Failure of Current Antibiotic First-Line Regimens and Mortality in Hospitalized Patients with Spontaneous Bacterial Peritonitis

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Abstract

Background: Increases in Gram-positive infections and infections with Enterobacteriaceae with antimicrobial resistance have been reported in patients with spontaneous bacterial peritonitis (SBP). This study was performed to investigate the rate of treatment failures of recommended empirical therapies and the impact on mortality.

Patients and Methods: A prospectively collected database comprising 101 patients with SBP (70 nosocomial, 31 community acquired) treated at a university hospital between 2002 and 2006 in Munich, Germany, was analyzed.

Results: 17 patients initially received a broader than recommended antibiotic regimen. Most of these were treated in the intensive care unit because of severe sepsis/septic shock. Hospital mortality in this group was 82%. A modification of therapy was necessary in 24 of the 84 patients receiving one of the published first-line therapies (cefotaxime, ampicillin/clavulanate, or ciprofloxacin). Mortality was significantly higher in these patients than in those with no change in treatment (66.7% vs 30%, $p = 0.002$). In 29 patients with positive cultures, mortality was also higher in those with an ineffective first-line treatment (90% vs 45%, $p = 0.032$). In the multivariable analysis, a modification of antibiotic treatment was an independent risk factor for mortality (odds ratio 5.876, 95% confidence interval 1.826–18.910, $p = 0.003$). In 41 culture-positive cases, the most commonly cultured pathogens were *Escherichia coli* (n = 17) and *Enterococcus faecium* (n = 10). Of the encountered bacterial microorganisms, 14 (33.3%) were resistant to cefotaxime, 17 (38.6%) were resistant to amoxicillin/clavulanate, and 19 (45.2%) were resistant to ciprofloxacin. 29 (64.4%) of the isolates were resistant to one of the recommended first-line antibiotic regimens, and 11 (24.4%) of the isolates were resistant to all three.

Conclusion: Recommended empirical antibiotic regimens fail to achieve the desired effect in a substantial number of hospitalized patients with SBP. This has a negative impact on mortality.

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Introduction

Cirrhosis has been characterized as the most prevalent cause of acquired immunodeficiency [1], and bacterial infections are frequent and the cause of 30%–50% of hospital admissions in these patients [2]. Similarly, 15%–35% of hospitalized cirrhotics develop bacterial infections, the most common of which is spontaneous bacterial peritonitis, a dreaded and characteristic complication of cirrhosis. With earlier recognition and improved treatment with antibiotics and albumin [3], mortality has dropped from 90% to 15% [4] and 23% [5], based on studies of a few years ago.

Cefotaxime [6, 7], or other third-generation cephalosporins [8, 9], are recommended as empirical treatment [10], but other regimens, namely amoxicillin/clavulanate [4, 11] or quinolones [5], have been equally effective. Current guidelines recommend cefotaxime, with other third-generation cephalosporins and amoxicillin/clavulanic acid listed as alternatives and quinolones recommended for patients with allergies to beta-lactams [10]. Studies establishing these regimens were performed during the 1980s and 1990s and achieved resolution rates of up to 90%, but the proportion of nosocomial cases in these studies was low, and there is still a scarcity of information on the causal factors and therapeutic consequences of treatment failure.

Attention has recently been drawn to changing microbial and resistance patterns attributed to the increasing use of antibiotic prophylaxis in ascitic patients and to the increasing frequency of invasive procedures,

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such as endoscopic variceal banding [12–14]. The steadily improving survival times of cirrhotic patients may add the problem of recurrent hospitalizations and colonization by resistant microorganisms. The rapid commencement of adequate antibiotic therapy has been shown to be of paramount importance in the treatment of septic patients. Thus, failure to cover causative microorganisms with an empirical antibiotic regimen may result in increased mortality among patients with spontaneous bacterial peritonitis (SBP).

In our institute, a database comprising medical histories, clinical, laboratory, and microbiological data of all patients with SBP treated in our department has been maintained since 2002. The aim of the study presented here was to investigate the impact of antibiotic failure on mortality in patients with SBP. We report the clinical spectrum of the disease, the incidence of antimicrobial resistance, and the course of treatment, especially the need to modify the initial empirical antibiotic therapy, and the parameters of outcome.

