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The Empirical Antibiotic Treatment of Nosocomial Spontaneous Bacterial Peritonitis: Results of a Randomized, Controlled Clinical Trial

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Spontaneous bacterial peritonitis (SBP) is a common, life-threatening complication of liver cirrhosis. Third-generation cephalosporins have been considered the first-line treatment of SBP. In 2014, a panel of experts suggested a broader spectrum antibiotic regimen for nosocomial SBP, according to the high rate of bacteria resistant to third-generation cephalosporins found in these patients. However, a broader-spectrum antibiotic regimen has never been compared to third-generation cephalosporins in the treatment of nosocomial SBP. The aim of our study was to compare meropenem plus daptomycin versus ceftazidime in the treatment of nosocomial SBP. Patients with cirrhosis and nosocomial SBP were randomized to receive meropenem (1 g/8 hours) plus daptomycin (6 mg/kg/day) or ceftazidime (2 g/8 hours). A paracentesis was performed after 48 hours of treatment. A reduction in ascitic fluid neutrophil count <25% of pretreatment value was considered a treatment failure. The primary outcome was the efficacy of treatment defined by the resolution of SBP after 7 days of treatment. Thirty-two patients were randomized and 31 were analyzed. The combination of meropenem plus daptomycin was significantly more effective than ceftazidime in the treatment of nosocomial SBP (86.7 vs. 25%; $P < 0.001$). Ninety-day transplant-free survival (TFS) was not significantly different between the two groups. In the multivariate analysis, ineffective response to first-line treatment (hazard ratio [HR]: 20.6; $P = 0.01$), development of acute kidney injury during hospitalization (HR: 23.2; $P = 0.01$), and baseline mean arterial pressure (HR: 0.92; $P = 0.01$) were found to be independent predictors of 90-day TFS. *Conclusion*: The combination of meropenem plus daptomycin is more effective than ceftazidime as empirical antibiotic treatment of nosocomial SBP. Efficacy of the empirical antibiotic treatment is a strong predictor of 90-day survival in patients with nosocomial SBP. (HEPATOLOGY 2016;63:1299-1309)

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Patients with cirrhosis have an increased risk of developing bacterial infections and sepsis, compared to the general population, and bacterial infection has been associated with a 4-fold increase in mortality risk in patients with cirrhosis.[1] Among infections, spontaneous bacterial peritonitis (SBP) is one of the most frequent, life-threatening in these patients.[2] SBP is defined as a bacterial infection of

Abbreviations: ACLF, acute-on-chronic liver failure; AEs, adverse events; AKI, acute kidney injury; BID, twice per day; bpm, beats per minute; CEF, cedtazidime; CI, confidence interval; CLIF-SOFA, Chronic Liver Failure consortium modified Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate; ESBL, extended-spectrum β-lactamase-producing; HCC, hepatocellular carcinoma; HR, hazard ratio; INR, international normalized ratio; IRB, institutional review board; IV, intravenously; MAP, mean arterial pressure; MER/DAPTO, meropenem and daptomycin; MDR, multidrug resistant; MELD, Model for End Stage Liver Disease; OR, odds ratio; PMNCs, polymorphonuclear cells; RCT, randomized, controlled trial; SAEs, serious AEs; SBP, spontaneous bacterial peritonitis; SD, standard deviation; SIRS, systemic inflammatory response syndrome; TID, three times per day; TFS, transplant-free survival; USG, ultrasonography.

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Potential conflict of interest: Dr. Cillo consults and advises Novartis. He advises Astellas.

ascitic fluid developed in patients without any intra-abdominal, surgically treatable source of infection.[3] Approximately 70% of episodes of SBP are present at time of hospital admission and others are acquired during hospitalization.[4,5] According to the available guidelines for empirical antibiotic treatment of SBP, a third-generation cephalosporin should be initiated immediately after diagnosis of SBP.[6,7] Use of third-generation cephalosporins was shown to be highly effective in treatment of SBP until 10 years ago, when Gram-negative bacteria were responsible for most of the episodes and at a time when classification of infections into community-acquired, health care–associated and nosocomial infections was not routinely used in clinical practice when referring to SBP.[3] However, the epidemiology of SBP in patients with cirrhosis differs when comparing community-acquired, health care–acquired and nosocomial SBP.[5,8-10] It has been observed that patients with nosocomial SBP have a high prevalence of multidrug resistant (MDR) bacteria[4,5,8-15] and fail to respond to third-generation cephalosporins in up to 33%-75% of cases.[4,5] Most important, an ineffective first-line empirical antibiotic treatment has been associated with poor survival.[5,12-14] Therefore, recently, a panel of experts has suggested modifying the available guidelines, by using broader-spectrum antibiotics in patients with cirrhosis and nosocomial SBP.[16] Nevertheless, to date, the effectiveness and safety of a broad-spectrum antibiotic regimen has yet to be compared with third-generation cephalosporins in a prospective, randomized, controlled trial (RCT) in patients with nosocomial SBP. Although different broad-spectrum antibiotic regimens have been suggested, carbapenems should be used in order to fully cover the spectrum of Gram-negative MDR bacteria. As regards Gram-positive MDR bacteria, glycopeptides, linezolid, or lipopeptides probably ought to be used. As for glycopeptides, there are some concerns owing to a high rate of vancomycin-resistant *Enterococci* in patients with cirrhosis and nosocomial infections[9,17] and the potential risk of nephrotoxicity. On the other hand, when teicoplanin was administered intravenously (IV) at 10 mg/kg of body weight, low concentrations were achieved in peritoneal fluid.[18] Linezolid cannot be used in the majority of patients with cirrhosis and bacterial infections because of thrombocytopenia. Daptomycin is a lipopeptide that is highly effective against MDR Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococci*. Daptomycin is not currently approved for treatment of intra-abdominal infections, even if several experiences regarding efficacy of daptomycin in treatment of peritonitis in patients with continuous ambulatory peritoneal dialysis have been reported.[19-22] However, this has never been used in patients with cirrhosis and SBP. This is the first controlled clinical trial comparing meropenem plus daptomycin (MER/DAPTO) versus ceftazidime (CEF) in treatment of nosocomial SBP. MER/DAPTO were chosen according to a retrospective review of the 21 culture-positive nosocomial SBP episodes, which occurred in Padua Center from 2007 to 2009. Approximately half of the episodes (48%) were owing to Gram-negative bacteria. *Escherichia coli* and *Pseudomonas aeruginosa* were the most commonly isolated Gram-negative bacteria (25% and 10%, respectively). Susceptibility of Gram-negative bacteria to third-generation cephalosporins, quinolones, and carbapenems were 60%, 40%, and 100%, respectively. The most commonly isolated Gram-positive bacteria were *Enterococci* (24%) and *Staphylococci* (19%). The latter were methicillin sensitive in 75% of cases. *Enterococci*, which are intrinsically resistant to cephalosporins, were resistant to other beta-lactams and vancomycin in 60% and 20% of cases, respectively.

