Extended infusion of β-lactams for bloodstream infection in patients with liver cirrhosis: an observational multicenter study

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Summary: Empiric continuous or extended infusion of β-lactam antibiotics was associated with improved survival in cirrhotic patients with bloodstream infection. Patients managed with continuous or extended infusion of β-lactams were discharged earlier than patients treated with intermittent administration of the same drugs.

ABSTRACT

We analyzed the impact of continuous/ extended infusion (C/EI) versus 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 enrolling 312 cirrhotic patients with BSI. In this secondary analysis we selected patients receiving TZP or carbapenems as adequate empiric 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 empiric treatment. Patients who received C/EI had a significantly lower mortality rate (16% vs 36%, P=0.047). In a Cox-regression model, the administration of C/EI was associated with a significantly lower mortality [HR 0.41(95% CI 0.11-0.936), P=0.04] 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<0.0001) estimated with propensity score matching. A significant reduction of 30-day mortality was also observed in the subgroups of patients with sepsis [HR 0.21 (95%CI 0.06-0.74), P=0.015)], acute-on-chronic liver failure [HR 0.29 (95%CI 0.03-0.99] and a MELD score ≥ 25 [HR 0.26 (95%CI 0.08-0.92), P=0.048)]. At competing risk analysis, C/EI of beta-lactams was associated with a significantly higher rates of hospital discharge [SHR (95%CI): 1.62 (1.06-2.47); P=0.026].

CONCLUSION

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

INTRODUCTION

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 requiring hospital admission in patients with liver cirrhosis are due to primary or secondary bacteremia with associated mortality rates between 25-58% [5, 6], which is significantly higher than that in non-cirrhotic patients with bacteremia [7, 8]. Several aspects 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 the renal clearance, significantly altering drugs pharmacokinetic/pharmacodynamic (PK/PD) behavior [10]. These pharmacokinetic changes may be driven by hypoalbuminemia and reduced binding to proteins as well as altered distribution due to the “third space” expansion, especially in patients with large volume of ascites [11].

Several studies have documented the importance of adequate empiric antibiotic treatment for reducing infection-related mortality in patients with liver cirrhosis [12-14]. In most studies, however, appropriate empiric 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 the cirrhotic population or the

impact of altered PK behavior of antibiotics on treatment outcome of bloodstream infection [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].

The aim of 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 empiric and definitive therapy for BSI.

METHODS

The present report is a secondary analysis of the BICHROME study, a prospective multicenter study conducted in nineteen 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 (>18 years) cirrhotic patients with BSI. Patients with previous liver transplantation and other concomitant infections were excluded. For each patient only the first episode of BSI was considered. 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 board in participating hospitals. Written informed consent was obtained from patients or from legal surrogates before enrolment.

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

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

Patients 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 till day 30 with either outpatient visit or telephone call.

Data collection and definitions

Data was 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 variables were collected at enrolment: 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 (HCC); presence of other co-morbidities according to the Charlson score [18]. BSI were 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 one antibiotic was active in vitro against the isolated pathogen. Definitive therapy was defined as treatment administration according with the susceptibility 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 h). Outcome variables included the need of intensive care unit (ICU) 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 the use of an automated blood culture detector system, the performance of Gram stain and/or rapid test (such as MALDI-TOF, PNA FISH) with immediate communication of the preliminary information to the attending physicians, the 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 done according with EUCAST guidelines [23]. Pathogens were classified as multidrug-resistant according to previous criteria [24].

Statistical analysis

Categorical variables were analyzed as absolute numbers and their relative frequencies. Continuous variables were analyzed as mean and standard deviation (SD) if normally distributed, or as median and interquartile range (IQR) if non-normally distributed. Categorical variables were compared using the $\chi 2$ test or Fisher exact test, whereas continuous variables were compared using the Mann-Whitney U or two-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 ($p < 0.1$) 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<0.05 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/IE 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 subject was estimated by using an average of the outcomes of similar subjects that receive the other infusion strategy. Similarity between subjects is based on estimated treatment probabilities, known as propensity scores (PS). The ATE is then computed by taking the average of the difference between the observed and potential outcomes for each subject. 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 sub distribution hazards (SHR). This model allows a simultaneous estimation of two independent competing events: discharge and death with death being the competing event that hindered the observation of the event of interest that was time to hospital discharge. Patients were considered from the index BCs up to discharge, death or 90 days. Statistical significance was set for P value <0.05. All analysis was performed using Stata IC 31.1 (Stata Corp, College Station, Texas).