Methods

From 2002 until August 2006, 101 patients with SBP were prospectively identified. For patients surviving until discharge from the hospital, follow-up data were collected by consulting our hospitals mainframe-database or by contacting the patient's admitting general practitioner. Patients lost to follow-up were eliminated from the analysis. Only those who initially received one of the established first-line regimens (i.e., cefotaxime or other third-generation cephalosporins, amoxicillin/clavulanate, or a second-generation quinolone) were divided into two groups and compared according to whether the initial empirical therapy had to be modified or not. A second analysis was performed to compare survivors to non-survivors. Risk factors associated with an escalation of treatment and mortality were analyzed. To assess for time-related changes in prescription patterns of the initial antibiotic treatment and the incidence of Gram-positive infection, all patients were dichotomized according to the time of diagnosis, and the earlier and later groups were compared.

Definitions

Spontaneous bacterial peritonitis was defined as an ascitic polymorphonuclear (PMN) cell count of $\geq 50\ \mu l^{-1}$ in a patient with cirrhosis, no history of any intra-abdominal surgical procedure or endoscopic biliary intervention during the past 4 weeks, and no malignant cells in the ascitic fluid cytology. To exclude cases of secondary bacterial peritonitis, patients with ascitic fluid cell counts $> 5{,}000\ \mu l^{-1}$ or two different cultured microorganisms were included only if appropriate laboratory and radiological investigations had been performed with negative results. Patients with polymicrobial infections (> two strains) were excluded.

Previous antibiotic treatment was defined as antibiotic treatment in response to an acute infectious condition or short-term antibiotic prophylaxis in response to an acute event (upper gastrointestinal [GI] hemorrhage) within the preceding 3 months.

Prophylactic treatment was defined as the long-term use of antibiotics to prevent a second or first episode of spontaneous bacterial peritonitis.

Infections were regarded as nosocomial, if they were diagnosed more than 48 h after hospital admission.

Model of end-stage liver disease (MELD) scores were calculated as $10 \times (0.957\ \ln[\text{serum-creatinine (mg/dl)}] + 0.378\ \ln[\text{serum - bilirubin (mg/dl)}] + 1.120\ \ln \text{INR [international normalized ratio]} + 0.643)$.

Microbiological Tests

For the microbiological analysis, one aerobic and one anaerobic blood culture bottle (BacTec system; Becton Dickinson, Heidelberg, Germany) were each inoculated at the bedside with 10 ml of ascitic fluid, according to our standard procedures.

The cultures were incubated at 37 °C for 5 days. For control purposes and to exclude any failure of the automatic detection of the BacTec system, each flask was subcultivated aerobically (chocolate agar in 10% CO_2) and anaerobically (Schädler anaerobic agar) after the end of the incubation period. Cultivable germs were identified using the ATB, API, or VITEK system (BioMérieux Deutschland, Nürtingen, Germany). Antibiotic susceptibility testing was performed using both disk diffusion testing or MIC testing using the VITEK system (BioMérieux Deutschland) or the Etest system (AB Biodisk, Solna, Sweden) according to the recommendations of the CLSI (Clinical Laboratoy Standards Institute; formerly NCCLS/National Committee for Clinical Laboratory Standards), as published in [15] and previous editions.

In vitro data indicating unimpaired susceptibility were reported as susceptible, and intermediate and resistant classifications were analyzed as resistant.

Statistical Analysis

Statistical analysis was conducted using SPSS ver. 15.0 for Windows (SPSS, Chicago, IL). Categorical variables were compared using the χ^2 or Fisher's exact test, as appropriate. Continuous data were compared using the Mann-Whitney test because assessment for normal distribution by the Kolmogorov-Smirnoff test suggested non-normal distribution in some parameters.

Patients initially treated with a standard antibiotic regimen were divided into groups according to whether an escalation of therapy had been necessary or not and whether they survived the hospital stay or not. Parameters unequally distributed between these groups in the univariate analysis were entered into binary logistic models to estimate the effect of multiple risk factors on the probability of treatment failure and mortality, respectively. Previous antibiotic therapy, ascitic PMN cell counts, nosocomial infection, and Child-Pugh-class were tested as independent variables affecting the need to change the antibiotic regimen. With mortality as the dependent variable, the need to escalate the initial therapy, the model of end-stage liver disease (MELD) score, and the INR were tested as independent variables. P-values of < 0.05 were regarded as significant and p-values of > 0.1 led to the backward exclusion of variables from the binary logistic model, in accordance to Ward. Parametric data are presented as mean (± standard deviation, SD), and non-parametric data are given as median (25th–75th percentile).

