bacteremia [7, 8]. Several things may explain the higher mortality, including cirrhosis-associated immune deficiency, the high rate of acute-on-chronic liver failure (ACLF) syndrome triggered by infections, and a higher prevalence of multidrug-resistant (MDR) pathogens [2, 5, 9]. Systemic antibiotic exposure may also be less predictable in disease-associated changes in the volume of distribution and in renal clearance, significantly altering drug pharmacokinetic/pharmacodynamic (PK/PD) behavior [10]. These PK changes may be driven by hypoalbuminemia and reduced binding to proteins as well as altered distribution due

Received 12 September 2018; editorial decision 28 December 2018; accepted 10 January 2019; published online January 14, 2019.

Correspondence: M. Bartoletti, Infectious Disease Unit–Policlinico S. Orsola-Malpighi, Via Massarenti, 11, 40138 Bologna, Italy (michele.bartoletti4@unibo.it).

Clinical Infectious Diseases® 2019;XX(XX):1–9

DOI: 10.1093/cid/ciz032

to the "third space" expansion, especially in patients with a large volume of ascites [11].

Several studies have documented the importance of adequate empirical antibiotic treatment for reducing infection-related mortality in patients with liver cirrhosis [12–14]. In most studies, however, appropriate empirical antimicrobial treatment was defined solely by in vitro susceptibility profiles assuming that standardized antibiotic doses are effective in cirrhotic patients. Virtually no studies have explored actual PK/PD target attainment in cirrhotic populations or the impact of altered PK behavior of antibiotics on treatment outcome of bloodstream infection (BSI) [15, 16]. This is surprising given the growing body of evidence in critically ill patients that has demonstrated that continuous or extended infusion (C/EI) of β-lactam antibiotics is associated with improved PK/PD target attainment, higher clinical cure, and lower in-hospital mortality compared with intermittent (bolus) infusion strategies [16, 17].

Our aim in this multicenter observational study was to analyze the impact of C/EI strategies for piperacillin-tazobactam (TZP) and carbapenems on 30-day mortality in cirrhotic patients receiving active empirical and definitive therapy for BSI.

METHODS

Here, we present a secondary analysis of the BICHROME study, a prospective multicenter study conducted in 19 tertiary centers from Italy (n = 10), Spain (n = 5), Germany (n = 2), Croatia (n = 1), and Israel (n = 1) from September 2014 to December 2015 designed to describe the current epidemiology of BSI in cirrhotic patients [6]. The core BICHROME study enrolled consecutive adult (aged >18 years) cirrhotic patients with BSI. Patients with previous liver transplantation and other concomitant infections were excluded. Only the first episode of BSI was considered for each patient. The diagnosis of liver cirrhosis was based on previous liver biopsy results or a composite of clinical signs and findings provided by laboratory test results, endoscopy, and radiologic imaging. Eligible patients were prospectively screened by study coordinators at each site through microbiological and admission records at the local liver units as previously described [6]. The study was approved by all local institutional review boards of the participating hospitals. Written informed consent was obtained from patients or from legal surrogates before enrollment.

For this analysis, we selected patients enrolled in the BICHROME study who received in vitro active empirical treatment (for at least 48 hours) with either TZP or a carbapenem.

To be included in the CE/I group, patients must have received a loading dose of TZP 4.5–9 g followed by 13.5–18 g per 24 hours (adjusted for renal function) by continuous infusion; a meropenem loading dose of 1–2 g followed by 2–6 g per 24 hours (adjusted for renal function) divided into 3–4 infusions of a length of 3–4 hours each; or a loading dose of 1 g (imipenem component) of imipenem/cilastatin followed by 2–3 g per 24 hours (adjusted for renal function) divided into 3–4 infusions of a length of 3–4 hours each. Use of a syringe or infusion pump was not dictated by study protocol. Patients included in the intermittent administration group received TZP 4.5 g every 6 hours (adjusted for renal function) or meropenem 1 g every 8 hours (adjusted for renal function) by 30-minute infusion. The choice of empirical treatment was based on current international and local guidelines, the latter mainly based on local prevalence of drug-resistant pathogens. The choice of targeted therapy was based on both international guidelines and results of a susceptibility test. The choice of CE/I or intermittent administration of antibiotics was based on clinical decision by the attending physician. In any case, the choice of therapy and modality of infusion was not dictated by study protocol.

Patient Follow-up

Patients were followed until death or hospital discharge. In case of early discharge (before day 30 after BSI onset defined by the first positive blood culture), patients were followed up until day 30 with either an outpatient visit or telephone call.

Data Collection and Definitions

Data were collected using an electronic case report form available at the study web site. The integrity of data was systematically checked, and queries were generated in case of inconsistent or missing data for reconciliation. The following information was collected at enrollment: demographic variables (sex, age); the cause and severity of liver disease according to the model for end-stage liver disease (MELD) collected at baseline and BSI onset presence of hepatocellular carcinoma; and presence of other comorbidities according to the Charlson score [18]. BSI was classified as hospital acquired, healthcare associated, or community acquired according to Friedman's criteria [19]. Infection severity was assessed according to sepsis criteria, sequential organ failure assessment (SOFA), and the chronic liver failure-SOFA (CLIF-SOFA) scores [20, 21]. We also collected events and grade of ACLF, as described by Moreau et al [22]. Empirical therapy was defined as treatment administration before the susceptibility tests were available and was considered as adequate when at least 1 antibiotic was active in vitro against the isolated pathogen. Definitive therapy was defined as the treatment administered after obtainment of the microbiological identification and susceptibility test results was considered as adequate when an active antimicrobial regimen, adjusted according to microbiological results, was administered until the end of antibiotic course (for at least 48 hours). Outcome variables included the need for intensive care unit admission, length of hospital stay, and 30-day transplant-free mortality.

