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Bacterascites: A study of clinical features, microbiological findings, and clinical significance

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Abstract

Background: Knowledge about bacterascites is limited and management guidelines are based on small patient series. The purpose of this study was to add further insight into the clinical characteristics, microbiological findings, and prognosis of patients diagnosed with bacterascites.

Methods: Retrospective analysis of patients with advanced chronic liver disease diagnosed with bacterascites and SBP between January 2003 and August 2016.

Results: In this study, 123 patients were included with 142 episodes of bacterascites. The median MELD score was 20 and clinical symptoms of infection were present in 78%. Empiric antibiotic treatment was initiated in 68%. In 26 untreated patients undergoing repeated paracentesis, 42% were diagnosed with either ongoing bacterascites or SBP. The presence of signs or symptoms of infection was not an independent predictor for mortality or spontaneous resolution of infection. The 1-month and 1-year mortality rates of the 123 patients studied, were 32% and 60%, respectively; these results were in line with data pertaining to the prognosis of SBP.

Conclusions: Patients with bacterascites and SBP are highly comparable with respect to severity of liver disease and overall prognosis. If left untreated, bacterascites is likely to persist or to evolve to SBP in a significant proportion of patients. The results of this study support current guidelines regarding the treatment of ascitic fluid infection, but could not confirm the prognostic relevance of symptomatic disease at the time of diagnosis. We suggest that the threshold to initiate antibiotic treatment, in particular in cases with severely advanced liver disease, should be low.

KEYWORDS

bacterascites, cirrhosis, microbiology, spontaneous bacterial peritonitis

1 | INTRODUCTION

Bacterascites is defined by an ascitic fluid polymorphonuclear neutrophil (PMN) count below 250/μL and a positive ascitic fluid culture results in the absence of an evident intra-abdominal, surgically treatable source of infection.[1] It is a different clinical entity than spontaneous bacterial peritonitis (SBP), which is characterized by a neutrophil reaction in ascites regardless of the bacterial culture

Abbreviations: CI, confidence interval; CP, Child-Pugh; ESBL, extended-spectrum beta-lactamase; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; HIV, human immunodeficiency virus; HR, hazard ratio; INR, international normalized ratio; IQR, interquartile range; MDR, multidrug-antibiotic resistant; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; PMN, polymorphonuclear neutrophil; SBP, spontaneous bacterial peritonitis; SD, standard deviation; WBC, white blood cell.

result. Bacterascites is prevalent in 8%-11% of all patients with cirrhosis and ascites, and the clinical significance seems to vary according to how the infection was acquired.[2-7]

Several hypotheses have been proposed to explain the potential underlying pathophysiological mechanisms. The most common theory implicates that the bacterial colonization of ascites is caused by bacterial translocation from the intestinal lumen or by secondary translocation from a concomitant infection from extraintestinal sites (eg, urogenital or respiratory tract). The absence of an inflammatory response could be interpreted as an early phase of SBP, in which the neutrophil response has not commenced yet, or a spontaneously resolving infection, determined by good host defences or less virulent pathogens.[1,4] In this context, the term 'symptomatic bacterascites' has been introduced for patients with bacterascites and clinical symptoms of infection, in order to identify those patients who may require treatment. Furthermore, bacterascites caused by commensal skin bacteria has been attributed to exogenous contamination of the ascitic fluid sample and bacterascites with multiple pathogens may be caused by traumatic paracentesis.[2,3] The indication for antibiotic treatment of bacterascites is generally regarded to be dependent on the supposed pathophysiological mechanism and the clinical situation.