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Patients and Methods

PATIENTS

From 2011 to 2014, patients with cirrhosis and ascites admitted to the University Hospital of Padova and the Private Hospital "Giovanni XXIII" of Monastier, both located in Italy, were followed up for development of SBP. Inclusion criteria were the following: (1) diagnosis of liver cirrhosis based on histological findings or on clinical, biochemical, ultrasonographic (USG), and/or endoscopic findings; (b) ascitic fluid polymorphonuclear cell (PMNC) count $\geq$250/mm^3 in the absence of signs of secondary SBP[23]; (3) onset of signs and symptoms of infection after 72 hours from hospitalization; and (4) age $\geq$18-75 years.

Exclusion criteria were the following: (1) abdominal surgery in the previous 4 weeks; (2) hepatocellular carcinoma (HCC) beyond the Milan criteria (i.e., a single lesion <5 cm or multiple lesions [maximum of three], the largest of which measures $\leq$3 cm); (3) clinical and/or radiological evidence of secondary peritonitis; (4) congestive heart failure and/or respiratory failure; (5) treatment with third-generation cephalosporins, carbapenems, or daptomycin at the time of diagnosis of SBP (prophylaxis with norfloxacin was allowed); (6) isolation of bacteria resistant to third-generation cephalosporins, carbapenems, and/or daptomycin in cultures performed in the previous 7 days; and (7) allergy to ceftazidime, meropenem, and/or daptomycin.

The protocol was approved by the institutional review board (IRB) of each participating hospital and followed the Guidelines for Good Clinical Practice in Clinical Trials. All patients provided written informed consent. The study was registered in ClinicalTrials.gov (identifier: NCT01455246).

PROTOCOL

A physical examination, routine laboratory tests, chest X-ray, abdominal X-ray, and abdominal USG were performed in all patients before initiation of therapy. In addition, samples of at least 60 mL of ascitic fluid and 20 mL of blood were taken for culture and other laboratory examinations at the patient's bedside. At least 20 mL of ascitic fluid were injected into two blood-culture bottles (aerobic and anaerobic, 10 mL each) at the patient's bedside. Fresh urine sediment and a urine culture were also performed. Diagnosis of SBP was based on a PMNC count in ascitic fluid $\geq$250/mm^3.[3] Nosocomial SBP was defined as an infection occurring >72 hours from hospital admission.[12]

Randomization was performed using consecutively numbered, computer-generated, sealed, opaque envelopes containing the treatment assigned. Randomization was independent for each hospital. Antibiotic treatment was started within 1 hour after randomization. A diagnostic paracentesis was repeated after 48 hours and 7 days after starting treatment for the assessment of ascitic fluid PMNC count and ascitic fluid culture. Independent laboratory examiners, blinded to the assigned treatment, manually assessed the ascitic fluid PMNC count.