Microbiology

Before study onset, the use of standard diagnostic methods was required and agreed upon with all the participating centers.

This included use of an automated blood culture detector system, performance of Gram stain and/or rapid test (such as matrix-assisted laser desorption/ionization time-of-flight, luorescence in situ hybridization using peptide nucleic acid probes) with immediate communication of the preliminary information to the attending physicians, and use of an automated system (Vitek n = 17, MicroScan n = 2) for susceptibility testing. Breakpoints, screening, and conformation of the main mechanisms of resistance were performed in accordance with European Committee on Antimicrobial Susceptibility Testing guidelines [23]. Pathogens were classified as MDR according to previous criteria [24].

Statistical Analyses

Categorical variables were analyzed as absolute numbers and their relative frequencies. Continuous variables were analyzed as mean and standard deviation if normally distributed or as median and interquartile range (IQR) if nonnormally distributed. Categorical variables were compared using the χ^2 test or Fisher exact test, whereas continuous variables were compared using the Mann-Whitney U or 2-tailed Student's *t*-test, when appropriate. Survival after 30 days from BSI diagnosis in patients receiving intermittent vs extended infusion of β-lactams was assessed by Kaplan-Meier curves.

Risk factors associated with 30-day mortality were analyzed by Cox regression as described previously [6]. Categorical risk factors associated ($P < .1$) with 30-day mortality in the univariable analysis were entered stepwise into a Cox regression model along with the patient CLIF-SOFA score as a continuous variable. Variables with a $P < .05$ were retained in the final model. Proportional hazards assumptions of the model were checked globally and for each variable individually by generalized linear regression of the scaled Schoenfeld residuals.

We also estimated the average treatment effect (ATE) of C/EI β-lactam infusions for reducing 30-day mortality using the treatment effects module implemented in Stata 13.1 [23]. Briefly, the potential outcome for each patient was estimated using an average of the outcomes of similar patients who receive the other infusion type. Similarity between patients is based on estimated treatment probabilities, known as the propensity score (PS). The ATE is then computed by taking the average of the difference between the observed and potential outcomes for each patient. The estimated densities of the probability of getting each treatment level were compared for both groups to ensure that the overlap assumption (adequate PS matching) required for ATE estimation was not violated.

Finally, the impact of antibiotic administration strategy for time to hospital discharge was analyzed using a competing-risk Cox proportional hazards regression (Fine and Gray) model for subdistribution hazard ratios (SHRs). This model allows a simultaneous estimation of 2 independent competing events: discharge and death, with death being the competing event that hindered the observation of the event of interest, which was time to hospital discharge. Patients were considered from the

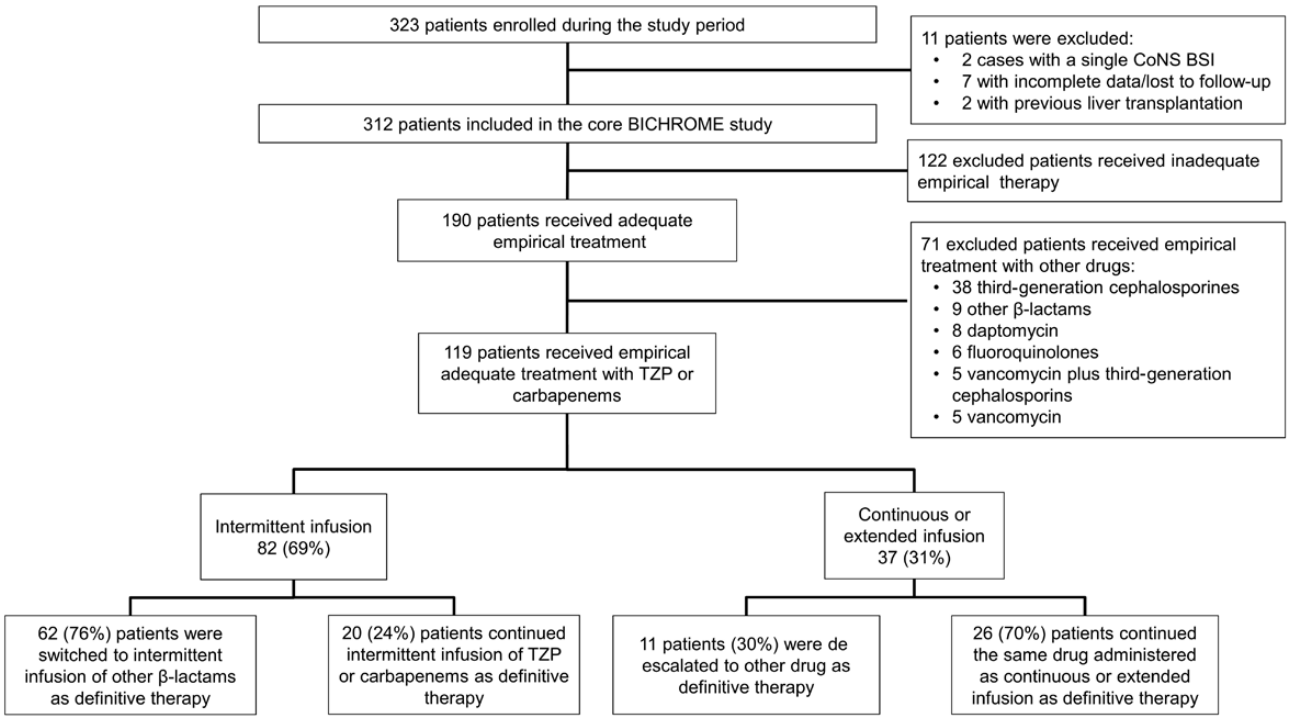

Figure 1. Study flowchart. Abbreviations: BSI, bloodstream infection; CoNS, coagulase-negative staphylococci; TZP, piperacillin-tazobactam.