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 CoNS (2 cases), were recipient of liver transplant (2 cases), received inadequate empirical treatment (122 cases) or received adequate empirical treatment with different drugs from 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 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 that continued TZP or carbapenem changed the modality of infusion (i.e. 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=0.02) and intra-abdominal infections (other than SBP) (32% vs 16%, P=0.04), which were more common in the C/EI group (Table1). In addition, patients treated with C/EI were more likely to fulfill sepsis criteria (30% vs 9%, P=0.003) when compared with patients treated with intermittent infusion of TZP and carbapenems.

Microbiology

Detailed pathogens distribution is shown in Table 2. Patients receiving C/EI of TZP or carbapenems had higher prevalence of Gram-negative infection (84% vs 56%, P=0.003), including non-*Escherichia coli* non-*Klebsiella pneumoniae* Enterobacteriaceae (22% vs 6%, P=0.02) and non-fermenting bacilli (21% vs 8%, P=0.04). We also found a trend toward higher incidence of carbapenem-resistant(CR)-Enterobacteriaceae (5% vs 0%) and extended spectrum β-lactamase(ESBL)-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=0.02).

Outcome

At the end of 30-day follow-up, 30 out of 119 patients (25%) died with a median (IQR) time to death of 9 days (2-20) from index BSI. Kaplan-Meier curves demonstrated that patients receiving C/EI of TZP or carbapenems had significantly higher survival rates (89% vs 68%, P=0.02) (Figure 2) with mortality HR 0.28 (95%CI 0.10-0.88, P=0.03).

To assess risk factors for mortality, survivors and non-survivors of 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. The administration of C/EI of TZP or carbapenem (either empiric or definite treatment) was associated with significantly lower mortality [HR 0.41(95% CI 0.11-0.96), P=0.04] (Table 3). When patients were matched on the basis of the presence of sepsis, biliary source of infection, CLIF-SOFA score, HBV infection, *Pseudomonas*

aeruginosa infection, admission diagnosis with infection, treatment of Gram-negative pathogen, and study site, the ATE of C/EI was estimated between as a 11.3 to 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 C/EI as part of an empiric antimicrobial regimen, with 25.6% reduction (95% CI 18.9-32.3, P<0.0001) 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=0.015)], ACLF [HR 0.29 (95%CI 0.03-0.99), P=0.048)], and higher MELD [HR 0.26 (95%CI 0.08-0.92), P=0.048)] or higher CLIF-SOFA [HR 0.28 (95%CI 0.08-0.92), P=0.04)], had a significant benefit from the receipt of empirical C/EI of TZP or carbapenems. Finally, C/EI was associated to a better outcome in patients with isolation of Gram-negative bacteria [HR 0.38 (95%CI 0.12-0.99), P=0.048] but not in case of Gram-positive cocci [HR 0.38 (95%CI 0.05-2.95) P=0.35].

Impact of empirical treatment with C/EI infusion of piperacillin-tazobactam or carbapenem on duration in-hospital stay

The median length of in-hospital stay after the diagnosis of BSI was of 15 (IQR 9-28) days. No differences were found between patients receiving C/EI or intermittent infusion of antibiotics [16 (11-29) vs 15 (7-29) days *P*=0.68]. However, after considering in-hospital mortality as a competing event, receipt of β-lactams by C/EI

of was associated with a significantly higher rate of hospital discharge within 90 days [SHR (95%CI):1.62 (1.06-2.47); P=0.026], (Supplementary Figure).

DISCUSSION

In this analysis of a prospective multicenter study of cirrhotic patients with BSI, the administration of C/EI infusion of TZP 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 versus 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 pharmacodynamics. Hence, bactericidal activity is maximized by maintaining free serum drug concentrations above the minimum inhibitory concentration (MIC) for at 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-life in patients without severe renal dysfunction [8, 25].