In patients randomized to receive ceftazidime (CEF group), ceftazidime (Glazidim; GlaxoSmithKline S.p.A., Verona, Italy) was administered at a dose of 2 g three times per day (TID), 2 g twice per day (BID), and 2 g/day by IV infusion according to an estimated glomerular filtration rate (eGFR) >50 mL/min, 10-50 mL/min, and <10 mL/min, respectively. In patients randomized to receive meropenem plus daptomycin (MER/DAPTO group), meropenem (Merrem; AstraZeneca S.p.A., Basiglio, Milan, Italy) was given 1 g TID, 1 g BID, and 0.5 g per day by IV infusion according to an eGFR >50 mL/min, 10-50 mL/min, and <10 mL/min respectively; daptomycin (Cubicin; Novartis Pharma GmbH, Nürnberg, Germany) was given at the dose of 6 mg/kg every 24 hours and 6 mg/kg every 48 hours according to an eGFR $\geq$30 mL/min and <30 mL/min, respectively. Patients were treated for at least 7 days. In patients without response to treatment with ceftazidime after 48 hours, ceftazidime was discontinued and replaced by a rescue therapy with MER/DAPTO as provided for the experimental arm. In patients without response after 48 hours of treatment with MER/DAPTO, fluconazole was added as rescue therapy (Fig. 1). In patients in which cultures showed a bacterial species resistant to the assigned treatment, this was discontinued and replaced by an individualized therapy, according to the *in vitro* susceptibility of isolated strains. In all patients randomized in the study, albumin (Albital; Kedrion S.p.A., Barga, Lucca, Italy) was given at a dose of 1.5 g/kg of body weight on day 1, followed by 1 g/kg on day 3.[24] Laboratory measurements were repeated every 2 days during the first 7 days after enrollment and at least every 3 days thereafter until discharge. Acute-on-chronic liver failure (ACLF) was defined according to the CANONIC study definition.[25] Other definitions are reported in the Supporting Materials and Methods. From 2012 onward, in patients enrolled in Padua Center, trough levels of daptomycin in ascitic fluid at

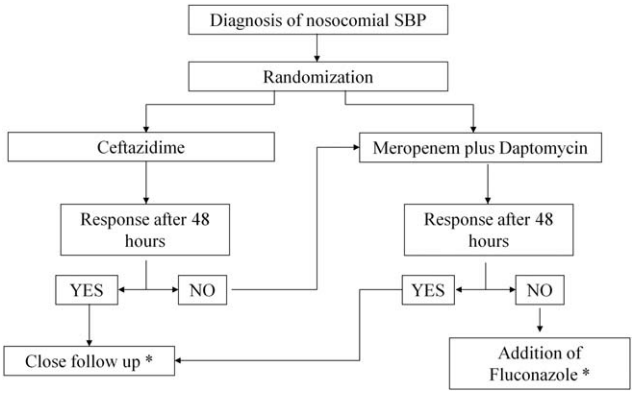

FIG. 1. Algorithm of the protocol. *In patients with positive cultures, antibiotic treatment was modified according to antimicrobial susceptibility of isolated bacteria.

48 hours were assessed by means of high-performance liquid chromatography.

Secondary prophylaxis of SBP with norfloxacin (or rifaximin in patients who developed SBP during norfloxacin prophylaxis) was started in all patients after resolution of SBP. Patients were followed up at regular intervals for 3 months after enrollment in the study. Costs for patient management, including hospital stay, laboratory tests, antibiotic treatment, and diagnostic and therapeutic procedures, were assessed in both groups.

STUDY ENDPOINTS

The primary endpoint of the study was the response to treatment defined as follows: (1) reduction of PMNC count in ascitic fluid >25% from baseline after 48 hours of treatment[3,26] and (2) PMNC count in ascitic fluid <250/mm^3 after 7 days of treatment in the absence of clinical signs of infection. If there was isolation of bacteria resistant to the assigned treatment in blood, ascitic fluid, or urine cultures, treatment was considered ineffective.

Secondary endpoints included: (1) 90-day transplant-free survival (TFS); (2) length of hospital stay; (3) cost of hospitalization (estimated using local costs for hospital stay, intensive care unit stay, drug use, and invasive procedures needed for management of complications); (4) cost of antibiotic treatment (estimated using local costs of the antibiotic treatments given during the treatment of SBP); (5) safety of the treatment (defined as the number of adverse events [AEs] and serious AEs [SAEs]) and (6) the efficacy of daptomycin in the treatment of intra-abdominal infections.

STATISTICAL ANALYSIS

Sample size was calculated according to the primary endpoint: efficacy of assigned antibiotic treatment. In 2009, Acevedo et al. reported that third-generation cephalosporins were effective in 44% of patients with nosocomial SBP and 83% of community-acquired SBP.[27] In our experience the efficacy of ceftazidime in community-acquired SBP was 84%.[28] We hypothesized to achieve the primary endpoint in 84% of patients treated with MER/DAPTO and in 44% of patients treated with CEF. Considering a drop-out rate of 10%, 30 patients per group would be needed to detect this difference, with a two-sided type I error rate of 5% and a type II error rate of 20%. Normally distributed continuous variables were reported as means with standard deviation (SD) and compared with Student *t* test. Non-normally distributed continuous variables were reported as median, minimum-maximum, and compared with Mann-Whitney's U test. Categorical variables were reported as proportions and compared with Fisher's exact test. Variables found to have a *P* value of less than 0.1 in the univariate analysis were included in a multivariate step-wise logistic regression analysis, with backward elimination, in order to identify independent predictors of the primary endpoint. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated. Ninety-day survival was estimated by Kaplan-Meier's method and compared by means of log-rank test. Patients transplanted during follow-up were considered censored at time of transplantation. A step-wise Cox's proportional hazards model, with backward elimination, was performed to identify independent predictors of 90-day survival. Hazard ratios (HRs) and their 95% CIs were calculated. When Model for End Stage Liver Disease (MELD)-Na score, Child-Turcotte-Pugh (CTP) score, and Chronic Liver Failure consortium modified Sequential Organ Failure Assessment (CLIF-SOFA) score were included in the multivariate analysis, their components were excluded to avoid multicollinearity. Similarly, when development of ACLF was included in the multivariate analysis, development of acute kidney injury (AKI) was excluded to avoid collinearity. An interim analysis was planned after enrollment of half of the sample. An independent statistician performed the statistical analysis. All tests were two-tailed and *P* values <0.05 were considered significant. The statistical analysis was performed with the use of the SPSS statistical package (version 20.0; SPSS, Inc., Chicago, IL). All authors had access to the study data and had reviewed and approved the final manuscript.