Table 1. Differences in Demographics, Underlying Disease, Comorbidities, and Characteristics of Infection Among Patients Receiving Intermittent Administration and Patients Receiving Continuous/Extended Infusion of Piperacillin-tazobactam or Carbapenems

Variable	Total (N = 119) (100%)	Intermittent Infusion (n = 82) (69%)	Continuous/Extended Infusion (n = 37) (31%)	*P* Value
Demographic data				
Age (y), mean (± standard deviation)	61 (±12)	59 (±12)	63 (± 9)	.12
Male sex	81 (68)	56 (68)	25 (68)	.93
Liver disease				
Viral cirrhosis	42 (35)	29 (35)	13 (35)	.98
Alcoholic cirrhosis	32 (27)	23 (28)	9 (24)	.82
Nonalcoholic fatty liver disease	12 (10)	8 (9)	4 (11)	.99
Cryptogenic	19 (16)	11 (13)	8 (22)	.28
Alcoholic + viral cirrhosis	11 (9)	8 (10)	3 (8)	.99
Autoimmune disorder	3 (2)	3 (3)	0 (0)	.55
Hepatocellular carcinoma	19 (16)	13 (16)	6 (16)	.99
Admission diagnosis				
Ascitic decompensation	17 (14)	14 (17)	3 (8)	.26
Acute kidney injury	5 (4)	5 (6)	0 (0)	.18
Worsening of liver disease	11 (9)	8 (10)	3 (8)	.99
Hepatic encephalopathy	11 (9)	6 (7)	5 (13)	.32
Suspected bacterial infection	50 (44)	36 (45)	14 (38)	.47
Comorbidities				
Charlson index, median (IQR)	6 (5–8)	7 (5–8)	6 (5–8)	.84
Previous (<90 days) hospital admission	75 (64)	54 (67)	21 (57)	.26
Previous (<90 days) ICU admission	11 (9)	10 (12)	1 (3)	.17
BSI data				
Site of infection acquisition				
Community acquired	21 (18)	16 (19)	5 (13)	.60
Hospital acquired	62 (52)	37 (45)	25 (68)	.02
Healthcare associated	36 (30)	29 (35)	7 (19)	.09
Source of BSI				
Primary	38 (32)	27 (33)	11 (30)	.72
Pneumonia	11 (9)	9 (11)	2 (5)	.50
SBP	21 (16)	17 (21)	4 (11)	.30
Intraabdominal (other than SBP)	25 (23)	13 (16)	12 (32)	.04
Urinary tract	16 (14)	12 (15)	4 (11)	.77
Infection severity				
Acute-on-chronic liver failure	55 (46)	41 (50)	14 (38)	.21
Grade 1	23 (19)	17 (21)	6 (15)	.68
Grade 2	18 (15)	14 (17)	4 (11)	
Grade 3	14 (11)	10 (12)	4 (11)	
CLIF-SOFA score, median (IQR)	7 (4–10)	7 (4–10)	7 (5–9)	.65
SOFA score, median (IQR)	6 (4–9)	6 (3–8)	6 (4–9)	.88
Model for end-stage liver disease at BSI, median (IQR)	19 (14–26)	19 (14–26)	19 (14–26)	.90
Sepsis	18 (15)	7 (9)	11 (30)	.003
Septic shock	22 (13)	18 (22)	4 (11)	.20
Renal failure (creatinine ≥2 mg/dL)	29 (24)	21 (26)	8 (22)	.81
Estimated clearance of creatinine (mL/min/1.73 m^2), median (IQR)	48 (30–78)	53 (28–80)	47 (31–76)	.93
ICU admission	41 (33)	30 (35)	11 (29)	.49
Need for mechanical ventilation	27 (23)	19 (23)	8 (22)	.99
Empiric treatment				
Piperacillin-tazobactam	82 (69)	52 (63)	30 (81)	.05
Meropenem	30 (25)	23 (28)	7 (19)	.29
Imipenem	7 (6)	7 (8)	0 (0)	.10
Empirical combination	55 (46)	41 (50)	14 (38)	.21
Anti-methicillin-resistant *Staphylococcus aureus* coverage[a]	35 (29)	26 (32)	9 (24)	.41
Fluoroquinolone	7 (6)	4 (5)	3 (8)	.68

Table 1. Continued

Variable	Total (N = 119) (100%)	Intermittent Infusion (n = 82) (69%)	Continuous/Extended Infusion (n = 37) (31%)	*P* Value
Antifungal therapy	6 (5)	6 (7)	0 (0)	.17
Other[b]	7 (6)	5 (6)	2 (5)	.99
Timing of empiric treatment (from infection onset)				
Less than 6 hours	101 (85)	69 (84)	32 (86)	.74
Between 6 and 24 hours	11 (9)	10 (12)	1 (3)	.17
More than 24 hours	7 (6)	3 (3)	4 (10)	.20
Definitive treatment				
Piperacillin-tazobactam	31 (26)	14 (17)	17 (46)	.001
Meropenem	11 (9)	5 (6)	6 (16)	.10
Mipenem	4 (5)	1 (1)	3 (8)	.09
Antibiotic daily dosages				
Piperacillin-tazobactam (g), median (IQR)	13.5 (9–13.5)	13.5 (9–13.5)	13.5 (9–18)	.12
Meropenem (g), median (IQR)	3 (2–3)	3 (2–3)	3 (2–4)	.75

Abbreviations: BSI, bloodstream infection; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; ICU, intensive care unit; IQR, interquartile range; SBP, spontaneous bacterial peritonitis.