Results

Patients' Characteristics and Initial Antibiotic Regimen

101 cases were included. Baseline characteristics, clinical, and important biochemical data are shown in table 1. The

Table 1
Baseline characteristics and clinical data of all patients with SBP.

Age (years)	55.9 (±10.1)
Gender, male/female	77 (76.2%)/ 24 (23.8%)
Type of admission, n	
Referral	39 (38.6%)
Emergency department/regular admission	62 (61.4%)
Previous admissions during past 3 months	72 (71.3%)
Type of infection, n	
Community acquired	31 (30.7%)
Nosocomial	70 (69.3%)
Child–Pugh class B/C	36 (35.6%)/ 65 (64.4%)
Cause of cirrhosis, n	
Alcoholic	76 (75.2%)
Viral	22 (21.8%)
Other	10 (9.9%)
Presenting symptom, n	
Hydropic decompensation	60 (59.4%)
GI bleed	17 (16.8%)
Encephalopathy > I°	18 (17.8%)
Fever	19 (18.8%)
Prophylaxis (selective intestinal decontamination), n	17 (16.8%)
Invasive endoscopic procedure, n	15 (14.9%)
Ascitic polymorphonuclear (PMN) cell count, cells/μl	816 (355.75–2,762.5)
Patients with positive cultures, n	41 (40.5%)
Patients with positive ascitic cultures, n	39 (38.6%)
Patients with positive blood cultures, n	6 (5.9%)
Serum bilirubin, mmol/l	86 (34–272)
Serum creatinine, mmol/l	132 (88–207)
INR	1.7 (1.35–2.0)
Septic shock, n	24 (23.8%)
Renal replacement therapy for acute renal failure, n	29 (28.7%)
Length of stay after diagnosis of SBP, days	15 (6.25–23.75)
Hospital mortality, n	48 (47.5%)

MELD: Model of end-stage liver disease; INR: international normalized ratio; SBP: spontaneous bacterial peritonitis; GI: gastrointestinal

70 patients with nosocomial SBP had originally been admitted because of ascites (n = 26), variceal hemorrhage (n = 8), gastrointestinal hemorrhages of other origin (n = 5), acute-on chronic liver failure (n = 8), renal failure (n = 7), evaluation for suspected hepatocellular carcinoma (n = 5), pneumonia (n = 3), hepatic encephalopathy (n = 2), and other conditions (n = 6).

17 patients received an initial antibiotic treatment that was already substantially broader than recommended regimens. In ten of these, vancomycin was added to cefotaxime or amoxicillin/clavulanate. Seven patients had received a carbapenem as first-line treatment. The reasons for the choice of antibiotic prescriptions with a broader spectrum were septic shock and multi-organ failure in 15 of these patients and a prolonged hospital stay with exposition to multiple antibiotic treatments in two. 16 (94.1%) of these patients were treated in the intensive care unit (ICU), and hospital mortality in this group was 82.4% (Table 2).

The remaining patients (n = 84) were initially treated with one of the established empirical therapies: cefotaxime (n = 52; 62%), amoxicillin/clavulanate (n = 17; 20%), or intravenous ciprofloxacin (n = 13; 15%). Of the patients treated with ciprofloxacin, none had been on prophylactic treatment with a quinolone, and five had received previous antibiotic treatment with beta-lactam antibiotics for infections unrelated to SBP. There was no significant difference in the choice of the initial antibiotic treatment between the earlier and later groups of patients.

In addition to antibiotic therapy, 40 out of 84 patients received albumin. There were no significant differences in the relative numbers of patients receiving albumin, or in the amount of albumin received, between survivors and non-survivors.

Escalation of Therapy

Table 2 details the clinical and laboratory parameters of patients who initially received a broader antibiotic regimen (n = 17, column 1) and patients treated with an established empirical first-line regimen (n = 84). The latter group was split according whether the initial antibiotic regimen had to be changed (n = 24, column 3) or not (n = 60, column 3), and data of these two groups were compared.

In 24 (28.6%) patients, the therapy was changed after 3 (2–5) days because of a deteriorating clinical condition (n = 4), antimicrobial resistance of cultured microorganisms (n = 11), or failure of ascitic fluid (PMN) cell counts to decrease by more than 25% within 48 h (n = 9). Mortality was higher in the patients requiring a change of antibiotic therapy in response to positive culture results (11/14; 78.6%) than in the group of patients where an empirical second-line therapy was chosen on clinical grounds (5/11; 45.5%), but the difference failed to reach statistical significance (p = 0.105). All patients responding to the modification of treatment with a resolution of infection survived (n = 8), whereas all patients with persistent infection died (n = 16).