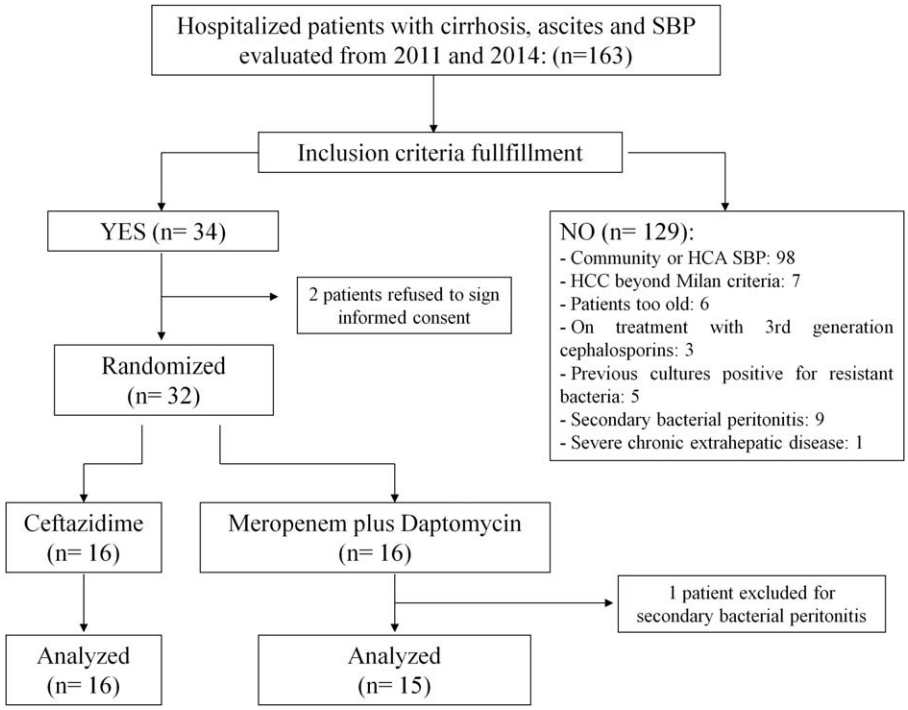

FIG. 2. Flow diagram of patients evaluated in the study. Abbreviation: HCA, health care–acquired.

Results

STUDY POPULATION

One hundred sixty-three patients with cirrhosis and ascitic fluid PMNC count $\geq 250/mm^3$ were evaluated (Fig. 2). Among them, 129 were excluded because they failed to meet inclusion criteria (98 had community- or health care–acquired SBP, 9 had secondary bacterial peritonitis, 7 had HCC beyond Milan criteria, 6 were too old, 3 were on treatment with third-generation cephalosporins, 5 had positive cultures performed in the previous 7 days positive for bacteria resistant to third-generation cephalosporins and/or carbapenems, and 1 had a severe ischemic heart disease) and 2 refused to provide written informed consent. Of the 32 patients randomized, 1 (randomized to MER/DAPTO) was excluded from the analysis because he had secondary bacterial peritonitis. Therefore, the final analysis of the trial included 31 patients: 15 in the MER/DAPTO group and 16 in the CEF group. Twenty-nine of thirty-one patients (93.5%) had a paracentesis at admission (within 48 hours) to rule out SBP. Two patients (both in CEF group) had no previous paracentesis; however, signs of infection appeared after 7 and 10 days from hospitalization.

There were no significant differences between the two groups as regarded demographic, clinical, and laboratory data (Table 1). Risk factors for development of infection resulting from third-generation cephalosporin-resistant bacteria and/or MDR bacteria, namely, norfloxacin prophylaxis at the time of SBP diagnosis, antibiotics use in the previous 3 months, and days from hospitalization to diagnosis of SBP were similar among the two groups. SBP was the second infection in 2 patients in the MER/DAPTO group and 1 patient in the CEF group (P = not significant). Prognostic scores of liver disease, such as MELD, MELD-Na, CTP, and CLIF-SOFA, were not significantly different between the two groups. A similar proportion of patients was on the transplant waiting list at the time of enrollment in the study.

RESPONSE TO ANTIBIOTIC TREATMENT

Resolution of infection was achieved with the assigned treatment in 13 patients in the MER/DAPTO group and in 4 in the CEF group (86.7% vs. 25%; $P < 0.001$). The reasons for treatment failure were: (1) failure to achieve a reduction in PMNC count in ascitic fluid >25% from baseline after 48 hours

TABLE 1. Baseline Demographics, Clinical and Laboratory Characteristics of All Patients and Patients Randomized to Ceftazidime (CEF Group) or Meropenem Plus Daptomycin (MER/DAPTO Group)