[a]A total of 14 patients received vancomycin, 8 teicoplanin, 4 daptomycin, 4 tigecycline, and 2 linezolid.

[b]A total of 4 patients received amikacin, 2 colistin, 1 gentamycin.

index BCs up to discharge, death, or 90 days. Statistical significance was set for a *P* value <.05. All analyses were performed using Stata IC 31.1 (Stata Corp, College Station, TX).

RESULTS

During the study period, 323 patients with BSI were enrolled in the core BICHROME study. Excluded patients had incomplete data (7 cases), had a single BSI caused by coagulase-negative staphylococci (2 cases), were recipients of a liver transplant (2 cases), received inadequate empirical treatment (122 cases), or received adequate empirical treatment with drugs other than TZP or carbapenems (71 cases). Thus, 119 unique patients receiving adequate empirical treatment with TZP or carbapenems were analyzed in this study (Figure 1). Overall, C/EI of TZP or

Table 2. Causative Pathogen Distribution Among Patients Treated With Piperacillin-tazobactam or Carbapenem. Differences of Isolates Among Patients Receiving Intermittent Administration and Among Patient Treated With Continuous/Extended Infusion of Antimicrobial

Variable	Total (N = 119) (100%)	Intermittent Infusion (n = 82) (69%)	Continuous/Extended Infusion (n = 37) (31%)	*P* Value
Gram-positive aerobic cocci	41 (37)	34 (41)	7 (19)	.02
Methicillin susceptible-*Staphylococcus aureus*	21 (18)	18 (22)	3 (8)	.07
Streptococcus spp.	8 (6)	8 (9)	0 (0)	.06
Enterococcus spp.	9 (8)	5 (6)	4 (11)	.45
Other gram-positives[a]	4 (3)	4 (5)	0 (0)	.31
Gram-negative aerobic bacilli	77 (65)	46 (56)	31 (84)	.003
Enterobacteriaceae	62 (52)	39 (48)	23 (62)	.14
Escherichia coli	38 (32)	29 (35)	9 (24)	.29
Klebsiella pneumoniae	11(9)	5 (6)	6 (16)	.09
Other Enterobacteriaceae[b]	13 (11)	5 (6)	8 (22)	.02
Extended-spectrum β-lactamase Enterobacteriaceae	18 (14)	9 (11)	9 (24)	.09
Carbapenem-resistant Enterobacteriaceae	2 (2)	0 (0)	2 (5)	.09
Nonfermenters	15 (12)	7 (8)	8 (21)	.04
Pseudomonas aeruginosa	11 (7)	5 (6)	6 (16)	.09
Other nonfermenters	4 (3)	2 (2)	2 (5)	.58
Multidrug resistant gram-negative	24 (20)	12 (15)	12 (32)	.02
Anaerobes	4 (3)	3 (4)	1 (3)	.99
Piperacillin-tazobactam MIC[c] (mg/L), median (IQR)	4 (4–4)	4 (4–4)	4 (4–8)	.01
Meropenem MIC[d] (mg/L), median (IQR)	0.25 (0.125–0.25)	0.25 (0.125–0.25)	0.25 (0.25–0.5)	0.02

Abbreviations: IQR, interquartile range; MIC, minimal inhibitory concentration.

[a]Three cases of methicillin susceptible coagulase-negative staphylococci, 1 case of *Listeria monocytogenes* bloodstream infection.

[b]Five cases of *Enterobacter* spp., 3 cases of *Klebsiella oxytoca*, 2 cases of Citrobacter spp., 1 case of *Proteus mirabilis*, 1 case of *Escherichia hermannii*, and 1 case of *Morganella morganii*.

[c]Available in 108 cases.

[d]Available in 102 cases.

carbapenems was used in 37 patients (31%) receiving empirical therapy and in 26 (21%) receiving both empirical and definitive therapy with the study drugs. No patients who continued TZP or carbapenem changed the modality of infusion (ie, from intermittent administration to C/EI or vice versa).

Patients treated with and without C/EI were compared. No differences were found in the antibiotic administration strategies when analyzed by demographics and cirrhosis characteristics. However, differences were found for hospital-acquired infections (68% vs 45%, $P = .02$) and intraabdominal infections (other than spontaneous bacterial peritonitis; 32% vs 16%, $P = .04$), which were more common in the C/EI group (Table 1). In addition, patients treated with C/EI were more likely to fulfill sepsis criteria (30% vs 9%, $P = .003$) when compared with patients treated with intermittent infusion of TZP and carbapenems.

Microbiology

Detailed pathogen distribution is shown in Table 2. Patients who received C/EI of TZP or carbapenems had higher prevalence of gram-negative infection (84% vs 56%, $P = .003$), including non-*Escherichia coli* non-*Klebsiella pneumoniae* Enterobacteriaceae (22% vs 6%, $P = .02$) and nonfermenting bacilli (21% vs 8%, $P = .04$). We also found a trend toward higher incidence of carbapenem-resistant Enterobacteriaceae (5% vs 0%) and extended spectrum β-lactamase–producing Enterobacteriaceae (24% vs 11%) among patients receiving TZP or carbapenems in C/EI infusion, with a significant difference in terms of any MDR gram-negatives (32% vs 15%, $P = .02$).

