Digestive and Liver Disease 51 (2019) 1300–1307

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Liver, Pancreas and Biliary Tract

# Evaluating the best empirical antibiotic therapy in patients with acute-on-chronic liver failure and spontaneous bacterial peritonitis

Andreas Wieser[a,b,c,1], Hanwei Li[d,*,1,2], Jiang Zhang[d], Ingrid Liss[d], Daniel Markwardt[d], Roman Hornung[e], Sebastian Suerbaum[a,c], Julia Mayerle[d], Alexander L. Gerbes[d], Christian J. Steib[d,*,2]

[a] Medical Microbiology and Hospital Epidemiology, Max von Pettenkofer Institute, Faculty of Medicine, LMU Munich, Germany
[b] Division of Infectious Diseases and Tropical Medicine, University Hospital, LMU Munich, Germany
[c] German Centre for Infection Research (DZIF), Partner Site Munich, Munich, Germany
[d] Department of Medicine II, University Hospital, LMU Munich, Germany
[e] Institute for Medical Information Processing, Biometry and Epidemiology (IBE), LMU Munich, Germany

ARTICLE INFO

*Article history:*
Received 12 October 2018
Accepted 25 February 2019
Available online 31 March 2019

*Keywords:*
Acute-on-chronic liver failure
Antimicrobial susceptibility
Empirical antibiotic therapy
Liver cirrhosis

ABSTRACT

*Background/aims:* Spontaneous bacterial peritonitis (SBP) is a life-threatening complication of advanced cirrhosis. By studying the susceptibility of isolated organisms and analyzing empirical antibiotic therapy combined with clinical outcomes, we aimed to find an improved empirical antibiotic therapy by considering the individual acute-on-chronic liver failure (ACLF) grade for patients with or without sepsis.
*Methods:* Clinical outcomes of 182 patients were assessed retrospectively with multivariable regression analysis. Each of the 223 isolates was individually evaluated regarding susceptibility results and intrinsic resistances.
*Results:* Piperacillin/tazobactam had the highest antimicrobial susceptibility among monotherapies/fixed combinations, which was significantly lower than combination therapies such as meropenem-linezolid (75.3% vs. 98.5%, $P < 0.001$). The sensitivity of pathogens to empirical antibiotic therapy correlated with significantly lower inpatient mortality (18.9% vs. 37.0%, $P = 0.018$), shorter inpatient stay ($16.3 \pm 10.2$ vs. $26.4 \pm 21.0$ days, $P = 0.053$) and shorter intensive care treatment ($2.1 \pm 4.5$ vs. $7.9 \pm 15.4$ days, $P = 0.016$). The largest difference of mortality was observed in patients with ACLF grade 3 (54.5% vs. 73.1% [sensitive vs. non-sensitive]).
*Conclusion:* All SBP patients benefited from efficient empirical antibiotic therapy, regarding the reduced inpatient mortality and complications. For SBP patients with ACLF grade 3 without sepsis, the combination therapy with meropenem-linezolid may be suitable considering the susceptibility results and the concentration in the peritoneal cavity.


## 1. Introduction

Acute-on-chronic liver failure (ACLF) is a common and serious complication of advanced liver cirrhosis [1–5]. Infection is one of the known risk factors for development of ACLF, which has been confirmed to be associated with high mortality [6,7]. In this context, patients with cirrhosis and spontaneous bacterial peritonitis (SBP) need special attention because of the significant 30-day mortality of about 20–40% [8–13]. The aim of the present work was therefore to systematically investigate the patients with cirrhosis, ACLF and SBP.

If symptoms and laboratory parameters indicate SBP, antibiotic therapy should be started immediately before the causative pathogen is identified [14,15]. This antimicrobial treatment is called empirical antibiotic therapy [14,15]. Since this treatment can improve prognosis, but probably increase the rate of antibiotic resistance and cause side effects in the patients, an antibiotic therapy based on the most commonly isolated bacteria and their resistance profile is recommended [14,15]. The pathogens in the ascites of SBP patients are described to be mainly Gram-negative bacteria [16–18]. Accordingly, a third generation cephalosporin is

* Corresponding authors at: Department of Medicine II, University Hospital, LMU Munich, Marchioninistr. 15, 81377 Munich, Germany.
*E-mail addresses:* hanwei.li@med.uni-muenchen.de (H. Li), christian.steib@med.uni-muenchen.de (C.J. Steib).
[1] These authors contributed equally.
[2] These authors share corresponding authorship.

https://doi.org/10.1016/j.dld.2019.02.015
1590-8658/

the standard empirical antibiotic therapy for SBP [16–18]. In July 2018, the European Association for the Study of the Liver (EASL) recommended cefotaxime as the empirical antimicrobial treatment for community-acquired SBP [14]. For patients with health care-associated and nosocomial SBP, it proposed that each hospital should develop its own regimen according to local resistance rates [14]. However, the impact of ACLF on SBP has not been analyzed up to now.

A prospective study with 32 patients in Italy provided evidence that combination therapy with meropenem and daptomycin had higher response rates in comparison with ceftazidime as empirical antibiotic therapy for nosocomial SBP [19]. This is not surprising as ceftazidime without avibactam has a narrow spectrum [20,21], and thus is not commonly applied for empirical antimicrobial treatment of SBP, though it is a third generation cephalosporin. Furthermore, with a serum albumin binding rate of 92%, daptomycin works mainly intravascularly [22].

In this study, we compared the clinical outcomes of patients with sensitive and non-sensitive empirical antibiotic therapy by applying multivariable regression analysis, in consideration of the individual ACLF grade, in order to detect which patient group would benefit the most from an effective empirical antimicrobial treatment. Furthermore, we processed the antimicrobial susceptibility testing (AST) results of 17 commonly used antibiotics in SBP patients over the last 11 years, taking into account the intrinsic resistances according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) [23], to evaluate a promising empirical antibiotic regimen. Thereby, the pharmacological properties of the considered antibiotics are also taken into account with a special focus on the peritoneal cavity and the bloodstream in the case of septic complications.