An important observation of our study is that a greater benefit of C/EI therapy was observed in the earliest phases of the infection. Indeed, empiric 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 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 also necessary dealing with difficult-to-treat MDR pathogens. In fact, earlier anecdotal studies suggested that pathogens with higher MIC can be adequately treated when C/EI of β-lactams is employed [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 receiving 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, it is of interest in the absence of randomized controlled trials, 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 MER when compared with patients receiving intermittent administration of the same drugs in our study. Indeed, patients who received β-lactams C/IE had higher prevalence of hospital-acquired infection and IAI, which are risk factors for antibiotic failure and poorer survival [32-

35]. Importantly, our data suggests 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 β-lactams, that would confirm improved PK/PD performance of the C/EI strategy. Additionally, we collected only MIC generated by automated systems (e.g., Vitek) which 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, e.g., variables related to the centers where C/EI is more commonly used. However, to address these potential biases, we re-evaluated our results after matching our population for the propensity of receiving C/EI of TZP or carbapenems including also the enrolling center. Despite these limitations, our results are consistent with previous report in non-cirrhotic population 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 achieve the best performance when used as empirical treatment in the early phase of infection.

Authors contribution

MiBa, MG, REL, MaBe, PC, GV, and PV contributed to the study design;

MiBa, MP, CS, TB, MM, NCT, ES, PR, MdC, PM, MT, PB, MTC, EC, BB, AEM, NP, MAGL, YZD, MD, JRB and GD gathered clinical data;

MiBa, MaBa, REL analysed the data;

MiBa, MG, ST, REL, and PV wrote the manuscript;

All authors read and approved the final manuscript.

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Conflict of Interest

JRB received honoraria for accredited educational activities funded through unrestricted grants from Merck and for coordinating a non-product related research project from AstraZeneca. Dr. Bruns reports personal fees from Intercept Pharmaceuticals, Falk Foundation, Abbvie, and Gilead, outside the submitted work. Dr. Burra reports personal fees and non-financial support from kEDRION, BIOTEST, and CHIESI FARMACEUTICI, outside the submitted work. Dr. Calbo reports personal fees from PFIZER, MSD, and ASTELLAS, outside the submitted work. All other authors declare no competing interests.

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Table 1. Differences in demographics, underlying disease, comorbidities and characteristics of infection among patients receiving intermittent administration and patients receiving continuous/extended infusion piperacillin-tazobactam or carbapenems

	Total, n=119 (100%)	**Intermittent infusion, n=82 (69%)**	**Continuous/ extended infusion n= 37 (31%)**	***P***
Demographic data				
Age (years) [mean (± SD)]	61 (±12)	59 (±12)	63 (± 9)	0.12
Male sex	81 (68)	56 (68)	25 (68)	0.93
Liver disease				
Viral cirrhosis	42 (35)	29 (35)	13 (35)	0.98
Alcoholic cirrhosis	32 (27)	23 (28)	9 (24)	0.82
NAFLD	12 (10)	8 (9)	4 (11)	0.99
Cryptogenic	19 (16)	11 (13)	8 (22)	0.28
Alcoholic + viral cirrhosis	11 (9)	8 (10)	3 (8)	0.99
Autoimmune disorder	3 (2)	3 (3)	0 (0)	0.55
Hepatocellular carcinoma	19 (16)	13 (16)	6 (16)	0.99
Admission diagnosis				