Outcome

At the end of the 30-day follow-up, 30 of 119 patients (25%) had died with a median (IQR) time to death of 9 days (2–20) from index BSI. Kaplan-Meier curves demonstrated that patients who received C/EI of TZP or carbapenems had significantly higher survival rates (89% vs 68%, $P = .02$; Figure 2) with a mortality hazard ratio (HR) of 0.28 (95% confidence interval [CI], 0.10–0.88; $P = .03$).

To assess risk factors for mortality, survivors and nonsurvivors from the entire cohort were compared (see Supplementary Table). The impact of C/EI on outcome was then analyzed using a Cox regression model adjusted for CLIF-SOFA and infection source. C/EI of TZP or carbapenem (either empirical or definite treatment) was associated with significantly lower mortality (HR, 0.41; 95% CI, 0.11–0.96; $P = .04$; Table 3). When patients were matched on the basis of the presence of sepsis, biliary source of infection, CLIF-SOFA score, hepatitis B virus infection, *Pseudomonas aeruginosa* infection, admission diagnosis with infection, treatment of gram-negative pathogen, and study site, the ATE of C/EI was estimated to be between 11.3% and 25.6% reduction in 30-day mortality depending on whether therapy was administered empirically or as a definitive therapy (Table 4). The greatest treatment effect was estimated for patients who received

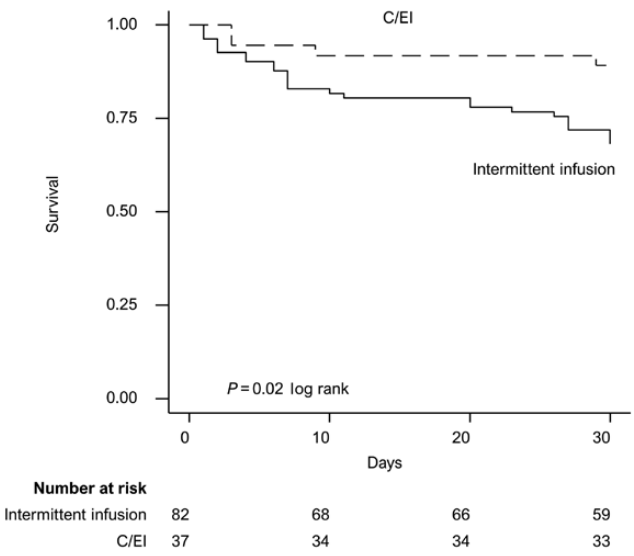

Figure 2. Kaplan-Meier curves for 30-day mortality. Comparison of outcome in patients receiving continuous/extended vs intermittent infusion of piperacillin-tazobactam or carbapenems in patients with liver cirrhosis and bloodstream infection. Abbreviation: C/EI, continuous/extended infusion.

C/EI as part of an empirical antimicrobial regimen, with 25.6% reduction (95% CI, 18.9–32.3; $P < .0001$) in 30-day mortality.

Subgroup Analysis

The efficacy of C/EI over intermittent administration was also assessed in critically ill cirrhotic patients. As shown in Figure 3, patients with sepsis or septic shock (HR, 0.21; (95% CI, 0.06–0.74; $P = .015$), ACLF (HR, 0.29; 95% CI, 0.03–0.99; $P = .048$), and higher MELD (HR, 0.26; 95% CI, 0.08–0.92; $P = .048$) or higher CLIF-SOFA (HR, 0.28; 95% CI, 0.08–0.92; $P = .04$) had a significant benefit from the receipt of empirical C/EI of TZP or carbapenems. Finally, C/EI was associated with a better outcome in patients with isolation of gram-negative bacteria (HR, 0.38; 95% CI, 0.12–0.99; $P = .048$) but not in case of gram-positive cocci (HR, 0.38; 95% CI, 0.05–2.95; $P = .35$).

Impact of Empirical Treatment With C/EI Infusion of TZP or Carbapenem on Duration of In-hospital Stay

The median length of in-hospital stay after the diagnosis of BSI was 15 (IQR, 9–28) days. No differences were found between patients who received C/EI or intermittent infusion of antibiotics (16 [11–29] vs 15 [7–29] days, $P = .68$). However, after considering in-hospital mortality as a competing event, receipt of β-lactams by C/EI was associated with a significantly higher rate of hospital discharge within 90 days (SHR [95% CI],1.62 [1.06–2.47]; $P = .026$; Supplementary Figure).

DISCUSSION

In this analysis of a prospective multicenter study of cirrhotic patients with BSI, the administration of C/EI infusion of TZP

Table 3. Multivariable Cox Regression Model for 30-Day Mortality

Model Covariate	Hazard Ratio	95% Confidence Interval	*P* Value
Chronic liver failure-sequential organ failure assessment	1.37	1.24–1.52	<.0001
Spontaneous bacterial peritonitis as source of bloodstream infection	2.43	1.14–5.20	.02
Continuous or extended infusion of piperacillin-tazobactam or carbapenem	0.41	0.11–0.96	.04

and carbapenems was associated with improved survival. To date, no studies have reported on the efficacy of C/EI of β-lactams in patients with liver cirrhosis. Previous randomized studies in different patient populations have demonstrated significant improvements in clinical outcome and survival in patients who received β-lactams or carbapenems by extended vs intermittent bolus infusion [15, 16, 25]. However, no patients with liver cirrhosis were reported in some of these studies [15] or were excluded in others [25].