## 2. Materials and methods

### 2.1. Ethical approval

All procedures within this study were in accordance with the ethical standards of the institutionally and nationally responsible committee on human experimentation (project number 17-500) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

### 2.2. Data collection

Based on microbiological culture results, 182 patients (59 with ACLF grade 3) with 223 proven pathogens in ascites were identified between 2007 and 2017. Herein, patients without liver cirrhosis or with proven malignant ascites, malignant extrahepatic tumor, secondary peritonitis, or immune defects such as HIV infection have been excluded. Patients with a suggestive clinical presentation and pathologic bacteriological findings were included as well, in the case of low neutrophil counts in ascites (<250/mm$^3$).

### 2.3. Design and operational definitions

In the AST assessment, isolates from the 17 patients without any empirical antibiotic therapy were included. However, their clinical data were not used for the significance tests of laboratory and clinical outcomes (Supplementary Fig. S1 in the online version at DOI: 10.1016/j.dld.2019.02.015). For this group, only the 165 patients with empirical antimicrobial treatment were included, who received therapy that can be considered as effective (all isolates susceptible in AST [sensitive]) or ineffective (isolate non-susceptible in AST [non-sensitive]). Since not every antibiotic was tested on each pathogen, the gaps were filled with intrinsic resistances according to EUCAST (Supplementary Table S1 in the online version at DOI: 10.1016/j.dld.2019.02.015) [23] and probable susceptibilities (Supplementary Fig. S2 in the online version at DOI: 10.1016/j.dld.2019.02.015).

A drug combination was considered as an antibiotic monotherapy if a standard formulation/fixed combination was used. Thus, piperacillin/tazobactam and amoxicillin/clavulanic acid were considered as monotherapies.

The *initial* creatinine, bilirubin and INR values at diagnosis were used to calculate the *initial* Model for End-stage Liver Disease (MELD) score, which served as an indicator for the *initial* liver function of the patients at treatment start. The highest creatinine, bilirubin and INR values during the inpatient therapy were applied to calculate the maximum MELD score. The most severely altered laboratory parameters were used to analyze the disease course during the in-hospital treatment, as most of the laboratory values would not reach their maximum until a few hours or even days after the onset of peritonitis.

Circulation failure was defined as when patients needed vasopressor or catecholamine to maintain a normal blood pressure [1]. It was not considered as circulation failure if the indication for vasopressor was hepatorenal syndrome [1]. If a patient had West Haven grade 3 or 4 in context of hepatic encephalopathy, it was considered cerebral failure [1].

### 2.4. Statistical analysis

Multivariable regression analysis was used to relate every inpatient laboratory parameter and clinical outcome to the group membership. Since the *initial* physical conditions could be confounders, the following adjustment variables were included in each multivariable regression analysis: the *initial* MELD score (at diagnosis), age, gender, etiology of cirrhosis (e.g. ethyl toxicity), origin of SBP (community-acquired vs. nosocomial), variceal bleeding and shock at diagnosis. Unfortunately, we do not have health care-associated SBP patients in this cohort. The binary outcomes (yes/no question) were analyzed using multivariable logistic regression, while the metric outcomes (the average values with standard deviation) using multivariable linear regression, for the whole cohort, the subgroup “ACLF grade 3” and the subgroup “ACLF grade 0 to grade 2”.

Since the MELD scores were not normally distributed, Mann-Whitney-U-Test was used to compare the difference of the MELD scores between the two groups with efficient and inefficient empirical antibiotic therapy, while Wilcoxon-Signed-Rank-Test was applied for the analysis of MELD score increase in each group. The Fisher’s exact test was used to compare the antimicrobial susceptibility results. The SPSS software package (Version 24.0. Armonk, NY: IBM Corp.) and GraphPad Prism (Version 7.0a for Mac OS X, GraphPad Software, La Jolla California USA) were used for statistical analysis.

## 3. Results

### 3.1. Baseline characteristics

Among the included 182 patients, 17 had not received any empirical antibiotic therapy because of merely mild symptoms, while 165 did. In 54 patients the pathogens were sensitive and in 111 patients the pathogens were not sensitive to the empirical antimicrobial treatment according to the AST results. The patients were 57.3 (SD, 11.4) years old on average at admission and 28.6% were women. Alcohol abuse was the most common etiology of cirrhosis (51.6%). All baseline demographics and laboratory characteristics of the patients in this cohort are described in Table 1.

**Table 1**
Baseline demographics and laboratory characteristics of SBP patients.

| | Microbes | | P Values | |
|---|---|---|---|---|
| | Not sensitive To empirical antibiotic therapy | Sensitive | Unadjusted | Adjusted† |
| | N = 54 | N = 111 | | |
| Demographics | | | | |
| Age [years], mean (SD) | 54.2 (12.4) | 58.4 (11.0) | **0.032** | |
| Gender, female, n (%) | 16 (29.6) | 31 (27.9) | 0.820 | |
| Etiology of cirrhosis, n (%) | | | | |
| Ethyl toxicity | 25 (46.3) | 56 (50.5) | 0.617 | |
| HCV | 8 (14.8) | 12 (10.8) | 0.461 | |
| Others | 21 (38.9) | 43 (38.7) | 0.985 | |
| *Initial* blood values, mean (SD) | | | | |
| Creatinine-min [mg/dl] | 2.08 (1.38) | 2.04 (1.14) | 0.858 | |
| Bilirubin-min [mg/dl] | 6.17 (8.95) | 5.78 (7.41) | 0.764 | |
| INR-min | 2.63 (5.84) | 1.63 (0.50) | 0.073 | |
| Min/max blood values during the inpatient treatment, mean (SD) | | | | |
| Sodium-min [mmol/l] | 127.8 (6.2) | 127.5 (6.0) | 0.772 | 0.974 |
| Creatinine-max [mg/dl] | 2.89 (1.75) | 2.60 (1.39) | 0.245 | 0.230 |
| Urea-max [mg/dl] | 124.1 (67.1) | 112.9 (62.7) | 0.328 | 0.430 |
| GFR-min [ml/min] | 33.7 (17.3) | 36.6 (19.8) | 0.361 | 0.725 |
| Bilirubin-max [mg/dl] | 10.5 (12.0) | 8.8 (10.5) | 0.352 | 0.625 |
| Albumin-min [g/dl] | 2.42 (0.59) | 2.52 (0.57) | 0.330 | 0.919 |
| INR-max | 3.02 (2.51) | 2.30 (1.53) | **0.024*** | 0.275 |
| Prothrombin-ratio-min | 34.0 (16.1) | 39.4 (16.2) | **0.048*** | 0.273 |
| Platelet-min [Tsd./mm³] | 52.1 (47.7) | 65.1 (63.1) | 0.181 | 0.503 |
| Hemoglobin-min [g/dl] | 7.25 (1.70) | 8.37 (1.95) | **<0.001*** | **0.033*** |
| Leucocyte-max [Tsd./mm³] | 17.3 (10.9) | 14.6 (9.1) | 0.089 | 0.290 |
| CRP-max [mg/dl] | 9.74 (6.31) | 10.40 (6.70) | 0.544 | 0.849 |
| PCT-max [ng/ml] | 2.32 (3.63) | 9.04 (13.93) | 0.098 | 0.084 |
| IL-6-max [pg/ml] | 15424 (37322) | 19716 (77286) | 0.776 | 0.625 |
| AST-max [U/l] | 559.4 (1811.9) | 386.9 (1158.4) | 0.470 | 0.838 |
| ALT-max [U/l] | 174.8 (546.8) | 103.4 (218.3) | 0.233 | 0.438 |
| Calcium-min [mmol/l] | 1.89 (0.20) | 1.99 (0.18) | **0.004*** | **0.017*** |
| Ascitic fluid tests, mean (SD) | | | | |
| Total cells-max [cells/mm³] | 6443 (17209) | 6125 (14646) | 0.904 | 0.581 |
| Neutrophils-max [cells/mm³] | 3186 (5203) | 6267 (15169) | 0.227 | 0.624 |
| Total protein-max [g/dl] | 1.47 (0.72) | 1.58 (0.79) | 0.408 | 0.426 |