The AASLD practice guideline regarding the management of ascites states that patients with ascites and convincing signs or symptoms of infection should receive empiric antibiotic treatment.[8] This recommendation is based on one study with 36 cases of bacterascites receiving a follow-up paracentesis, in which 62% of the cases spontaneously resolved and 38% progressed to SBP.[4] The EASL clinical practice guideline endorses this recommendation and further states asymptomatic patients should undergo a second paracentesis when culture results come back positive. Patients in whom the repeated ascitic PMN count is greater as or equal to 250/μL should be treated for SBP, and the remaining patients (ie, PMN count below 250/μL) should be followed up.[9] This guideline is based on a consensus document of the International Ascites Club in 2000.[1]

Although bacterascites is not an uncommon condition, relatively few studies on prognostic factors and outcome of this ascitic fluid infection have been reported.[2-7] Therefore, the purpose of this study was to assess the clinical characteristics, microbiological findings, and clinical course in consecutive patients diagnosed with bacterascites. We further attempted to study the prognostic impact of bacterascites in comparison to SBP, and to define the most logical therapeutic approach.

Key Points

- Bacterascites is an ascitic fluid infection with a positive bacterial culture and PMN count below 250/μL. Patients with bacterascites and SBP present with a similar degree of liver insufficiency and have a comparable poor prognosis. Current guidelines state patients with symptomatic bacterascites should receive antibiotic treatment. However, the present study could not confirm the prognostic importance of presence of symptoms at the time of diagnosis.

2 | PATIENTS AND METHODS

2.1 | Study design and data collection

All consecutive ascites cultures performed in patients with advanced chronic liver disease between January 2003 and August 2016 at Erasmus MC, University Medical Center, were retrospectively reviewed to identify patients fulfilling the diagnostic criteria for bacterascites. The Medical Ethics Committee Erasmus MC, approved the study protocol on February 27th, 2017 and stated that written informed patient consent was not necessary considering the design of the study.

All ascites samples obtained during the study period were reviewed, implying that, if applicable, multiple bacterascites episodes per patient were taken into account. The lowercase letter n was used to indicate the number of patients and the capital letter N for the number of bacterascites episodes.

Paracentesis was performed in patients with new-onset ascites, clinical deterioration, and large-volume removal in refractory ascites.[9] White blood cell (WBC) and PMN count in ascites were automatically determined and aerobic and anaerobic blood culture bottles (Bactec®) were used for bacterial cultures. Blood cultures taken within two hours before or after ascites cultures were considered to be concomitant.

Demographic, clinical, biochemical, and survival data from patient hospital records were collected.

To determine the prognostic impact of bacterascites in comparison with reported outcomes of SBP, a control cohort was established with patients from our centre with SBP, performed as described in a previous publication.[10] In order to create homogenous groups for survival analyses, patients with both episodes of bacterascites and SBP were categorized as SBP when the first ascites infection was SBP or bacterascites developed within 48 h to SBP. Patients with bacterascites developing SBP after 48 h, but within 30 days were excluded from survival analysis. In addition, the MELD score-dependent relation of the prognosis of bacterascites patients was studied and compared with SBP patients.[11,12]

Furthermore, a PubMed search was performed on December 1st, 2017 with the following search terms: spontaneous bacterial peritonitis (ALL) AND (outcome (ALL) OR mortality (ALL)) AND prognos* (ALL). The studies were reviewed and included when the following criteria were met: (1) observational studies, (b) study population consisted of patients with SBP defined as a PMN count of 250/μL or greater in ascites, (c) minimum study population of 50 adult patients, (d) reporting survival analysis and 1-month or