Ascitic decompensation	17 (14)	14 (17)	3 (8)	0.26
Acute kidney injury	5 (4)	5 (6)	0 (0)	0.18
Worsening of liver disease	11 (9)	8 (10)	3 (8)	0.99
Hepatic encephalopathy	11 (9)	6 (7)	5 (13)	0.32
Suspected bacterial infection	50 (44)	36 (45)	14 (38)	0.47
Co-morbidities				
Charlson index [median (IQR)]	6 (5-8)	7 (5-8)	6 (5-8)	0.84
Previous (<90 days) hospital admission	75 (64)	54 (67)	21 (57)	0.26
Previous (<90 days) ICU admission	11 (9)	10 (12)	1 (3)	0.17
BSI data				
Site of infection acquisition				
Community-acquired BSI	21 (18)	16 (19)	5 (13)	0.60
Hospital-acquired BSI	62 (52)	37 (45)	25 (68)	0.02
Healthcare associated	36 (30)	29 (35)	7 (19)	0.09
Source of BSI				
Primary	38 (32)	27 (33)	11 (30)	0.72
Pneumonia	11 (9)	9 (11)	2 (5)	0.50
SBP	21 (16)	17 (21)	4 (11)	0.30
Intra-abdominal (other than SBP)	25 (23)	13 (16)	12 (32)	0.04
Urinary tract	16 (14)	12 (15)	4 (11)	0.77
Infection severity				

ACLF	55 (46)	41 (50)	14 (38)	0.21
Grade 1	23 (19)	17 (21)	6 (15)	0.68
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)	0.65
SOFA score [median (IQR)]	6 (4-9)	6 (3-8)	6 (4-9)	0.88
MELD at BSI [median (IQR)]	19 (14-26)	19 (14-26)	19 (14-26)	0.90
Sepsis	18 (15)	7 (9)	11 (30)	0.003
Septic shock	22 (13)	18 (22)	4 (11)	0.20
Renal failure (creatinine ≥ 2 mg/dL)	29 (24)	21 (26)	8 (22)	0.81
Estimated clearance of creatinine (mL/min/1.73 m^2) [median (IQR)]	48 (30-78)	53 (28-80)	47 (31-76)	0.93
ICU admission	41 (33)	30 (35)	11 (29)	0.49
Need for mechanical ventilation	27 (23)	19 (23)	8 (22)	0.99
Empiric treatment				
Piperacillin-tazobactam	82 (69)	52 (63)	30 (81)	0.05
Meropenem	30 (25)	23 (28)	7 (19)	0.29
Imipenem	7 (6)	7 (8)	0 (0)	0.10

Empirical combination	55 (46)	41 (50)	14 (38)	0.21
Anti-MRSA coverage[a]	35 (29)	26 (32)	9 (24)	0.41
Fluoroquinolone	7 (6)	4 (5)	3 (8)	0.68
Antifungal therapy	6 (5)	6 (7)	0 (0)	0.17
Other[b]	7 (6)	5 (6)	2 (5)	0.99
Timing of empiric treatment (from infection onset)				
Less than 6 hours	101 (85)	69 (84)	32 (86)	0.74
Between 6 and 24 hours	11 (9)	10 (12)	1 (3)	0.17
More than 24 hours	7 (6)	3 (3)	4 (10)	0.20
Definitive treatment				
Piperacillin-tazobactam	31 (26)	14 (17)	17 (46)	0.001
Meropenem	11 (9)	5 (6)	6 (16)	0.10
Imipenem	4 (5)	1 (1)	3 (8)	0.09
Antibiotic daily dosages				
Piperacillin-tazobactam, grams, [median (IQR)]	13.5 (9-13.5)	13.5 (9-13.5)	13.5 (9-18)	0.12
Meropenem, grams [median (IQR)]	3 (2-3)	3 (2-3)	3 (2-4)	0.75

Abbreviations: SD standard deviation, NAFLD non-alcoholic fatty liver disease, BSI bloodstream infection, MELD model for end-stage liver disease, IQR interquartile range, ICU intensive care unit, ACLF acute-on-chronic liver failure, CLIF-SOFA chronic liver failure-sequential organ failure assessment, SOFA sequential organ failure assessment SBP spontaneous bacterial peritonitis

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

[b] 4 patients received amikacin, 2 colistin, 1 gentamycin

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.