*Abbreviations*: HCV, hepatitis C virus; INR, international normalized ratio; GFR, glomerular filtration rate; Tsd, thousand; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; AST, aspartate aminotransferase; ALT, alanine transaminase.

† Adjusted P values: the values were assessed together with *initial* MELD score, age, gender, etiology of liver cirrhosis (ethyl toxicity), origin (community-acquired vs. nosocomial), variceal bleeding and shock at diagnosis by means of multivariable regression analysis.

* $P < 0.05$.

### 3.2. Efficacy of the empirical antibiotic therapy

Piperacillin/tazobactam was used with the highest frequency in our SBP patients as empirical antibiotic therapy (57 times), followed by ceftriaxone (40 times) and cefotaxime (24 times). Meropenem was applied progressively more due to the local antimicrobial resistance profiles (4.8% in the first 6 years vs. 14.2% in the last 5 years). The other empirical antimicrobial treatments were used according to the microbiological resistance profiles of isolates from each patient in previous hospitalizations.

The *initial* MELD scores, reflecting the liver function of the patients at the time of diagnosis, were almost identical in the two groups with effective and ineffective empirical antibiotic therapy ($22.9 \pm 7.2$ vs. $22.0 \pm 7.0$, $P = 0.411$; Fig. 1A). However, the subsequent scores reached significantly higher values in the patients with ineffective empirical antimicrobial treatment than in the patients with effective *initial* antibiotic therapy during their inpatient stay (maximum MELD scores: $30.2 \pm 8.6$ vs. $27.5 \pm 8.2$, $P = 0.042$). The MELD score thereby increased significantly more in the inefficiently treated group than in the efficiently treated group ($14.4 \pm 7.6$ vs. $11.7 \pm 6.4$ [non-sensitive vs. sensitive], $P = 0.017$).

The maximum ACLF grade in the inefficiently treated group was higher than in the efficiently treated group ($1.91 \pm 1.23$ vs. $1.40 \pm 1.21$, weakly significant: $P = 0.058$; Fig. 1B). When inpatient mortality was compared at each ACLF grade, the greatest difference was observed at ACLF grade 3 (73.1% vs. 54.5% [non-sensitive vs. sensitive], weakly significant: $P = 0.096$; Fig. 1C), whereas there was almost no difference in lower ACLF grades. The total in-hospital mortality in the inefficiently treated group was significantly higher than that of the efficiently treated group (37.0% vs. 18.9%, $P = 0.018$; Fig. 1D).

If isolates were not sensitive to the empirical antibiotic therapy, the patients were more likely to be catecholamine-dependent (51.9% vs. 22.5%, $P = 0.003$; Fig. 2A) and to suffer from circulation failure (53.7% vs. 25.2%, $P = 0.008$; Fig. 2B). The West Haven grade was higher in context of hepatic encephalopathy ($1.65 \pm 1.52$ vs. $1.02 \pm 1.31$, $P = 0.031$; Fig. 2C) and cerebral failure also occurred more frequently (38.9% vs. 15.3%, $P = 0.004$; Fig. 2D).

Additionally, patients with inefficient *initial* antimicrobial treatment had to receive significantly longer renal replacement therapy ($4.44 \pm 8.24$ vs. $1.30 \pm 3.09$ days, $P = 0.008$; Fig. 3A). Intensive care unit (ICU) treatment ($7.9 \pm 15.4$ vs. $2.1 \pm 4.5$ days, $P = 0.016$; Fig. 3B) and total inpatient stay ($26.4 \pm 21.0$ vs. $16.3 \pm 10.2$ days, weakly significant: $P = 0.053$; Fig. 3C) were observed to be longer in this patient group as well.

Furthermore, inefficient empirical antibiotic therapy correlated with significantly higher cumulative daily doses of systemic antimicrobials ($45.9 \pm 48.2$ vs. $19.8 \pm 15.9$ days, $P < 0.001$; Fig. 3D), more different classes of antibiotics ($4.70 \pm 2.72$ vs. $2.96 \pm 1.97$ types, $P = 0.001$; Fig. 3E) and the need for more red blood cell concen-