TABLE 1 Baseline demographic and clinical patient characteristics

	Patients with bacterascites (n = 123)
Male, n (%)	76 (62%)
Age in years, mean (SD)	63 (±14)
Aetiology of cirrhosis, n (%)	
Alcohol	35 (29%)
Viral	26 (21%)
Autoimmune-related	19 (15%)
Alcohol + viral	10 (8%)
NASH	9 (7%)
Other	24 (20%)
MELD score, median (IQR)	20 (14-25)
Child-Pugh score, median (IQR)	8 (7-10)
Child-Pugh class, n (%)	
Class A	30 (24%)
Class B	61 (50%)
Class C	32 (26%)
HCC, n (%)	21 (17%)
Sodium (mmol/L), mean (SD)	136 (±8)
Creatinin (μmol/L), median (IQR)	109 (73-168)
Albumin (g/L), mean (SD)	29 (±6)
Total bilirubin (μmol/L), median (IQR)	51 (26-135)
INR, mean (SD)	1.7 (±0.7)
Ascites, n (%)	
Diuretic-responsive	33 (27%)
Diuretic-refractory	90 (73%)
Hepatic encephalopathy, n (%)	
None	73 (59%)
West Haven grade 1-2	32 (26%)
West Haven grade 3-4	18 (15%)
PMN count in ascites (cells/μL), mean (SD)	48 (±61)
Protein level in ascites (g/L), mean (SD)	16 (±10)
Recent GI bleed, n (%)	35 (28%)
Use of norfloxacin, n (%)	27 (22%)
Primary prophylaxis	-
Secondary prophylaxis	
Admission status during paracentesis, n (%)	
Inpatient	103 (84%)
Outpatient	20 (16%)

GI, gastrointestinal; HCC, hepatocellular carcinoma; INR, international normalized ratio; IQR, interquartile range; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; PMN, polymorphonuclear neutrophil; SD, standard deviation.

in-hospital mortality rate, and (e) written in English. Interventional studies (eg, randomized controlled trials), studies with a selected population (eg, HIV patients), and abstracts were excluded. Study and clinical characteristics were collected from the included studies.

2.2 | Definitions

Bacterascites was defined as an ascitic fluid sample with a PMN count below 250/μL and a positive bacterial culture, in the absence of evidence for an intra-abdominal source of infection.[1] Infection acquisition was categorized as nosocomial (infection was detected after 48 h after hospital admission), healthcare-associated (<48 h after hospital admission in patients with any 90-day prior healthcare contact), or community-acquired (within 48 h after hospital admission in patients without any 90-day prior healthcare contact).[13] Ascites was graded as diuretic-responsive or diuretic-refractory, and hepatic encephalopathy (HE) as none, or West Haven grade 1-4. Patients were categorized as symptomatic, when one or more of the following symptoms, shown to be frequently present in patients with SBP, were recorded: abdominal discomfort (feeling of fullness), abdominal pain/tenderness, fever, and a change in mental status (recorded as HE grade).[14] Recent gastrointestinal (GI) bleeding was defined as a diagnosed upper GI bleeding in the 72 h prior to index paracentesis. During the study period, the standard primary antibiotic treatment in patients with variceal bleeding was oral norfloxacin 400 mg twice daily or intravenous ceftriaxone 1 g daily during five days. The secondary prophylaxis for SBP was norfloxacin 400 mg once daily.[8,9]

2.3 | Statistical analysis

Continuous variables were reported as mean with standard deviation (SD), after visual confirmation of approximate normality, and compared using the Student's *t*-test. Categorical variables were reported as count with proportion and compared using the Chi-square test. A two-sided *P*-value <0.05 was considered significant.

Transplantation-free survival was analysed using Kaplan-Meier survival analysis. Follow-up started at the time of the first ascitic fluid analysis. A multivariable logistic regression analysis was carried out to identify predictors for treatment of bacterascites, a multivariable logistic regression analysis in the untreated patient group to identify risk factors for worse outcome (ie, liver-related death before culture results were known, SBP development, and persisting bacterascites), and a multivariable Cox's proportional hazard analysis to identify independent predictors for 3-month mortality. These analyses were performed using the candidate predictor variables: age, gender, aetiology of liver disease, MELD score, hepatocellular carcinoma, gastrointestinal bleeding, HE, grade of ascites, symptoms of infections, immunosuppressive medication use, antibiotic prophylaxis use, Staphylococci cultured, and PMN count in ascites, with the addition of initiation of antibiotic treatment for bacterascites in the Cox's regression. The regression models were employed using the backward stepwise selection method with removal testing based on the probability of the likelihood-ratio statistic. Statistical analyses were performed using SPSS Statistics for Windows, Version 21.0. (IBM Corp., Armonk, NY, USA).