β-lactams are considered to exhibit time-dependent PD. Hence, bactericidal activity is maximized by maintaining free serum drug concentrations above the minimum inhibitory concentration (MIC) for a minimum 40%–60% of the dosing, although dosing to achieve 100% of time above the MIC or exceeding 4 times the MIC value has been advocated in the critically ill and to suppress the development of resistance, respectively [26, 27]. C/EI strategies are critical for achieving these PK/PD targets for antibiotics such as TZP and most carbapenems, which have relatively short serum half-lives in patients without severe renal dysfunction [8, 25].

An important observation from our study is that a greater benefit of C/EI therapy was observed in the earliest phases of the infection. Indeed, empirical C/EI infusion of β-lactam was an independent factor related to lower odds of mortality, even after adjustment for confounders. Previous studies reported that C/EI of β-lactams achieves or maintains higher antibiotic exposures in the serum, interstitial, and epithelial lining fluid of the lung in critically ill patients compared to bolus infusions [28]. This aspect is particularly important during the early phase of sepsis as insufficient exposures with β-lactam antibiotics are common in this population with conventional dosages [29]. In patients with liver cirrhosis, edema and ascites result in markedly increased volume of distribution compounded by lower antibiotic protein binding and potentially increased antibiotic clearance of free drug, resulting in an insufficient drug serum concentration during the first days of antimicrobial treatment when the bacterial inoculum is highest [11, 29].

Continuous infusion of β-lactams may be necessary to deal with difficult-to-treat MDR pathogens. In fact, earlier anecdotal studies suggested that pathogens with a higher MIC can be adequately treated when C/EI of β-lactams is used [17]. This aspect is of interest in the field of cirrhotic patients as this setting is particularly involved by the spread of MDRs [30]. In our study, 20% of isolates where classified as MDR gram-negatives, and the prevalence was higher in the group of patients who received C/EI of TZP or carbapenems. Recent expert recommendations have endorsed unit-wide adoption of C/EI strategies for β-lactams when local data report a higher rate of MDR pathogens [31]. Therefore, in the absence of randomized, controlled trials, it is of interest whether data from prospective multicenter observational trials support these recommendations, particularly in the cirrhotic population.

Beyond the major prevalence of MDR pathogens, other significant differences were found in patients treated with C/EI of TZP and carbapenems when compared with patients who received intermittent administration of the same drugs in our study. Indeed, patients who received β-lactams via C/EI had higher prevalence of hospital-acquired infection and IAI, which are risk factors for antibiotic failure and poorer survival [32–35]. Importantly, our data suggest that C/EI was particularly useful in cirrhotic patients with sepsis or septic shock, ACLF, higher MELD, and higher CLIF-SOFA.

Our study has several limitations. First, the core BICHROME study was designed to explore the contemporary epidemiology of BSI in patients with liver cirrhosis. Thus, we did not collect several important variables, including serum trough levels of

Table 4. Estimated Average Treatment Effect of Continuous or Extended Infusion Strategies of Piperacillin-tazobactam or Meropenem on 30-Day Mortality of Bloodstream Infection

Propensity-adjusted Treatment Group[a]	Average Treatment Effect (% Reduction in 30-Day Mortality)	*P* Value
Receipt of empiric continuous/extended infusion piperacillin-tazobactam or meropenem (empiric therapy)	25.6 (18.9–32.3)	<.0001
Receipt of both empiric and definitive continuous/extended piperacillin-tazobactam or meropenem (definitive therapy group)	11.3 (0.9–23.6)	.002

[a]Variables used to create propensity score were sepsis, biliary source of infection, chronic liver failure-sequential organ failure assessment score, hepatitis B virus infection, *Pseudomonas aeruginosa* infection, admission diagnosis with infection, infection with gram-negative pathogen, and treatment site.

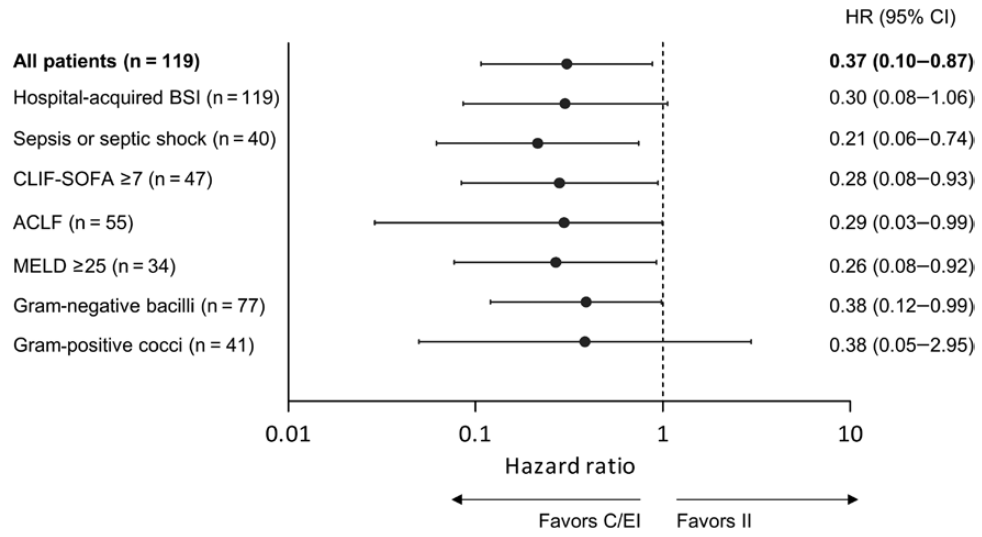

Figure 3. Effect of β-lactam C/EI in critically ill cirrhotic patients and among patients with isolation of gram-positive cocci or gram-negative bacilli. Abbreviations: ACLF, acute-on-chronic liver failure; BSI, bloodstream infection; C/EI, continuous/extended infusion; CI, confidence interval; CLIF-SOFA, chronic liver failure-sequential organ failure assessment; HR, hazard ratio; MELD, model for end-stage liver disease.