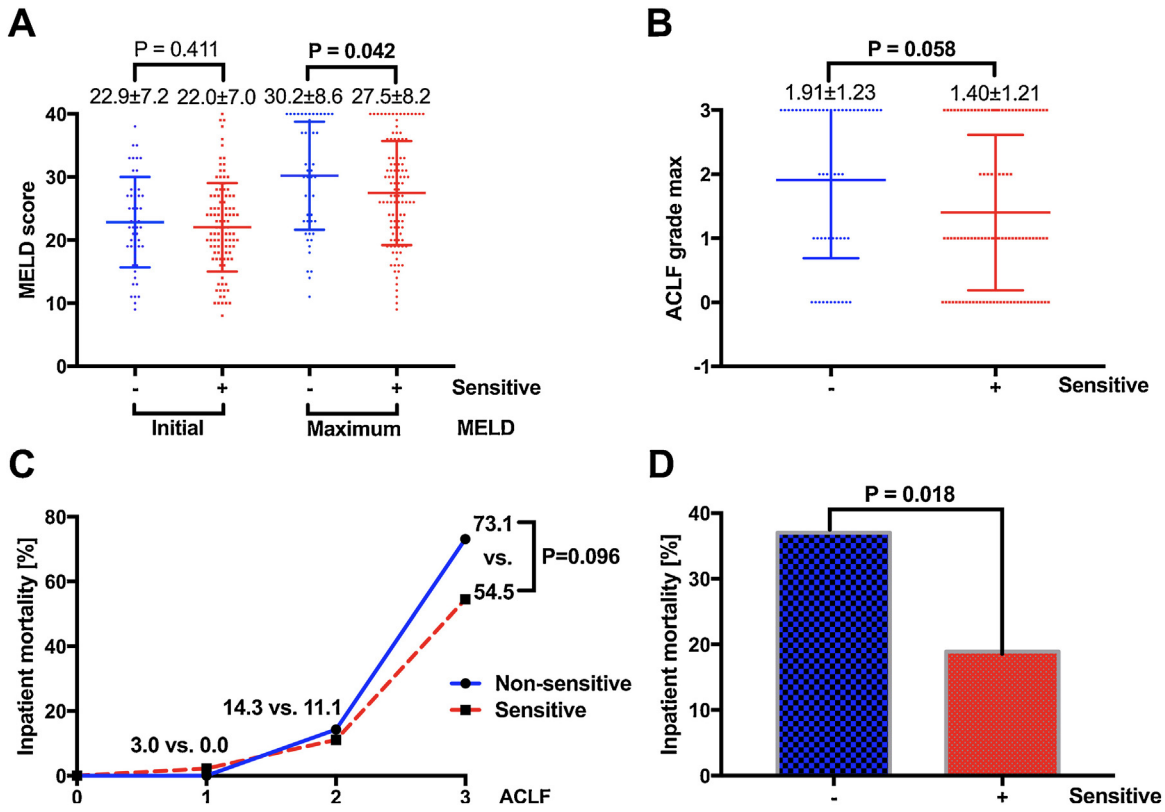


**Fig. 1.** Correlation between clinical scores and inpatient mortality. (A) The *initial* Model for End-stage Liver Disease (MELD) scores were similar in the two groups. During inpatient stay, the scores of the group with inefficient empirical antibiotic therapy (sensitive −) reached significantly higher levels compared to the group with efficient antimicrobial treatment (sensitive +). (B) The maximum acute-on-chronic liver failure (ACLF) grade in patients with inefficient empirical antibiotic therapy was higher than in patients with efficient antimicrobial treatment (weakly significant). (C) The greatest difference of inpatient mortality between these two groups could be observed in ACLF grade 3. (D) The total inpatient mortality in the group with inefficient empirical antibiotic therapy was almost twice as high as in the efficiently treated group.

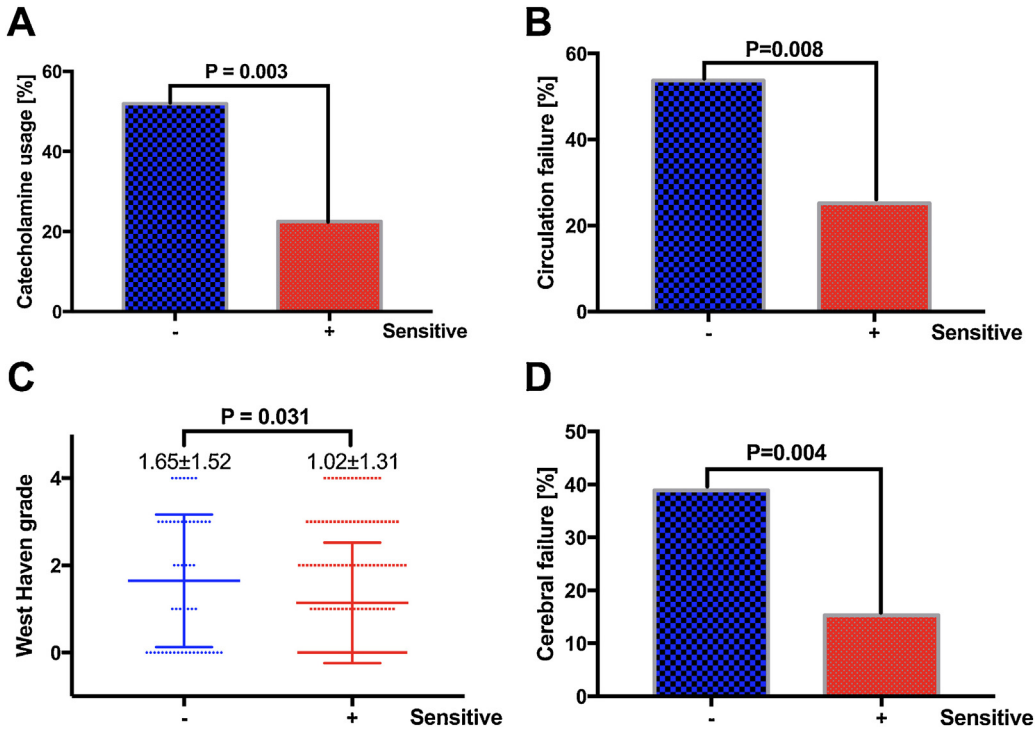


**Fig. 2.** Organ system impairment (circulation and brain function) in the patient group initially treated with efficient antimicrobials (sensitive +) or inappropriate substances (sensitive −). The proportion of patients with ineffective *initial* antimicrobial treatment (A) had double chance of becoming catecholamine-dependent and (B) suffering from circulation failure. In the context of hepatic encephalopathy, (C) the average West Haven grade and (D) cerebral failure rate in the inefficiently treated group were significantly higher as well.