The multivariable analysis revealed that the need for an escalation of antibiotic therapy was associated with a higher Child-Pugh class C vs B; parameter estimate [PE] 1.281; standard error [SE] 0.570; estimated odds ratio [OR] 3.6, 95% confidence interval [CI] 1.179–10.995, p = 0.025). Previous antibiotic therapy, ascitic PMN cell counts, and nosocomial infection were eliminated from the model.

Table 2
Baseline characteristics and clinical data of patients with no change in therapy and patients with an escalation of antibiotic treatment.

Baseline characteristics and clinical data	Column 1: 17 patients with broad initial therapy	Column 2: 60 patients with no escalation of therapy	Column 3: 24 patients with an escalation of therapy	Column 2 vs column 3 (p)
Age, years	54 (±10.0)	57 (± 8.7)	55 (± 13.1)	0.178
Gender, male	12 (71%)	12 (20%)	7 (29.2%)	0.364
Referral, n	12 (71%)	18 (30%)	9 (37.5%)	0.506
Previous admission during past 3 months, n	14 (82.4%)	40 (66.7%)	18 (75%)	0.455
Community acquired, n	3 (17.6%)	19 (31.7%)	9 (37.5%)	0.608
Recent antibiotic therapy, n	4 (23.5%)	5 (8.3%)	3 (12.5%)	0.278
Antibiotic prophylaxis, n	6 (35.3%)	7 (11.7%)	4 (16.7%)	0.539
Endoscopic intervention, n	2 (11.8%)	10 (16.7%)	3 (12.5%)	0.613
Child–Pugh class C, n	16 (94.1%)	31 (51.7%)	18 (75.0%)	0.042
MELD score	23.4 ± 8.7	21.4 ± 8.2	24.0 ± 7.9	0.170
Serum creatinine, µmol/l	177 (109–336)	106 (88–186)	137 (88–248)	0.848
Serum bilirubin, µmol/l	275 (60.9–487)	87 (31.3–198.4)	72.2 (34.8–189.7)	0.909
INR	1.8 (1.4–2.3)	1.6 (1.2–2.0)	2.0 (1.6–2.2)	0.006
Ascitic PMN cell count, per µl	725 (392–1710)	546 (306–2381)	1141 (540–3100)	0.074
Positive culture results, n	8 (47.1%)	19 (31.7%)	14 (58.3%)	0.029
Cultured pathogens resistant to first line treatment received, n	1 (12.5%)	0	9 (69.2%)	< 0.001
ICU treatment, n	16 (94.1)	22 (36.7%)	17 (70.8%)	0.005
Hospital mortality, n	14 (82.3%)	18 (30%)	16 (66.7%)	0.002

Mortality

Overall, hospital mortality was 47.5%, and 3-month mortality was 64.9%. For the group of patients initially receiving one of the established antibiotic first-line regimens, differences in the clinical and laboratory parameters of those who died in hospital and those who could be discharged are presented in table 3. The multivariable analysis revealed that mortality was independently associated with an escalation of antibiotic therapy (PE 1.771, SE 0.596, OR 5.876, 95% CI 1.826–18.910, p = 0.003); ascitic PMN cell counts (per 500 cells: PE 0.207, SE 0.081, OR 1.230, 95% CI 1.050–1.440, p = 0.010), and MELD score (PE 0.07, SE 0.036, OR 1.073, 95% CI 0.999–1.152, p = 0.052). The Child–Pugh score and INR were eliminated from the model.

Microbiological Results

Positive culture results were obtained in 41 patients. In 37 patients, a single microorganism was grown, in four patients two microorganisms each were cultured. *Candida albicans* was cultured from two specimens, accompanying *Escherichia coli* and *Enterococcus faecium*, respectively. In two cases, *E. coli* and *E. faecium* were found. Of the patients with dual infections, only one survived. Secondary bacterial peritonitis had been excluded by laboratory studies, plain abdominal X-rays (n = 1) or computed

Table 3
Parameters unequally distributed between survivors and non-survivors among the 84 patients initially receiving one of the recommended empirical antibiotic therapies.