	Whole Population	CEF Group	MER/DAPTO Group	*P* Value
No.	31	16	15	—
Age, years, mean (SD)	60.0 (8.9)	60.3 (9.5)	59.7 (8.6)	0.88
Gender, male, n (%)	19 (61.3)	10 (62.5)	9 (60)	1.00
Etiology, n (%)				0.61
HCV	8 (25.8)	5 (31.2)	3 (20)	
Alcohol	20 (64.5)	9 (56.3)	11 (73.3)	
Others	3 (9.7)	2 (12.5)	1 (6.7)	
MELD score, mean (SD)	21.0 (7.5)	20.6 (9.2)	21.4 (5.3)	0.78
MELD Na, mean (SD)	23.8 (7.5)	23.3 (9.1)	24.3 (5.7)	0.69
Child Pugh score, median (min-max)	11 (7-14)	12 (7-14)	11 (9-14)	0.80
Child Pugh class, n (%)				0.22
A	0	0	0	
B	8 (25.8)	6 (37.5)	2 (13.3)	
C	23 (74.2)	10 (62.5)	13 (86.7)	
MAP (mm Hg), mean (SD)	75.4 (9.9)	76.8 (9.5)	73.9 (10.5)	0.42
Heart rate (bpm), median (min-max)	80 (60-130)	83.5 (60-106)	79 (60-130)	0.55
CLIF SOFA score, mean (SD)	8.6 (3.4)	7.9 (4.1)	9.3 (2.4)	0.26
ACLF, n (%)*	18 (58.1)	9 (56.3)	9 (60.0)	1.00
SIRS, n (%)	15 (48.4)	8 (50.0)	7 (46.7)	1.00
Ascitic fluid PMNC count (cells/μL), median (min-max)	1,080 (256-6,217)	1,037 (256-5,000)	1,083 (360-6,217)	0.86
Serum leukocyte count (cells $\times 10^3$/μL), median (min-max)	6.8 (0.63-16.62)	6.6 (0.6-16.6)	6.9 (2.9-15.9)	0.98
INR, median (min-max)	1.5 (1.1-2.6)	1.6 (1.1-2.6)	1.5 (1.2-2.2)	0.92
Bilirubin, μmol/L, median (min-max)	84.1 (8.6-383.0)	63.6 (8.6-383.0)	91.6 (14.2-160.8)	0.50
Albumin, g/dL, mean (SD)	3.0 (0.5)	2.9 (0.6)	3.1 (0.4)	0.37
Serum creatinine, μmol/L, median (min-max)	137 (44-489)	139.5 (57-272)	137 (44-489)	0.80
Serum sodium, mmol/L, mean (SD)	133.6 (4.7)	133.6 (4.0)	133.7 (5.5)	0.92
Antibiotic use in previous 3 months, n (%)	18 (58.1)	9 (56.3)	9 (60.0)	1.00
Norfloxacin prophylaxis, Y/N, n (%)	8 (25.8)	5 (31.2)	3 (20.0)	0.69
Days from hospitalization to SBP, days, mean (SD)	7.6 (9.3)	5.3 (2.5)	10.1 (12.8)	0.17
Beta-blockers use, Y/N, n (%)	11 (35.5)	6 (37.5)	5 (33.3)	1.00
On transplant waiting list, Y/N, n (%)	13 (41.9)	6 (37.5)	7 (46.7)	0.72

*ACLF was defined according to the CLIF consortium definition.[25]
Abbreviations: M, male; F, female; HCV, hepatitis C virus; Y/N, yes/no.

of treatment (7 patients in the CEF group and 1 in the MER/DAPTO group); (2) isolation of bacteria resistant to the assigned treatment (4 patients in the CEF group); (3) failure to obtain a complete response (PMNC count on ascitic fluid <250 cells/μL) after 7 days of treatment (1 patient in CEF group and 1 in the MER/DAPTO group). Two of three patients (67%) on norfloxacin prophylaxis responded to treatment in MER/DAPTO group versus 1 of 5 patients (20%) in the CEF group (p = not significant). Nonresponders in the CEF group were allocated to: meropenem plus daptomycin (10) and meropenem plus vancomycin (1). One patient died before the rescue treatment was assigned. A final resolution of SBP was obtained in 9 (90%) CEF nonresponders subsequently treated with MER/DAPTO; 1 patient had no response and was subsequently treated effectively with tigecycline. The patient treated with meropenem and vancomycin died before resolution of SBP. Nonresponders to the MER/DAPTO group were treated adding fluconazole (1) and meropenem plus tigecycline and fluconazole (1). The former required treatment with tigecycline and achieved a resolution of SBP, whereas the latter had no response. A final resolution of SBP was achieved in 14 patients in the CEF group and 14 in the MER/DAPTO group (87.5% vs. 93.3%; *P* = not significant). Globally, resolution of infection was obtained in 22 of 25 patients treated with meropenem plus daptomycin (88%). When responders versus nonresponders to first-line treatment were compared, the latter had a higher baseline heart rate (92 vs. 75 beats per minute [bpm]; *P* = 0.001) and prevalence of systemic inflammatory response syndrome (SIRS; 71.4% vs. 28.6%; *P* = 0.03; Table 2). There was a trend toward a higher blood leukocytes count in nonresponders versus responders (9,135 vs. 6,400 cells/μL; *P* = 0.08). In the multivariate logistic regression analysis, treatment with MER/DAPTO (OR = 302.1; CI = 2.8-32,443; *P* = 0.017) and HR (OR = 0.83; CI = 0.71-0.97; *P* = 0.023) were found to be independent predictors of