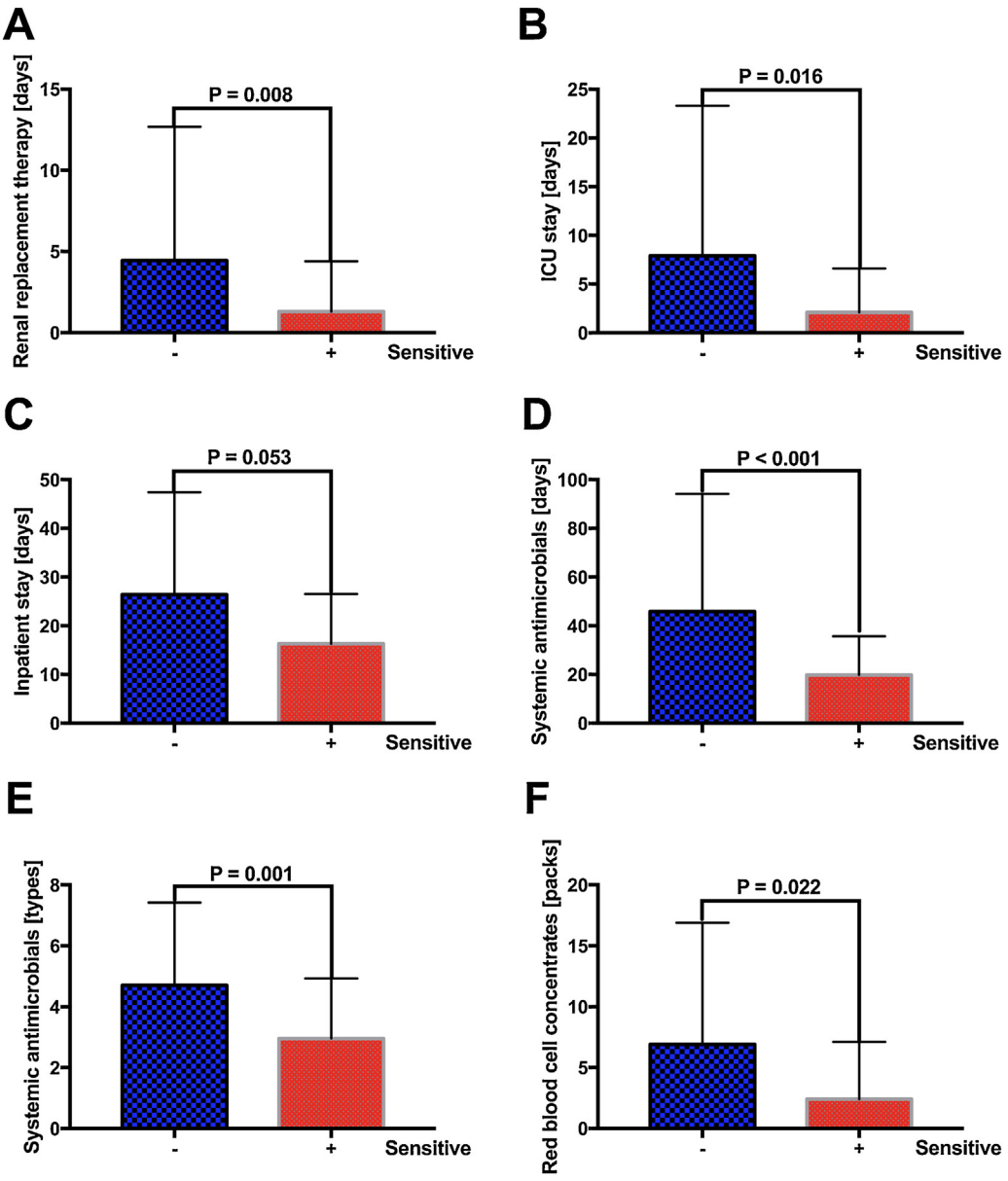


**Fig. 3.** The necessity for invasive therapeutic interventions in the two groups with efficient or inefficient empirical antibiotic therapy. If the microbial isolates were not sensitive to the empirical antimicrobial treatment, (A) the length of renal replacement therapy was doubled (P = 0.008), (B) the average ICU stay was nearly 6 days longer (P = 0.016) and (C) the average inpatient stay was prolonged by about 10 days (P = 0.053, weakly significant). (D) The cumulative antimicrobial daily doses (P < 0.001), (E) the number of different types of systemic antimicrobials (P = 0.001) and (F) the cumulative packs of red blood cell concentrate (P = 0.022) were administered almost double in the non-sensitive group.

trates (6.9 ± 10.0 vs. 2.4 ± 4.7 packs, 250 ml in each pack, P = 0.022; Fig. 3F).

### 3.3. ACLF grade 0 to grade 2 vs. ACLF grade 3

In the context of ACLF, we divided the patients into two groups in Supplementary Table S2 in the online version at DOI:10.1016/j.dld.2019.02.015: one group includes the patients with ACLF grade 0 to grade 2 (101 patients) and the other includes the patients with ACLF grade 3 (59 patients); Seventeen patients without empirical antibiotic therapy and five patients with insufficient data were not included in this analysis. In total, 15 clinical parameters in patients with or without efficient empirical antibiotic therapy were compared. It is obvious that there were more significant clinical outcomes in the patient group with ACLF grade 3 compared to the other group (significant clinical outcomes: 4 vs. 0 [P < 0.05]; weakly significant clinical outcomes: 4 vs. 1 [0.05 < P < 0.1]).

### 3.4. Antimicrobial susceptibility testing (AST)

In the 182 patient samples, 223 relevant microbial isolates grew in the first ascites punctures. If each isolate is considered separately, Gram-positive bacteria were identified almost twice as often as Gram-negative bacteria (63.7% vs. 36.3%). If one patient is regarded as one case, 33.5% of the patients had only Gram-negative bacteria, 60.4% had only Gram-positive bacteria and 6.1% had mixed infections.