	Total, n=119 (100%)	**Intermittent infusion, n=82 (69%)**	**Continuous/ extended infusion n= 37 (31%)**	***P***
Gram-positive aerobic cocci	41 (37)	34 (41)	7 (19)	0.02
Methicillin susceptible-*Staphylococcus aureus*	21 (18)	18 (22)	3 (8)	0.07
Streptococcus spp	8 (6)	8 (9)	0 (0)	0.06
Enterococcus spp	9 (8)	5 (6)	4 (11)	0.45
Other gram-positive[a]	4 (3)	4 (5)	0(0)	0.31
Gram-negative aerobic bacilli	77 (65)	46 (56)	31 (84)	0.003
Enterobacteriaceae	62 (52)	39 (48)	23 (62)	0.14

Escherichia coli	38 (32)	29 (35)	9 (24)	0.29
Klebsiella pneumoniae	11(9)	5 (6)	6 (16)	0.09
Other Enterobacteriaceae[b]	13 (11)	5 (6)	8 (22)	0.02
ESBL-Enterobacteriaceae	18 (14)	9 (11)	9 (24)	0.09
CR-Enterobacteriaceae	2 (2)	0 (0)	2 (5)	0.09
Non-fermenters	15 (12)	7 (8)	8 (21)	0.04
Pseudomonas aeruginosa	11 (7)	5 (6)	6 (16)	0.09
Other non-fermenters	4 (3)	2 (2)	2 (5)	0.58
MDR-Gram-negative	24 (20)	12 (15)	12 (32)	0.02
Anaerobes	4 (3)	3 (4)	1 (3)	0.99
Piperacillin-tazobactam MIC[c] mg/L, [median (IQR)]	4 (4-4)	4 (4-4)	4 (4-8)	0.01

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: BSI bloodstream infection; ESBL, extended-spectrum beta-lactamase, CR carbapenem-resistant, MDR multidrug resistant, MIC minimal inhibitory concentration

[a] 3 cases of methicillin susceptible coagulase-negative staphylococci, 1 case of *Listeria monocytogenes* BSI

[b] 5 cases of *Enterobacter* spp, 3 cases of *Klebsiella oxytoca*, 2 cases of Citrobacter spp, 1 case of *Proteus mirabilis*, 1 case of *Escherichia hermannii*, 1 case of *Morganella morganii*

[c] Available in 108 cases

[d] Available in 102 cases

Table 3. Multivariable Cox regression model for 30-day mortality

Model Covariate	**Hazard ratio**	**95% CI**	***P***
CLIF-SOFA	1.37	1.24-1.52	<0.0001
SBP as source of BSI	2.43	1.14-5.20	0.02
Continuous or extended infusion of piperacillin-tazobactam or carbapenem	0.41	0.11-0.96	0.04

Abbreviations: CLIF-SOFA chronic liver failure sequential organ failure assessment; SBP spontaneous bacterial peritonitis; BSI bloodstream infection; CI confidence interval

Table 4. The estimated average treatment effect (ATE) 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)	<0.0001
Receipt of both empiric and definitive continuous/ extended piperacillin-tazobactam or meropenem (definitive therapy group)	11.3 (0.9-23.6)	0.002

[a] Variables used to create propensity score were: Sepsis, biliary source of infection, CLIF-SOFA score, HBV infection, *P. aeruginosa* infection, admission diagnosis with infection, Infection with Gram-negative pathogen, treatment site**.**

Figure Legends:

Figure 1. Study flow-chart

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

Figure 3. Effect of beta-lactam continuous/extended infusion in critically-ill cirrhotic patients and among patients with isolation of Gram-positive cocci or Gram-negative bacilli

Abbreviations: HA hospital acquired, CLIF-SOFA chronic liver failure- sequential organ failure assessment; ACLF acute-on-chronic liver failure; MELD model for end-stage liver disease; HR hazard ratio; CI confidence interval