TABLE 2. Baseline Demographics, Clinical and Laboratory Characteristics in Responders and Nonresponders to First-Line Treatment

	Responders	Nonresponders	*P* Value
No.	17	14	—
Age, years, mean (SD)	60.3 (9.9)	59.6 (8.0)	0.84
Gender, male, n (%)	10 (58.8)	9 (64.3)	1.00
Etiology, n (%)			0.69
HCV	5 (29.4)	3 (21.4)	
Alcohol	11 (64.7)	9 (64.3)	
Others	1 (5.9)	2 (14.3)	
MELD score, mean (SD)	19.5 (5.3)	22.8 (9.4)	0.26
MELD Na, mean (SD)	22.3 (5.6)	25.6 (9.3)	0.26
Child Pugh score, median (min-max)	11 (8-14)	12 (7-14)	0.16
MAP, mm Hg, mean (SD)	77.5 (8.7)	72.9 (11.0)	0.22
Heart rate, bpm, median (min-max)	75 (60-100)	92 (65-130)	0.001
CLIF SOFA score, mean (SD)	8.1 (2.4)	9.1 (4.5)	0.42
ACLF, n (%)*	5 (29.4)	8 (57.1)	0.16
SIRS, n (%)	5 (29.4)	10 (71.4)	0.03
Ascitic fluid PMNC count, cells/μL, median (min-max)	848 (290-6,217)	1,473 (256-4,455)	0.17
Serum leukocyte count (cells/μL), median (min-max)	6,400 (2,900-14,560)	9,135 (630-16,620)	0.08
INR, median (min-max)	1.5 (1.2-1.9)	1.7 (1.1-2.6)	0.17
Bilirubin, μmol/L, median (min-max)	84.1 (14.2-179.5)	79.9 (8.6-383.0)	0.95
Albumin, g/dL, mean (SD)	30.8 (4.1)	28.5 (5.6)	0.22
Serum creatinine, μmol/L, median (min-max)	124 (44-489)	152 (62-285)	0.16
Serum sodium, mmol/L, mean (SD)	134.7 (5.1)	132.4 (3.9)	0.18
Antibiotic use in previous 3 months, n (%)	8 (47.1)	10 (71.4)	0.28
Norfloxacin prophylaxis, n (%)	4 (23.5)	4 (28.6)	1.00
Days from hospitalization to SBP, days, mean (SD)	8.9 (12.3)	6.1 (2.7)	0.92
Beta blockers use, n (%)	6 (35.3)	5 (35.7)	1.00
Randomization, CEF versus MER/DAPTO, n (%)	4 (23.5)/13 (76.5)	12 (85.7)/2 (14.3)	<0.001

*ACLF was defined according to the CLIF consortium definition.[25]
Abbreviations: M, male; F, female; HCV, hepatitis C virus.

response to first-line treatment. According to results of the interim analysis, the trial monitoring committee (two IRB members and one investigator) decided to stop the trial in order to avoid harm to the CEF group.

Sixteen patients (10 in the CEF group and 6 in the MER/DAPTO group) had at least one positive culture. Characteristics and antibiotic susceptibility of isolated strains are reported in Supporting Table 1. Gram-positive bacteria were the most common isolated bacteria (62.5% vs. 37.5%). Among them, *Enterococci* were the most frequently isolated bacteria. Among Gram-negative bacteria, *E. coli* was the most common isolated strain. Thirteen of sixteen bacteria (81.3%) were resistant to third-generation cephalosporins. There was no significant difference between the two groups in the prevalence of bacteria-resistant to third-generation cephalosporins (80% vs. 83.3%; *P* = not significant). Six MDR bacteria were isolated (37.5%): 3 extended-spectrum *β*-lactamase-producing (ESBL) *E. coli* and 3 *Enterococcus faecium*. During their hospitalization, 9 patients (4 in the CEF group and 5 in the MER/DAPTO group) developed a second non-SBP infection (4 pneumonia, 3 urinary tract infection, and 2 spontaneous bacteremia).

In 5 patients, trough daptomycin concentrations were evaluated in peritoneal fluid after 48 hours of treatment. In all of them, daptomycin levels (mean = 8.7 ± 3.1 μg/mL) were above the minimum inhibitory concentration for *Enterococci* (4.0 μg/mL).

SURVIVAL

During the 90-day follow-up, 5 patients (16.1%) were transplanted (3 in the MER/DAPTO group and 2 in the CEF group) and 8 patients died (3 in the MER/DAPTO group and 5 in the CEF group). In-hospital mortality was 13.3% in the MER/DAPTO group and 25% in the CEF group (*P* = not significant). Probability of 30-day TFS was 86.7% in the MER/DAPTO group and 81.3% in the CEF group (*P* = not significant). Ninety-day TFS was not different in the two groups (79.4% in the MER/DAPTO group vs. 68.8% in the CEF group; *P* = not significant). Causes of death in the MER/DAPTO group and the CEF group were: multiorgan failure (2 vs. 1); septic shock (2 in the CEF group); liver failure (1 vs. 1); and gastrointestinal bleeding (1 in CEF group).