3 | RESULTS

3.1 | Patients

Between January 2003 and August 2016, 142 episodes of bacterascites were diagnosed in 123 patients. The demographic, clinical, and laboratory data are summarized in Table 1. Patients with bacterascites were mainly male with a mean age of 63 years (±14) and a median MELD score of 20 (IQR 14-25).

3.2 | Bacterascites

The infection was in 11% of the bacterascites episodes community acquired, in 55% healthcare-associated, and in 34% nosocomial acquired.

One or more clinical symptoms of infection were present in the majority (78%) of patients with bacterascites. Sole abdominal discomfort was reported by 18%, HE by 16%, abdominal pain by 9%, and fevers or chills by 3%. A combination of these symptoms were present in 32%: 13% had HE and abdominal pain, 11% HE, fever and abdominal pain, 5% fever and abdominal pain, and 3% HE and fever.

Symptomatic patients had a similar age (mean 64 vs 63 years; $P = 0.907$), MELD score (median 20 vs 19 points; $P = 0.313$), serum creatinine (median 106 vs 104 mmol/L; $P = 0.606$) and PMN count in ascites (median 23 vs 19 cells/μL; $P = 0.576$) compared to asymptomatic patients. Table 2 shows additional characteristics in relation to the presence of symptoms. Monomicrobial bacterascites was just as likely to be symptomatic as polymicrobial bacterascites ($P = 0.660$). Seventeen percent of patients with bacterascites were diagnosed with concomitant infections of the respiratory tract (6%), urinary tract (5%), or skin (6%). Concomitant blood cultures were obtained in 42% and 17% of symptomatic and asymptomatic cases respectively. The proportion of positive blood cultures did not statistically differ between the groups.

Fourteen patients were diagnosed with more than one episode of bacterascites. In five patients, the second episode was diagnosed within 5 days, and in nine patients after a median time of 31 days. Of these 14 patients, nine patients died, four patients received a liver transplant, and one patient was lost to-follow-up. The median time till one of the endpoints was reached was 74 days. When patients

TABLE 2 Clinical and infection characteristics according to symptoms associated with bacterascites (N = 142 episodes)

	No symptoms (N = 31)	Any symptoms (N = 111)	Abdominal discomfort (N = 26)[a]	Abdominal pain (N = 52)[a]	New-onset/ worsening HE (N = 56)[a]	Fever (N = 32)[a]
Clinical characteristics						
MELD score, median (IQR)	19 (10)	20 (11)	17 (7)	21 (12)	23 (11)	25 (10)
PMN count in ascites (cells/μL), median (IQR)	19 (44)	23 (50)	28 (41)	30 (62)	21 (48)	40 (79)
Infection characteristics						
Acquisition infection, N (%)						
Community-acquired	4 (13%)	11 (10%)	3 (11%)	6 (12%)	3 (5%)	3 (9%)
Healthcare-associated	15 (48%)	63 (57%)	14 (54%)	35 (67%)	30 (54%)	18 (56%)
Nosocomial	12 (39%)	37 (33%)	9 (35%)	11 (21%)	23 (41%)	11 (35%)
Repeated paracenteses after 48 h, N (%)	15 (48%)	70 (63%)	17 (65%)	30 (58%)	32 (57%)	18 (56%)
Ascites culture monomicrobial, N (%)	26 (84%)	89 (80%)	21 (81%)	39 (75%)	46 (82%)	24 (75%)
Concomitant infection, N (%)						
Respiratory tract	1 (3%)	8 (7%)	0	3 (6%)	7 (12%)	6 (19%)
Skin	1 (3%)	8 (7%)	1 (4%)	6 (12%)	4 (7%)	2 (6%)
Urinary tract	0	7 (6%)	0	3 (6%)	3 (5%)	4 (12%)
Concomitant blood culture, N (%)						
Non taken	25 (80%)	65 (59%)	23 (88%)	24 (46%)	27 (48%)	10 (31%)
Negative	3 (10%)	21 (19%)	1 (4%)	13 (25%)	15 (27%)	8 (25%)
Positive	3 (10%)	25 (22%)	2 (8%)	15 (29%)	14 (25%)	14 (44%)