β-lactams, that would confirm improved PK/PD performance of the C/EI strategy. Additionally, we collected only MIC generated by automated systems (eg, Vitek) that do not provide precise MICs above resistance breakpoints. Second, as the use of C/EI or intermittent administration was not dictated by study protocol, the outcomes associated with infusion strategies may be biased by other unrecorded factors, for example, variables related to the centers where C/EI is more commonly used. However, to address these potential biases, we reevaluated our results after matching our population for the propensity of receiving C/EI of TZP or carbapenems, including the enrolling center. Despite these limitations, our results are consistent with previous reports in noncirrhotic populations and come from a prospective multicenter study. This latter aspect represents the main strength of our report.

In conclusion, C/EI of β-lactams to treat BSI in cirrhotic patients is associated with improved outcome and achieves the best performance when used as empirical treatment in the early phase of infection.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. Mi. Ba., M. G., R. E. L., Ma. Be., P. C., G. V., and P. V. contributed to the study design; Mi. Ba., M. P., C. S., T. B., M. M., N. C. T., E. S., P. R., M. C., P. M., M. T., P. B., M. T. C., E. C., B. B., A. E. M., N. P., M. A. G. L., Y. Z. D., M. D., J. R-B., and G. D. gathered clinical data; Mi. Ba., Ma. Ba., and R. E. L. analyzed the data; Mi. Ba., M. G., S. T., R. E. L., and P. V. wrote the manuscript; all authors read and approved the final manuscript.

Acknowledgments. The authors thank the ESGBIS and BICHROME study groups (collaborators): Caterina Campoli, Renato Pascale (Infectious Diseases Unit, Department of Medical and Surgical Sciences, Sant'Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy); Andreas Stallmach (Department of Internal Medicine IV, Jena University Hospital, Friedrich Schiller University, Jena, Germany); Mario Venditti (Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy); Cristina Lucidi (Division of Gastroenterology, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy); Serena Ludovisi (Department of Infectious Diseases, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy); Marina de Cueto, Navarro Maria Dolores, Lopez Cortes Eduardo (Unidad Clínica Intercentros de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospitales Universitarios Virgen Macarena y Virgen del Rocío-IBIS, Seville, Spain); Emilo Bouza, Maricela Valerio, Alia Eworo (Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Madrid, Spain); Raffaella Losito, (Institute of Infectious Diseases, Policlinico Universitario Agostino Gemelli, Rome, Italy); Marco Senzolo, Elena Nadal (Multivisceral Transplant Unit, Department of Surgery, Oncology, and Gastroenterology, Padova University Hospital, Italy); Antonio Ottobrelli (Gastrohepatology Unit, AOU Città della Salute e della Scienza di Torino, University of Turin, Turin, Italy); Martina Varguvic (Infectious Diseases, University Hospital for Infectious Diseases "Dr Fran Mihaljevic", Zagreb, Croatia); Cristina Badia (Infectious Disease Unit, Service of Internal Medicine, Hospital Universitari Mútua de Terrassa, Terrassa, Barcelona, Spain); Borgia Guglielmo, Ivan Gentile, Antonio Riccardo Buonomo (Department of Clinical Medicine and Surgery, Section of Infectious Diseases, University of Naples Federico II, Naples, Italy); Evangelo Boumis (2nd Infectious Diseases Division, National Institute for Infectious Diseases L. Spallanzani, Rome, Italy); Alicia Beteta-Lopez (Clinical Microbiology, Nuestra Senora del Prado Hospital); Alessia Rianda (Hepatology and Infectious Diseases Unit, National Institute for Infectious Diseases L. Spallanzani, Rome, Italy); and Gloria Taliani, Stefania Grieco (Infectious and Tropical Diseases Unit, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy).

Financial support. J. R.-B. and P. R. receive funds for research from Plan Nacional de I+D+i 2013-2016 and Instituto de Salud Carlos III, Subdirección General de Redes y Centros de Investigación Cooperativa, Ministerio de Economía, Industria y Competitividad, Spanish Network for Research in Infectious Diseases (REIPI RD16/0016/0001), cofinanced by European Development Regional Fund "A Way to Achieve Europe," Operative Programme Intelligent Growth 2014–2020.