The susceptibility rates of isolated pathogens to the 17 commonly used antibiotics are outlined in Table 2. Against Gram-negative bacteria (first and second columns in Table 2), meropenem had the highest antimicrobial susceptibility rates of

**Table 2**
The susceptibility of Gram-negative and Gram-positive bacteria to each antibiotic (one microbe one case).

| Antibiotics | Susceptibility to Gram-negative bacteria [%] | Antibiotics | Susceptibility to Gram-positive bacteria [%] |
|---|---|---|---|
| Meropenem | 98.8 | Tigecycline | 100.0 |
| Amikacin | 92.3 | Daptomycin | 97.3 |
| Pip/Taz | 91.3 | Linezolid | 97.3 |
| Cefepime | 91.1 | Vancomycin | 93.4 |
| Ceftriaxone | 88.6 | Amox/Clav | 66.6 |
| Cefotaxime | 87.3 | Pip/Taz | 66.1 |
| Moxifloxacin | 87.3 | Moxifloxacin | 55.2 |
| Ciprofloxacin | 86.3 | Meropenem | 54.6 |
| Cefuroxime | 63.3 | Ceftriaxone | 51.4 |
| Amoxi/Clav | 50.6 | Cefuroxime | 50.8 |
| Tigecycline | 44.7 | Cefotaxime | 50.8 |
| Ceftazidime | 31.2 | Cefepime | 48.5 |
| Metronidazole | 3.7 | Clindamycin | 45.9 |
| Linezolid | 0.0 | Ciprofloxacin | 43.4 |
| Daptomycin | 0.0 | Amikacin | 19.1 |
| Vancomycin | 0.0 | Metronidazole | 14.8 |
| Clindamycin | 0.0 | Ceftazidime | 0.0 |

*Abbreviations*: Pip/Taz, Piperacillin/Tazobactam; Amoxi/Clav, Amoxicillin/Clavulanic acid.

all (98.8%), followed by amikacin (92.3%), piperacillin/tazobactam (91.3%) and cefepime (91.1%). The Gram-positive isolates (third and forth columns in Table 2) had the highest susceptibility rates to tigecycline (100%), daptomycin (97.3%), linezolid (97.3%) and vancomycin (93.4%).

Combining the antibiotic substances of the highest antimicrobial susceptibility rates in Gram-negative bacteria with those in Gram-positive bacteria, it was possible to calculate the best theoretic combination therapies. Since tigecycline is rather bacteriostatic with worse clinical outcomes compared to many other antibiotics, several studies discourage its use [24–26]. Thus, it was not considered as a first line therapeutic option for severe SBP.

Meropenem-daptomycin (99.5%; Fig. 4), meropenem-linezolid (98.5%) and meropenem-vancomycin (96.8%) had the highest antimicrobial susceptibility rates among the antibiotic combinations, considering all of the Gram-negative and Gram-positive bacteria. These susceptibility rates were significantly higher than that of piperacillin/tazobactam (75.3%, $P < 0.05$). However, the antimicrobial susceptibility rate of piperacillin/tazobactam was significantly higher compared to most other monotherapies such as ceftriaxone (64.9%), cefotaxime (64.1%), amoxicillin/clavulanic acid (60.8%) and ciprofloxacin (59.0%). Interestingly, meropenem was not significantly different to piperacillin/tazobactam regarding the level of antimicrobial susceptibility (70.7% vs. 75.3%, $P = 0.337$).

## 4. Discussion

### 4.1. Key results

Based on our results, it can be inferred that the sensitivity of pathogens to empirical antibiotic therapy is crucial for inpatient mortality and complications in patients with SBP. Combination therapies such as meropenem-linezolid and meropenem-daptomycin had the highest susceptibility rates of all, while piperacillin/tazobactam had the highest antimicrobial susceptibility rates among the monotherapies/fixed combinations. SBP patients with ACLF grade 3 are more likely to benefit from aggressive antibiotic treatment with comprehensive effects than patients with ACLF grade 0 to grade 2.

### 4.2. Pharmacological considerations

Besides in vitro susceptibility rates, the pharmacological properties and side effect profiles of the potential antimicrobial substances for use in empirical antibiotic therapy of SBP should also be taken into account.

Owing to rapid penetration and as a result a high concentration in tissue, linezolid could be an ideal choice for peritonitis caused by Gram-positive bacteria [27]. Pharmacokinetic data show that the concentration of linezolid in the peritoneal fluid was greater than 4 mg/l 4 and 8 h after oral administration [28]. Such levels are above the minimum inhibitory concentration (MIC) of linezolid as tested for most pathogens [27]. However, in patients with concomitant sepsis, it might not be the best option because the effect is more towards the bacteriostatic side, and thus might be too weak to ideally treat the bacteremia component [27].

In contrast to linezolid, vancomycin has a lower concentration in tissue due to its large molecular mass and weak penetrability [29]. In our opinion, it might not be suitable for the treatment of infections in the peritoneum, but a good choice for sepsis [29], in spite of its nephrotoxic and ototoxic side effects.

The serum albumin binding rate of daptomycin can reach up to 92% [22]. As a result, its concentration in the peritoneal cavity is described to be only 6% of that in serum [30]. Owing to its bactericidal effect and high concentration in the bloodstream [30], it could be very effective for bacteremia like vancomycin but less so for peritonitis.

Thanks to their moderate volume of distribution and excellent penetrability (0.2–0.6 l/kg), both piperacillin/tazobactam and meropenem could be used for infection in peritoneum as well as bacteremia [31,32].

Besides these pharmacokinetic considerations, possible toxic side effects might arise especially in patients with SBP and underlying hepatic impairment. In the present study, 37% of SBP patients already suffered from renal failure at the beginning of SBP, while another 26% developed end-stage kidney disease during the hospitalization due to hepatorenal syndrome or drug toxicity. Thus, vancomycin might only be considered as a second choice in the case of sepsis, as an alternative to daptomycin. Linezolid may be advantageous in the case of renal failure because of its almost unchanged concentration (about 15% increase in serum) even if creatinine clearance is as low as 10–40 ml/min [33]. Bone marrow suppression with thrombocytopenia and anemia as side effect of linezolid normally only occurs after prolonged administration for more than 15 days. Therefore, its use in *initial* therapy until microbiological results are available should not be problematic [34].