[a]Patients could have multiple symptoms per episode. More details are described in the Results section in the paragraph Bacterascites.

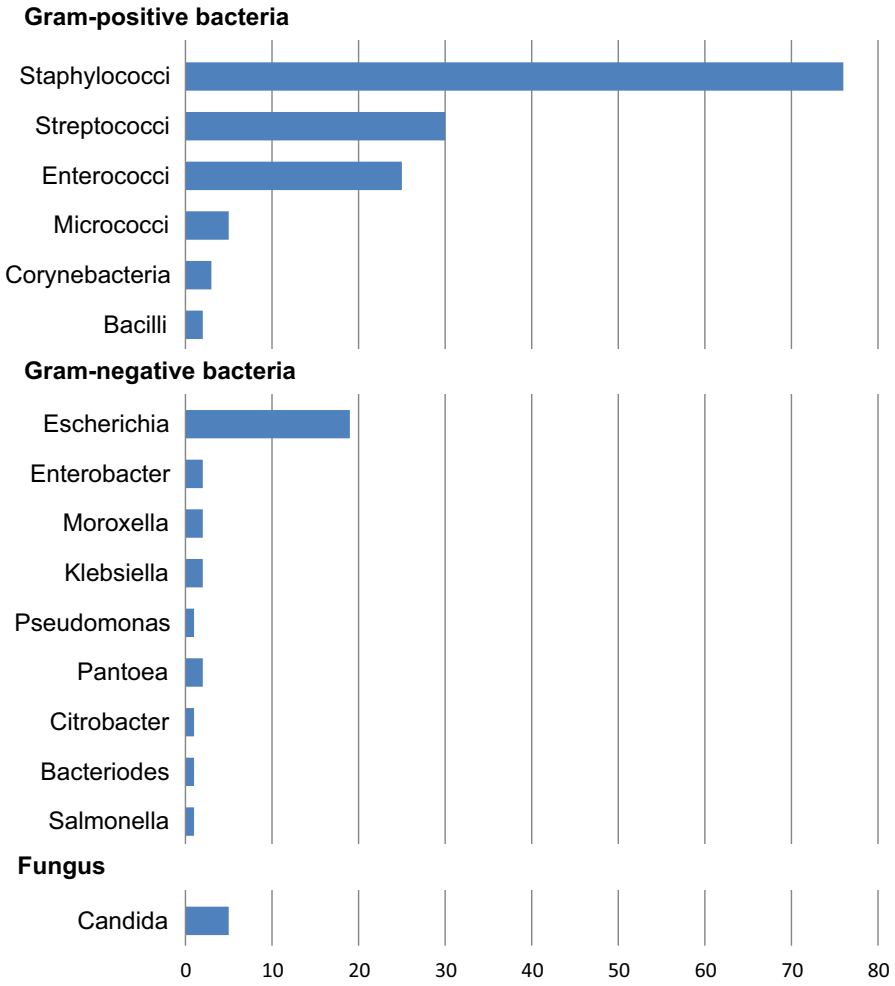

FIGURE 1 Type of pathogens cultured in 142 bacterascites episodes classified by genus

with a single episode were compared with patients with multiple episodes, there were no statistical differences in age, gender, MELD score, PMN count in ascites, presence of symptoms, antibiotic prophylaxis use, or presence of a GI bleed.