Potential conflicts of interest. J. R-B. received honoraria for accredited educational activities funded through unrestricted grants from Merck and for coordinating a nonproduct-related research project from AstraZeneca. T. B. reports personal fees from Intercept Pharmaceuticals, Falk Foundation, AbbVie, and Gilead outside the submitted work. P. B. reports personal fees and nonfinancial support from kEDRION, BIOTEST, and CHIESI FARMACEUTICI outside the submitted work. E. C. reports personal fees from Pfizer, Merck Sharp & Dohme, and ASTELLAS outside the submitted work. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Leon DA, McCambridge J. Liver cirrhosis mortality rates in Britain from 1950 to 2002: an analysis of routine data. Lancet **2006**; 367:52–6.
2. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol **2014**; 60:1310–24.
3. Fernández J, Acevedo J, Castro M, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology **2012**; 55:1551–61.
4. Pant C, Olyaee M, Gilroy R, et al. Emergency department visits related to cirrhosis: a retrospective study of the nationwide emergency department sample 2006 to 2011. Medicine **2015**; 94:e308.
5. Bartoletti M, Giannella M, Lewis RE, Viale P. Bloodstream infections in patients with liver cirrhosis. Virulence **2016**; 7:309–19.
6. 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–e8.
7. Kalil AC, Syed A, Rupp ME, et al. Is bacteremic sepsis associated with higher mortality in transplant recipients than in nontransplant patients? A matched case-control propensity-adjusted study. Clin Infect Dis **2015**; 60:216–22.
8. Rodríguez-Baño J, López-Prieto MD, Portillo MM, et al; SAEI/SAMPAC Bacteraemia Group. Epidemiology and clinical features of community-acquired, healthcare-associated and nosocomial bloodstream infections in tertiary-care and community hospitals. Clin Microbiol Infect **2010**; 16:1408–13.
9. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. J Hepatol **2014**; 61:1385–96.
10. Bartoletti M, Lewis RE, Giannella M, Tedeschi S, Viale P. The role of extended infusion β-lactams in the treatment of bloodstream infections in patients with liver cirrhosis. Expert Rev Anti Infect Ther **2018**; 16:771–9.
11. Westphal JF, Jehl F, Vetter D. Pharmacological, toxicologic, and microbiological considerations in the choice of initial antibiotic therapy for serious infections in patients with cirrhosis of the liver. Clin Infect Dis **1994**; 18:324–35.
12. Fernandez J, Acevedo J, Wiest R, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut **2018**; 67:1870–1880.
13. Bartoletti M, Giannella M, Caraceni P, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. J Hepatol **2014**; 61:51–8.
14. Hsieh CC, Lee CC, Chan TY, Hong MY, Chi CH, Ko WC. Clinical features and impact of empirical therapy in cirrhotic adults with community-onset bacteremia. Am J Emerg Med **2015**; 33:222–8.
15. Dulhunty JM, Roberts JA, Davis JS, et al. Continuous infusion of beta-lactam antibiotics in severe sepsis: a multicenter double-blind, randomized controlled trial. Clin Infect Dis **2013**; 56:236–44.
16. Roberts JA, Abdul-Aziz MH, Davis JS, et al. Continuous versus intermittent β-lactam infusion in severe sepsis. a meta-analysis of individual patient data from randomized trials. Am J Respir Crit Care Med **2016**; 194:681–91.
17. Moriyama B, Henning SA, Childs R, et al. High-dose continuous infusion beta-lactam antibiotics for the treatment of resistant *Pseudomonas aeruginosa* infections in immunocompromised patients. Ann Pharmacother **2010**; 44:929–35.
18. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis **1987**; 40:373–83.
19. Friedman ND, Kaye KS, Stout JE, et al. Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med **2002**; 137:791–7.
20. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA **2016**; 315:801–10.
21. Piano S, Bartoletti M, Tonon M, et al. Assessment of Sepsis-3 criteria and quick SOFA in patients with cirrhosis and bacterial infections. Gut **2018**; 67:1892–9.
22. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology **2013**; 144:1426–37, 37 e1-9.
23. EUCAST guidelines for detection of resistance mechanisms and specific resistances of clinical and/or epidemiological importance. European Committee on Antimicrobial Susceptibility Testing, **2013**. Available at: http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_v1.0_20131211.pdf.
24. 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**; 18:268–81.
25. Abdul-Aziz MH, Sulaiman H, Mat-Nor MB, et al. Beta-Lactam Infusion in Severe Sepsis (BLISS): a prospective, two-centre, open-labelled randomised controlled trial of continuous versus intermittent beta-lactam infusion in critically ill patients with severe sepsis. Intensive Care Med **2016**; 42:1535–45.
26. Fantin B, Farinotti R, Thabaut A, Carbon C. Conditions for the emergence of resistance to cefpirome and ceftazidime in experimental endocarditis due to *Pseudomonas aeruginosa*. J Antimicrob Chemother **1994**; 33:563–9.
27. Osthoff M, Siegemund M, Balestra G, Abdul-Aziz MH, Roberts JA. Prolonged administration of β-lactam antibiotics—a comprehensive review and critical appraisal. Swiss Med Wkly **2016**; 146:w14368.
28. Roberts JA, Kirkpatrick CM, Roberts MS, Robertson TA, Dalley AJ, Lipman J. Meropenem dosing in critically ill patients with sepsis and without renal dysfunction: intermittent bolus versus continuous administration? Monte Carlo dosing simulations and subcutaneous tissue distribution. J Antimicrob Chemother **2009**; 64:142–50.
29. Taccone FS, Laterre PF, Dugernier T, et al. Insufficient β-lactam concentrations in the early phase of severe sepsis and septic shock. Crit Care **2010**; 14:R126.
30. Fernández J, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. J Hepatol **2016**; 65:1043–54.
31. Roberts JA, Abdul-Aziz MH, Lipman J, et al; International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis **2014**; 14:498–509.
32. Boussekey N, Cantrel J, Dorchin Debrabant L, et al. Epidemiology, prognosis, and evolution of management of septic shock in a French intensive care unit: a five years survey. Crit Care Res Pract **2010**; 2010:436427.
33. Adnan S, Paterson DL, Lipman J, et al. Pharmacokinetics of beta-lactam antibiotics in patients with intra-abdominal disease: a structured review. Surg Infect (Larchmt) **2012**; 13:9–17.
34. Campillo B, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of infection. Clin Infect Dis **2002**; 35:1–10.
35. Cheong HS, Kang CI, Lee JA, et al. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. Clin Infect Dis **2009**; 48:1230–6.