Figure 1

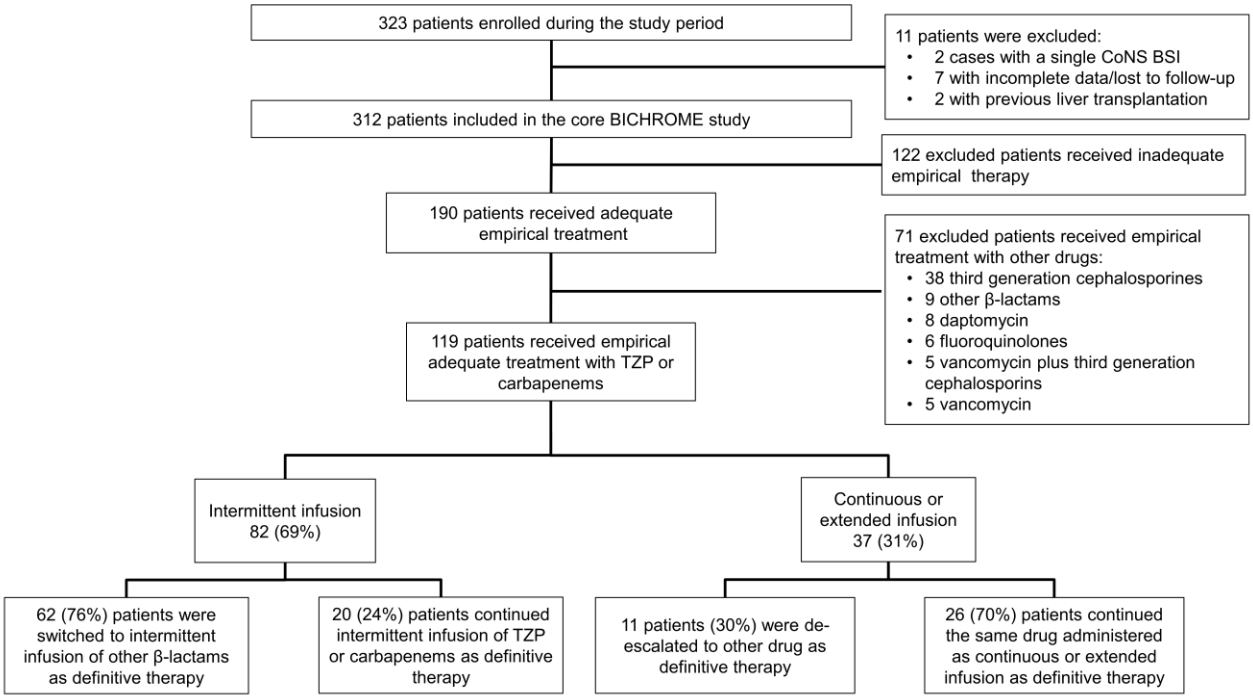
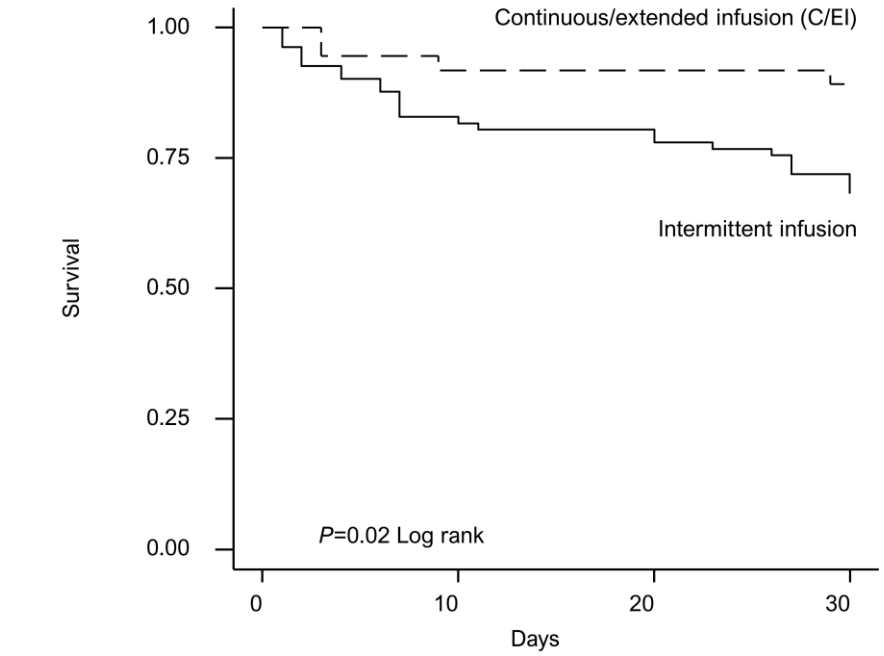
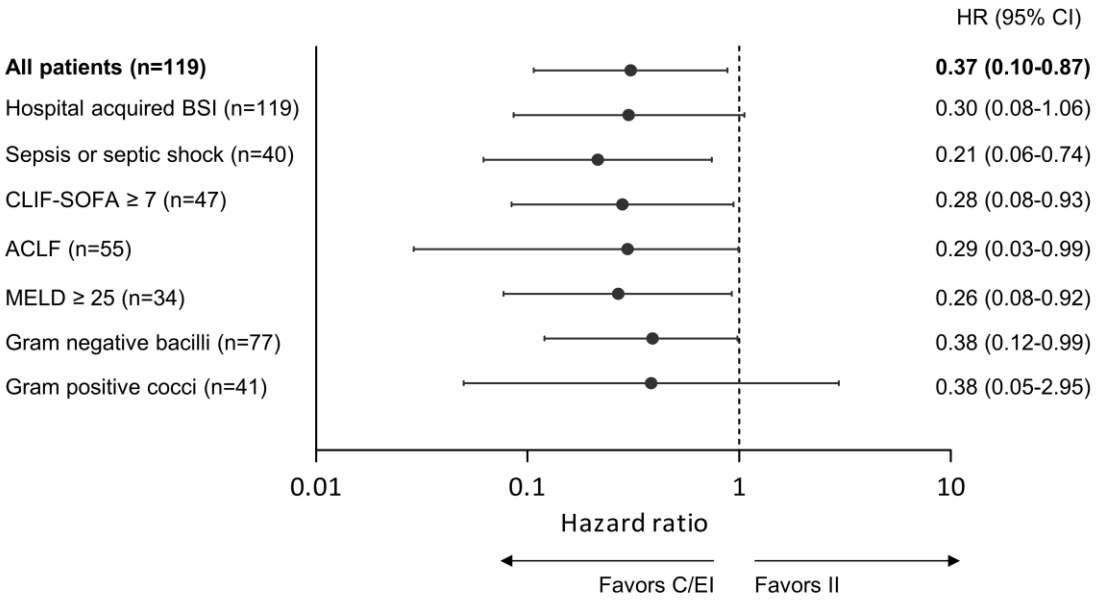