In 36 of 142 bacterascites episodes (25.4%), an admission to the intensive care unit (ICU) was necessary; 14 cases (9.9%) of bacterascites were diagnosed on the ICU and in 22 cases (15.5%) patients were admitted to the ICU after organ failure development following bacterascites diagnosis. ICU admission was less than 7 days in 21 cases, between 7 and 14 days in six cases, between 14 and 30 days in four cases, longer than 30 days in five cases.

3.3 | Microbiology

Monomicrobial bacterascites was found in 81% of all episodes, consequently multiple pathogens were cultured in 19% of all episodes. In polymicrobial bacterascites, two or three different organisms were cultured. Gram-positive bacteria were predominantly cultured in monomicrobial bacterascites. The 177 species cultured in monomicrobial and polymicrobial bacterascites are listed in Figure 1. Staphylococci were most often isolated (43%), followed by Streptococci (17%), Enterococci (14%), and Escherichia (11%). The cultured species of these four most common found genera are subtyped in Figure S1.

Multidrug antibiotic-resistant (MDR) organisms were isolated in 25% of all episodes. Methicillin-resistant Staphylococci were the most frequently found MDR organism (N = 26), followed by extended-spectrum beta-lactamase (ESBL) producing bacteria (N = 8). A similar proportion of patients using primary antibiotic prophylaxis were infected with a MDR organism (29.0%) compared to patients without prophylaxis (23.1%) ($P = 0.506$).

3.4 | Antibiotic therapy

In 96 (68%) of the total 142 episodes of bacterascites antibiotic treatment was initiated: in 49 episodes after paracentesis and before culture results became available, in 47 episodes after culture results were known. In 16 cases, the antibiotic treatment was modified based on culture results. Amoxicillin-clavulanic acid combination was most often prescribed (30%), followed by cephalosporin (14%) and vancomycin (10%). Symptomatic patients more often received treatment compared to asymptomatic patients (72% vs 52%; $P = 0.031$). Patients with higher MELD score (HR 1.156 per point, 95%CI 1.060-1.260, $P = 0.001$), higher PMN count in ascites (HR 1.017 per point, 95%CI 1.005-1.030, $P = 0.007$), an infection with another bacterial genus than Staphylococci (HR 3.512, 95%CI 1.333-9.253, $P = 0.011$), and a female gender (HR 2.837, 95%CI