TABLE 3. Univariate Analysis of Predictors of 90-Day TFS

	HR	CI	*P* Value
Age, years	1.01	0.94-1.09	0.73
MELD	1.12	1.03-1.22	0.012
MELD Na	1.14	1.03-1.26	0.011
Child Pugh score	1.89	1.12-3.18	0.016
Heart rate, bpm	1.04	1.00-1.09	0.071
MAP, mm Hg	0.91	0.84-0.99	0.029
CLIF SOFA score	1.67	1.19-2.35	0.003
ACLF, yes versus no*	5.31	1.08-26.4	0.041
SIRS, yes versus no	9.98	1.22-81.46	0.032
Serum leukocyte count, cells/μL	1.18	0.98-1.43	0.083
INR	4.73	1.07-20.9	0.041
Bilirubin, μmol/L	1.00	1.00-1.01	0.249
Albumin, g/dL	0.84	0.71-0.99	0.036
Serum creatinine, μmol/L	1.00	1.00-1.01	0.299
Serum Na, mmol/L	0.90	0.77-1.06	0.223
Randomization, CEF vs. MER/DAPTO	1.64	0.39-6.87	0.498
Beta-blockers use, Y/N	3.20	0.76-13.39	0.112
Development of AKI, yes versus no†	9.74	1.19-79.5	0.034
Development of ACLF, yes versus no	13.53	1.65-110.67	0.015
Development of a second infection, yes versus no	4.48	1.07-18.78	0.04
Response to first line treatment, no versus yes	11.43	1.40-93.39	0.023

*ACLF was defined according to the CLIF consortium definition.[25]
†AKI was defined as an increase in serum creatinine ≥0.3 mg/dL (26.5 μmol/L) in 48 hours or ≥50% from baseline in 48 hours.
Abbreviations: Y/N, yes/no.

An unadjusted analysis of predictors of 90-day survival is reported in Table 3. Baseline scores of liver disease (MELD, MELD-Na, CTP, and CLIF-SOFA), mean arterial pressure (MAP), serum albumin, international normalized ratio (INR), and the presence of ACLF and SIRS were significantly associated with mortality. Development of AKI, ACLF, second bacterial infections, and inappropriate first-line treatment were found to be significant predictors of mortality. In the multivariate Cox's regression analysis two models were investigated in order to avoid collinearity between variables. In the first model, response to first-line treatment, MAP, and development of AKI were found to be independent predictors of 90-day TFS (Table 4). When development of ACLF was included in the model, response to the first-line treatment and development of ACLF were found to be the only independent predictors of 90-day TFS (Table 4). Probability of survival according to efficacy of assigned first-line treatment is reported in Fig. 3. Ninety-day probability of survival was 93.8% in responders and 50.0% in nonresponders to first-line treatment ($P = 0.004$). In-hospital mortality was 0% in responders and 43% in nonresponders to first-line treatment ($P = 0.004$). Thirty-day probability of survival was 100% and 64.3% in responders and nonresponders to first-line treatment, respectively ($P = 0.008$).

AEs

AEs in the study population are reported in Supporting Table 2. The most common AEs were encephalopathy, nausea, diarrhea, AKI, and development of second infections. The overall rate of AEs and SAEs were similar in the two groups. AEs were considered to be related to study treatment in 4 (25%) patients in the CEF group and 3 (20%) in the MER/DAPTO group. These related AEs were nausea (3 patients in the CEF group and 3 in the MER/DAPTO group) and diarrhea (1 patient in the CEF group). No AEs led to withdrawal of study drugs. No patients had a significant increase in creatine phosphokinase from baseline.

Discussion

The main result of this controlled trial was that administration of MER/DAPTO was found to be more effective than CEF in treatment of nosocomial SBP. Only 25% of patients randomized to CEF achieved a response to treatment of SBP, compared to 86.7% of patients randomized to MER/DAPTO ($P < 0.001$). Furthermore, MER/DAPTO was effective in 90% of nonresponders to CEF. The low efficacy of CEF in our study population is in agreement with the data of Fernandez et al., who reported a clinical efficacy in only 26% of patients with nosocomial SBP treated with third-generation cephalosporins.[4] The difference in efficacy between MER/DAPTO and CEF is well explained by the high proportion (80%) of SBP sustained by either Gram-negative or -positive bacteria who were resistant to CEF. In our series, all Gram-negative bacteria who were resistant to CEF were sensitive to meropenem. As for Gram-positive

TABLE 4. Multivariate Cox's Regression Analysis of Predictors of 90-Day TFS

	HR	CI	*P* Value
Model 1			
MAP, mm Hg	0.92	0.84-0.99	0.04
Development of AKI, yes versus no	23.24	2.13-253.14	0.01
Response to first-line treatment, no versus yes	20.63	2.10-202.89	0.009
Model 2			
Development of ACLF, yes versus no	14.60	1.74-122.65	0.014
Response to first-line treatment, no versus yes	12.33	1.47-103.42	0.021