323 patients enrolled during the study period
11 patients were excluded:
• 2 cases with a single CoNS BSI
• 7 with incomplete data/lost to follow-up
• 2 with previous liver transplantation
312 patients included in the core BICHROME study
122 excluded patients received inadequate empirical therapy
190 patients received adequate empirical treatment
71 excluded patients received empirical treatment with other drugs:
• 38 third generation cephalosporines
• 9 other β-lactams
• 8 daptomycin
• 6 fluoroquinolones
• 5 vancomycin plus third generation cephalosporins
• 5 vancomycin
119 patients received empirical adequate treatment with TZP or carbapenems
Intermittent infusion 82 (69%)
Continuous or extended infusion 37 (31%)
62 (76%) patients were switched to intermittent infusion of other β-lactams as definitive therapy
20 (24%) patients continued intermittent infusion of TZP or carbapenems as definitive therapy
11 patients (30%) were de-escalated to other drug as definitive therapy
26 (70%) patients continued the same drug administered as continuous or extended infusion as definitive therapy

Figure 2



Number at risk				
Intermittent infusion	82	68	66	59
C/EI	37	34	34	33

Figure 3


HR (95% CI)
All patients (n=119)
0.37 (0.10-0.87)
Hospital acquired BSI (n=119)
0.30 (0.08-1.06)
Sepsis or septic shock (n=40)
0.21 (0.06-0.74)
CLIF-SOFA ≥ 7 (n=47)
0.28 (0.08-0.93)
ACLF (n=55)
0.29 (0.03-0.99)
MELD ≥ 25 (n=34)
0.26 (0.08-0.92)
Gram negative bacilli (n=77)
0.38 (0.12-0.99)
Gram positive cocci (n=41)
0.38 (0.05-2.95)
0.01
0.1
1
10
Hazard ratio
Favors C/EI
Favors II