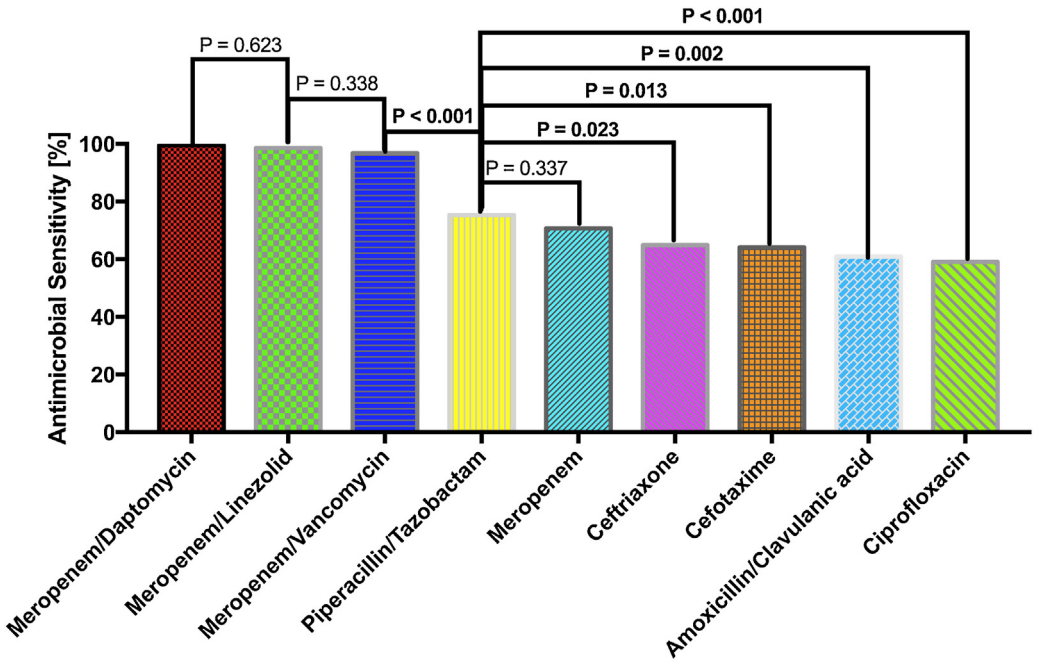


**Fig. 4.** Comparing the antimicrobial susceptibilities of antibiotic monotherapies/fixed combinations with those of antibiotic combinations (one microbe one case). Combination therapies such as meropenem-linezolid had significantly higher antimicrobial susceptibility rates than any monotherapy, while piperacillin/tazobactam had the highest antimicrobial susceptibility rate among the monotherapies/fixed combinations.

### *4.3. Choice of antibiotic therapy on the basis of the retrospective study*

Taking into account the antimicrobial susceptibility patterns, pharmacokinetics and side effect profiles of each antibiotic, the following therapeutic approaches could be recommended:

i) In patients with typical symptoms of SBP and ACLF grade 0 to grade 2, without suspected sepsis, piperacillin/tazobactam could be the first choice for empirical antibiotic treatment. Antibiotic combinations with more comprehensive effects might not be suggested in order to avoid an increase in antibiotic resistance rates in this patient population.
ii) If a patient is diagnosed with SBP and ACLF grade 3 without sepsis, a combination therapy with meropenem-linezolid could be proposed instead of the regimen suggested above, because this patient group benefits the most from effective empirical antimicrobial treatment and linezolid works mainly in tissue [27].
iii) In case that the clinical symptoms and laboratory parameters indicate the onset of sepsis, combination therapy with meropenem-daptomycin could be considered, as daptomycin works better in the bloodstream [22,30].

After the antimicrobial susceptibility testing results of the pathogens isolated from ascites become available, empirical antibiotic therapy should be deescalated to a targeted treatment [14,15]. However, the local resistance spectrum is still important. In order to prove our hypothesis, a prospective randomized double-blind study should be performed.

### *4.4. Economic aspect*

Overall, the economic benefits due to reduced need for medical treatment in the patients with effective empirical antibiotic therapy could be substantial. One extra day of ICU treatment alone equals additional costs of about $3000 (US) in the USA [35]. In our study, patients with isolates susceptible to the empirical antimicrobial treatment spent an average of 6 days less in the ICU. This alone would save $18,000 (US) per patient. Additional spending for medication and organ replacement therapy, which is also a severe driver of treatment cost, would also be spared.

### *4.5. Limitations of the study*

A retrospective study cannot prove whether combination therapy would bring about a survival advantage. In the efficacy analysis of empirical antibiotic therapy, our research has shown that the sensitivity of pathogens to empirical antimicrobial treatment can significantly reduce inpatient mortality and complications in multivariable regression analysis. From this we can indirectly infer that antibiotic therapy with broad antimicrobial coverage and specific pharmacokinetics would probably improve clinical outcomes if toxic side effects can be controlled or avoided.

## 5. Conclusions

This is the first study to analyze SBP patients with respect to the existence of ACLF. Diligent analysis of 223 microbial isolates was performed according to the EUCAST guidelines [23]. The patients with cirrhosis, SBP and ACLF grade 3 benefited the most from efficient empirical antibiotic therapy, as inpatient mortality could be reduced by about 20% in this cohort. Meropenem combined with linezolid could be a therapeutic option for patients with ACLF grade 3 without sepsis in consideration of the susceptibility results and the concentration in the peritoneal cavity.

**Conflict of interest**
None declared.

## Funding

This work was supported by the Deutsche Forschungsgemeinschaft (DFG STE 1022-2-4) and the China Scholarship Council (NO. 201606230249).

## Acknowledgement

The authors thank Prof. Martin Storr for careful reading of the manuscript.