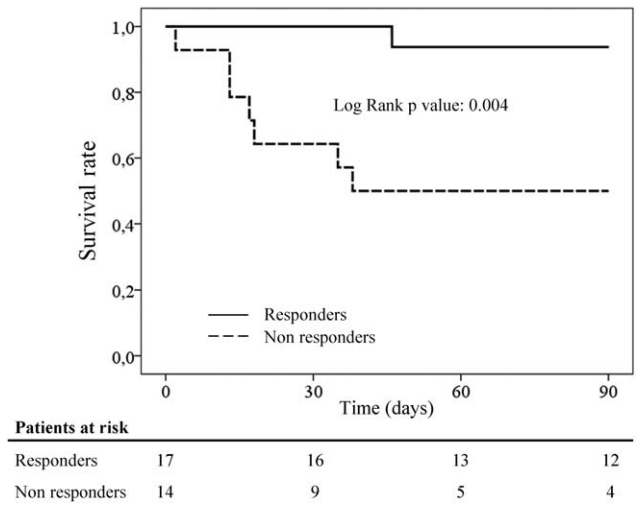

FIG. 3. Probability of 90-day TFS according to efficacy of first-line treatment. Ninety-day TFS in patients categorized according to efficacy of first-line treatment. Continuous line, responders to first-line treatment; dashed line, nonresponders to first-line treatment.

bacteria, a high prevalence of *Enterococci* was found, these being intrinsically resistant to cephalosporins. The high prevalence of *Enterococci* in our series is well in agreement with the data reported by other centers across Europe and Asia.[11,12,29] In this regard, it should be outlined that no isolate of *E. faecium* was sensitive to meropenem. This finding highlights the role of daptomycin in the combined empirical antibiotic treatment of nosocomial SBP and confirms the need to cover the spectrum of Gram-positive bacteria beyond what is realized by carbapenems alone. Preliminary data showed that carbapenems were effective in only 51.7% of patients with "difficult-to-treat SBP" (nosocomial episodes or nonresponders to third-generation cephalosporins).[30] Of course, our proposal to use MER/DAPTO in treatment of nosocomial SBP requires external validation, given that the high rate *Enterococci*-related SBP found in our series may not be the same in other countries or even in other centers within the same country. Currently, the antibiotic treatment of choice cannot be generalized without taking into account the local epidemiology of bacteria. Local resistance pattern is critical for proper selection of the empirical antibiotic treatment, and all centers across the world should evaluate their own epidemiology of nosocomial infections. In some centers, with a low prevalence of MDR bacteria, broad-spectrum antibiotics may be not necessary and an overtreatment may be avoided. However, use of MER/DAPTO may be a good option in countries and/or centers with a high rate of MDR bacteria, such as ESBL *Enterobacteriaceae*, methicillin-resistant *S. aureus*, and *Enterococci*. Some concerns may arise regarding the impact of early treatment with broad-spectrum antibiotics because of the possible development of more-extended antibiotic resistance. These concerns are justified and may be partially overcome by adopting an early de-escalation to the most appropriate antibiotic treatment whenever microbiological results are available[31] and by using antibiotics at the highest tolerated doses for the shortest period of time. The latter is not a new paradigm, given that Ehrlich's concept of "hit hard and fast" was first described a century ago.[32]

The second main result of this study was to show that in-hospital, 30-day, and 90-day TFS was significantly higher in responders than nonresponders to first-line antibiotic treatment (Fig. 3). Indeed, several previous studies have reported the same result.[5,12-14] However, this is the first prospective, RCT to show the efficacy of first-line treatment is an independent predictor of survival. These data further support the concept that an effective antibiotic treatment must be started as soon as possible in patients with nosocomial SBP. One may argue that no difference was found in mortality rate between the two groups, despite that MER/DAPTO was more effective than CEF. However, several reasons may explain the lack of significant difference in survival between the two groups: (1) The sample size was not adequate to estimate a difference in survival; (2) the design of the study, providing the possibility to change antibiotic treatment after 48 hours, was not optimal to identify a difference in survival between the two treatments; and (3) there was nonsignificance, but a trend toward a sicker population in the MER/DAPTO group.

As regards the other predictors of 90-day survival, the independent prognostic relevance of MAP, AKI, and ACLF deserves some comment. MAP has been shown to be a good predictor of survival in patients with cirrhosis and ascites.[33] As far as AKI is concerned, several studies have shown the prognostic relevance of renal impairment as well as the importance of preserving renal function in patients with cirrhosis and SBP.[24,34] Finally, ACLF has been shown to be a strong predictor of survival in patients with decompensated cirrhosis,[25] and the development of extrahepatic organ failures, the hallmark of ACLF, was found to be the main determinant of mortality in patients with cirrhosis and bacterial infections.[35]

Admittedly, our study has some limitations. The main one is its early termination after the inclusion of only half of the provided sample size. However, the decision to terminate the study after the interim analysis, which was planned in the study protocol, was taken by the monitoring committee on the basis of two data: (1) the difference in primary endpoint between the two groups was highly significant and (2) the finding that the response to first-line treatment was an independent predictor of survival. A second limitation is whether such a study was needed. However, when the study was planned in 2010, both the American Association for the Study of Liver Diseases and European Association for the Study of the Liver updated guidelines still suggested using third-generation cephalosporins as the first-line empirical treatment of SBP.[6,7] Furthermore, we strongly believe that the changes in the management of nosocomial SBP recently proposed needed to be supported by evidence on the efficacy and safety of the proposed regimens and not only by epidemiological findings. Consequently, our study appears to be a step forward in the right direction.

In conclusion, the study shows that MER/DAPTO is more effective than CEF in the treatment of nosocomial SBP, in centers with a high prevalence of MDR bacteria. Thus, in centers with high prevalence of MDR bacteria, a broad-spectrum antibiotic regimen, such as MER/DAPTO, should be considered as first-line empirical treatment in patients with cirrhosis and nosocomial SBP.

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Supporting Information

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep.27941/suppinfo.