Clinical parameters	34 patients who died	50 patients who lived	p
Child–Pugh class C	26 (76.5%)	23 (46.0%)	0.005
MELD score	24 (18–29)	20 (15–25)	0.014
Serum–bilirubin, µmol/l	3,197 (479–7,722)	505 (322–1,053)	0.055
INR	1.96 (1.58–2.33)	1.50 (1.2–2.00)	0.004
Ascitic PMN cell count, per µl	3,197 (479–7,722)	505 (322–1,053)	0.002
Positive culture results, n	20 (58.8%)	13 (26.0%)	0.002
Pathogens resistant to first treatment/cultured pathogens	8/17 (47.1%)	1/12 (5.3%)	0.043
ICU treatment, n	24 (70.6%)	15 (30.0%)	< 0.001
Escalation of antibiotic treatment, n	15 (44.1%)	9 (18.0%)	0.009
Albumin substitution, g/kg body weight	0.77 (0–3.17)	0.5 (0–1.3)	0.169

ICU: Intensive care unit

Table 4
Cultured microorganisms and their antimicrobial resistance to cefotaxime, amoxicillin/clavulanate and ciprofloxacin.

Cultured microorganisms	Culture site	Resistant to
Escherichia coli (n = 17)	Ascites (n = 16) Blood cultures (n = 2)	CTA: 1 (5.9%) ACA: 9 (52.9%) CIP: 5 (29.4%)
Other Enterobacteriaceae (n = 4) *Proteus vulgaris* (n = 1) *Klebsiella oxytoca* (n = 1) *Pseudomonas aeruginosa* (n = 1) Unclassified (n = 1)	Ascites (n = 4)	CTA: 3 (75%) ACA: 2 (50%) CIP: 2 (50%)
Bacteroides fragilis (n = 1)	Blood cultures (n = 1)	CTA: 0 ACA: 0 CIP: 0
Enterococcus faecium (n = 10)	Ascites (n = 10) Blood cultures (n = 1)	CTA: 10 (100%) ACA: 6 (60%) CIP: 8 (80%)
Other gram-positive cocci (n = 10) *Streptococcus pneumoniae* (n = 4) *Streptococcus agalactiae* (n = 2) *Streptococcus viridans* (n = 2) *Streptococcus downei* (n = 1) *Staphylococcus aureus* (n = 1)	Ascites (n = 9) Blood cultures (n = 3)	CTA: 0 ACA: 0 CIP: 4 (40%)
Candida albicans (n = 2)	Ascites (n = 2)	FLU: 0

CTA: cefotaxime; ACA: amoxicillin/clavulanic acid; CIP: ciprofloxacin; FLU: fluconazole

tomography (n = 3), and autopsy in two cases. Overall, resistance testing could be performed on 45 strains. Cultured microorganisms are presented in table 4.

There were no infections due to methicillin-resistant *Staphylococcus aureus* or due to extended-spectrum beta-lactamase-producing Enterobacteriaceae. All enterococci were susceptible to vancomycin. Of the encountered bacterial microorganisms, 14 (33.3%) were resistant to cefotaxime, 17 (38.6%) were resistant to amoxicillin/clavulanate, and 19 (45.2%) were resistant to ciprofloxacin. 29 (64.4%) of the isolates were resistant to one of the antibiotic agents, and 11 (24.4%) of the isolates were resistant to all three. Mortality was significantly higher in patients with positive culture results. There were no differences in the incidence of enterococcal or Gram-positive infections between the earlier and later group of patients. Mortality was not significantly higher in patients with enterococcal infections or with Gram-positive infections than in patients with other offending microorganisms.

Discussion

We found that there was a high rate of failure associated with the first-line antibiotic regimens in the treatment of SBP. This failure of treatment and the need to change antibiotic treatment in individual patients was in turn associated with a higher mortality. This finding was corroborated by microbiological analysis of the cultured causative microorganisms, with a large proportion being resistant to the applied first-line antibiotic regimen and a higher mortality in patients being infected with a resistant strain.

Interestingly, the majority of episodes in our study were nosocomial infections, which is in contrast with results reported earlier by other researchers [12]. As all patients with SBP that were treated at our hospital during the study period were included, inclusion bias is unlikely. The high proportion of nosocomial cases may be due to the fact that our hospital acts as a referral and liver-transplant center for a number of other hospitals and that there is only a relatively small liver outpatients department. Consequently, more than one third of the patients analyzed in our study were referrals, being admitted for reasons other than SBP, and only a minority of all patients had been admitted for SBP.