## References

[1] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. cute-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.
[2] Trebicka J. Predisposing factors in acute-on-chronic liver failure. Semin Liver Dis 2016;36:167–73.
[3] Laleman W, Verbeke L, Meersseman P, Wauters J, van Pelt J, Cassiman D, et al. Acute-on-chronic liver failure: current concepts on definition, pathogenesis, clinicalmanifestations and potential therapeutic interventions. Expert Rev Gastroenterol Hepatol 2011;5:523–37.
[4] Garg H, Kumar A, Garg V, Sharma P, Sharma BC, Sarin SK, et al. Clinical profile and predictors of mortality in patients of acute-on-chronic liver failure. Dig Liver Dis 2012;44:166–71.
[5] Di Campli C, Zocco MA, Saulnier N, Grieco A, Rapaccini G, Addolorato G, et al. Safety and efficacy profile of G-CSF therapy in patients with acute on chronic liver failure. Dig Liver Dis 2007;39:1071–6.
[6] Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018;67:1870–80.
[7] Shalimar, RoutG, Jadaun SS, Ranjan G, Kedia S, Gunjan D, et al. Prevalence, predictors and impact of bacterial infection in acute on chronic liver failure patients. Dig Liver Dis 2018;50:1225–31.
[8] Alexopoulou A, Vasilieva L, Agiasotelli D, Siranidi K, Pouriki S, Tsiriga A, et al. Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia. World J Gastroenterol 2016;22:4049–56.
[9] Goel A, Biewald M, Huprikar S, Schiano T, Im G. A real-world evaluation of repeat paracentesis-guided management of spontaneous bacterial peritonitis. J Clin Gastroenterol 2017;51:278–84.
[10] Jindal A, Kumar M, Bhadoria A, Maiwall R, Sarin S. A randomized open label study of 'imipenem vs. cefepime' in spontaneous bacterial peritonitis. Liver Int 2016;36:677–87.
[11] Kim J, Lim K, Min Y, Lee H, Min B, Rhee P, et al. Proton pump inhibitors do not increase the risk for recurrent spontaneous bacterial peritonitis in patients with cirrhosis. J Gastroenterol Hepatol 2017;32:1064–70.
[12] Tandon P, Garcia-Tsao G. Renal dysfunction is the most important independent predictor of mortality in cirrhotic patients with spontaneous bacterial peritonitis. Clin Gastroenterol Hepatol 2011;9:260–5.
[13] Tandon P, Kumar D, Seo Y, Chang H, Chaulk J, Carbonneau M, et al. The 22/11 risk prediction model: a validated model for predicting 30-day mortality in patients with cirrhosis and spontaneous bacterial peritonitis. Am J Gastroenterol 2013;108:1473–9.
[14] European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018;69:406–60.
[15] Runyon BA. Introduction to the revised American Association for the Study of Liver Diseases Practice Guideline management of adult patients with ascites due to cirrhosis 2012. Hepatology (Baltimore, Md) 2013;57:1651–3.
[16] Felisart J, Rimola A, Arroyo V, Perez-Ayuso R, Quintero E, Gines P, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. Hepatology (Baltimore, Md) 1985;5:457–62.
[17] Navasa M, Follo A, Llovet JM, Clemente G, Vargas V, Rimola A, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. Gastroenterology 1996;111:1011–7.
[18] Rimola A, Salmerón J, Clemente G, Rodrigo L, Obrador A, Miranda M, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology (Baltimore, Md) 1995;21:674–9.
[19] Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, et al. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: results of a randomized, controlled clinical trial. Hepatology (Baltimore, Md) 2016;63:1299–309.
[20] Roberts JA, Webb SA, Lipman J. Cefepime versus ceftazidime: considerations for empirical use in critically ill patients. Int J Antimicrob Agents 2007;29:117–28.
[21] Varotto F, Maria GD, Azzaro R, Bellissima P, Amato R, Fogliani V, et al. An observational study on the epidemiology of respiratory tract bacterial pathogens and their susceptibility to four injectable beta-lactam antibiotics: piperacillin, piperacillin/tazobactam, ceftazidime and ceftriaxone. J Chemother (Florence, Italy) 2001;13:413–23.
[22] Lawson W, Nathwani D, Eckmann C, Corman S, Stephens J, Solem C, et al. Weight-based antibiotic dosing in a real-world European study of complicated skin and soft-tissue infections due to methicillin-resistant *Staphylococcus aureus*. Clin Microbiol Infect 2015;21(Suppl. 2):S40–6.
[23] Leclercq R, Canton R, Brown DF, Giske CG, Heisig P, MacGowan AP, et al. EUCAST expert rules in antimicrobial susceptibility testing. Clin Microbiol Infect 2013;19:141–60.
[24] Tasina E, Haidich AB, Kokkali S, Arvanitidou M. Efficacy and safety of tigecycline for the treatment of infectious diseases: a meta-analysis. Lancet Infect Dis 2011;11:834–44.
[25] Prasad P, Sun J, Danner R, Natanson C. Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis 2012;54:1699–709.
[26] Yahav D, Lador A, Paul M, Leibovici L. Efficacy and safety of tigecycline: a systematic review and meta-analysis. J Antimicrob Chemother 2011;66:1963–71.
[27] Dryden M. Linezolid pharmacokinetics and pharmacodynamics in clinical treatment. J Antimicrob Chemother 2011;66(Suppl. 4):iv7–15.
[28] DePestel DD, Peloquin CA, Carver PL. Peritoneal dialysis fluid concentrations of linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* peritonitis. Pharmacotherapy 2003;23:1322–6.
[29] Marsot A, Boulamery A, Bruguerolle B, Simon N. Vancomycin: a review of population pharmacokinetic analyses. Clin Pharmacokinet 2012;51:1–13.
[30] Cardone KE, Lodise TP, Patel N, Hoy CD, Meola S, Manley HJ, et al. Pharmacokinetics and pharmacodynamics of intravenous daptomycin during continuous ambulatory peritoneal dialysis. Clin J Am Soc Nephrol 2011;6:1081–8.
[31] Ulldemolins M, Vaquer S, Llauradó-Serra M, Pontes C, Calvo G, Soy D, et al. Beta-lactam dosing in critically ill patients with septic shock and continuous renal replacement therapy. Crit Care 2014;18:227.
[32] Karjagin J, Lefeuvre S, Oselin K, Kipper K, Marchand S, Tikkerberi A, et al. Pharmacokinetics of meropenem determined by microdialysis in the peritoneal fluid of patients with severe peritonitis associated with septic shock. Clin Pharmacol Ther 2008;83:452–9.
[33] Brier ME, Stalker DJ, Aronoff GR, Batts DH, Ryan KK, O'Grady M, et al. Pharmacokinetics of linezolid in subjects with renal dysfunction. Antimicrob Agents Chemother 2003;47:2775–80.
[34] Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrob Agents Chemother 2002;46:2723–6.
[35] Dasta J, McLaughlin T, Mody S, Piech C. Daily cost of an intensive care unit day: the contribution of mechanical ventilation. Crit Care Med 2005;33:1266–71.