Interestingly, we found no differences in microbiological patterns or outcome between community-acquired and nosocomial cases. High rates of previous hospitalization and recent use of antibiotics, either for prophylaxis or treatment of infectious conditions, may explain the fact that the boundaries between community-acquired and nosocomial cases become blurred in a population so intensively exposed to healthcare environments and antibiotics [16].

The microbial spectrum observed in our study is similar to those found in other recent studies [12–14] in that it reveals a high proportion of Gram-positive infections and a noteworthy occurrence of fungal infections. Our finding of a large number of enterococcal infections is consistent with other recent reports detailing causative microorganisms in SBP [13, 14]. One reason for such infections may be the high rate of exposure to beta-lactams in these patients. In comparison to other recent

studies on SBP, infections with *S. aureus* were of minor importance, and we did not find any cases caused by methicillin-resistant *S. aureus* or extended-spectrum beta-lactamase-producing Gram-negative bacteria, which may be a reflection of regional patterns of prevalence [17].

Historically, Gram-negative bacteria – almost exclusively Enterobacteriaceae – have been isolated in the overwhelming majority of cases of SBP. More recently, several studies have found an increasing rate of infections with Gram-positive cocci and resistant Gram-negative bacteria. This development has been attributed to more frequent instrumentation, exposure to hospital environments, and antibiotic prophylaxis.

Amoxicillin–clavulanic acid was substituted for ceftriaxone in a number of cases, possibly in view of the evidence for an increase in Gram-positive infections. A small number of patients were initially treated with ciprofloxacin. None of the latter were critically ill, and some (n = 4) had been exposed to beta-lactams previously. Whereas in these cases the recommended regimen was replaced by other well-established treatment options of similar efficacy [4, 5, 11, 18], in some patients, obviously those most severely ill, much broader antibiotic regimens were used as first-line treatment. This latter approach may be explained by recent publications on the impact of inefficient antibiotic therapy on mortality in critically ill patients affected by a variety of infectious conditions.

It has been shown that mortality from pneumonia acquired in an ICU setting is higher in patients requiring any modification of the empirical treatment [19, 20]. In a study on nosocomial pneumonia, mortality was 37.5% in patients with an appropriate initial empirical therapy but 91.2% when the therapy was inappropriate [21]. For other infections in ICU patients, the same has been reported, with differences in the crude mortality rate ranging from 10% to 24.3% [22–25]. In contrast, a study including all hospitalized patients with microbiologically proven infection in one hospital found no association between inefficient initial treatments and mortality. However, even in this study, in the few ICU patients included, there was a trend towards higher mortality when there had been an inappropriate empirical therapy [26]. The emerging picture suggests that in more severely ill patients the impact of inappropriate empirical therapy is substantial and that any delay in time in the initiation of an efficient therapy costs lives [27]. This is reflected by current guidelines for the treatment of sepsis requiring the rapid initiation of an antibiotic regimen likely to cover all expected causative microorganisms [28].

In agreement with earlier reports, we found an association between the need to modify the initial empirical antibiotic therapy and mortality in patients with SBP. This study represents a single-center experience with a high percentage of referrals and inpatients. Our findings cannot be generalized to other clinical settings without caution. Another main limitation to our study is the observational design. Without randomization, we cannot exclude the presence of unknown risk factors being unequally distributed among the groups at baseline. Moreover, any factor causing a worse clinical course may have obliged worried clinicians to change the antibiotic treatment, thus giving a wrong impression of antibiotic failure being associated with mortality. We believe that this is an unlikely explanation of our findings for two reasons: Firstly, in culture-positive cases with tested susceptibility of the causative microorganism to the administered antibiotic treatment, there were no changes in therapy, even in fatal courses. Secondly, differences in mortality were present, no matter whether only treatment-changes based on microbiological tests in culture-positive cases or treatment changes in the whole cohort were considered. To quantify the impact of failing empirical treatment on mortality, we conducted a multivariable analysis. Factors found to be independently associated with mortality were the MELD score, which has previously been reported to be predictive of mortality in acutely critically ill cirrhotic patients [29], ascitic PMN cell counts, probably indicating the delay between the onset of disease and the diagnostic tap, and, with an OR of 5.9, the need to modify the antibiotic treatment. We interpret these findings as indicating that empirical regimens still recommended in current guidelines and reviews [2, 10, 30] may be inefficient in many hospitalized patients with SBP today. This may adversely affect outcome, and continuing efforts should be aimed at improving antimicrobial efficiency of the initial empirical treatment of SBP.

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