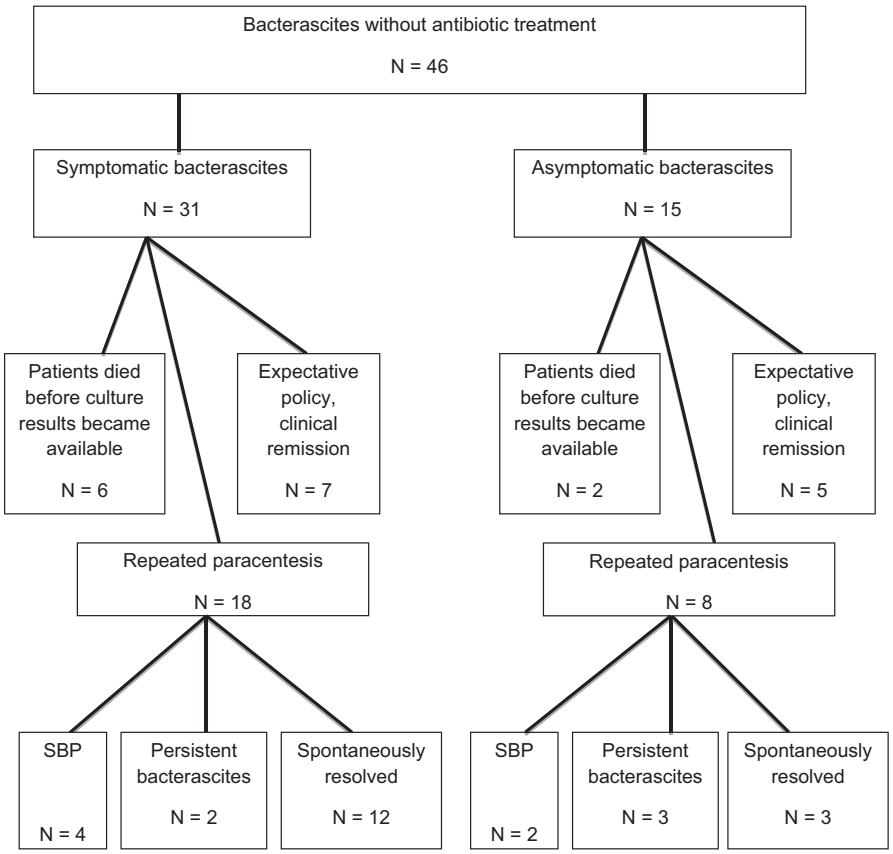

FIGURE 2 The clinical course of patients with bacterascites without antibiotic treatment

1.066-7.547, $P = 0.037$) were more likely to receive antibiotic treatment for bacterascites.

In 46 episodes of bacterascites, antibiotic treatment was not initiated. In 31/46 episodes (67%), patients had signs or symptoms of infection. A total of 111 episodes of bacterascites were symptomatic. The ascitic PMN count in 80 patients who were treated with antibiotics was significantly higher (median 31, range 0-235) than the PMN count (median 13, range 0-71) in those patients (n = 31) who did not receive antibiotic treatment ($P = 0.002$). Figure 2 shows a flow chart of the clinical course of the untreated episodes of bacterascites. Of these 46 bacterascites episodes, the patient died before culture results were known in eight cases, in all these cases of decompensating liver disease. These eight patients had a median MELD score of 29 (IQR 18-30), median serum creatinine of 147 μmol/L (IQR 100-250), and 5/8 patients were admitted at the ICU; either before paracentesis (two patients), or after paracentesis (three patients). SBP developed in six cases, and bacterascites persisted in five cases. The latter group and those diagnosed with SBP were immediately treated with antibiotics. A logistic regression analysis was performed in the untreated patients to identify risk factors for liver-related death before culture results were known, SBP development, and persisting bacterascites (19/46) compared to clinical remission (27/46). We found that MELD score (HR 1.286 per point, 95%CI 1.071-1.546, $P = 0.007$) and age (HR 1.113 per year, 95%CI 1.027-1.205, $P = 0.009$) were independent risk factors.

3.5 | Clinical course and outcome

The survival analyses included 114 patients with bacterascites and 88 patients with SBP, after the exclusion of patients with both SBP and bacterascites. The median follow-up time in 114 patients was 38 days (IQR 15-272). In this study cohort, 27 patients were alive or lost to follow-up, 16 patients received a liver transplant, and 71 patients died. The causes of death were in 36 patients (50.7%) liver disease-related, in 29 patients (40.9%) unknown, and in six patients (8.4%) a combination of liver disease-related and nonliver disease-related.

The cumulative mortality rates in bacterascites patients (1-month: 36%; 3-month: 56%; 6-month: 62%; 1-year: 66%) are statistically comparable to that reported for SBP patients (1-month: 34%; 3-month: 54%; 6-month: 67%; 1-year: 77%) (log-rank test $P = 0.397$) (Figure 3).

The most important predictive factors for 3-month mortality after bacterascites diagnosis were: MELD score and the presence of hepatic encephalopathy (Table 3). Figure 4 shows the MELD score-dependent relation of survival in 114 patients with bacterascites and 88 patients with SBP.

3.6 | Bacterascites in comparison with SBP in the literature

Our literature search for relevant studies of SBP identified 17 publications (Table 4).[10,15-30] The reported baseline clinical characteristics

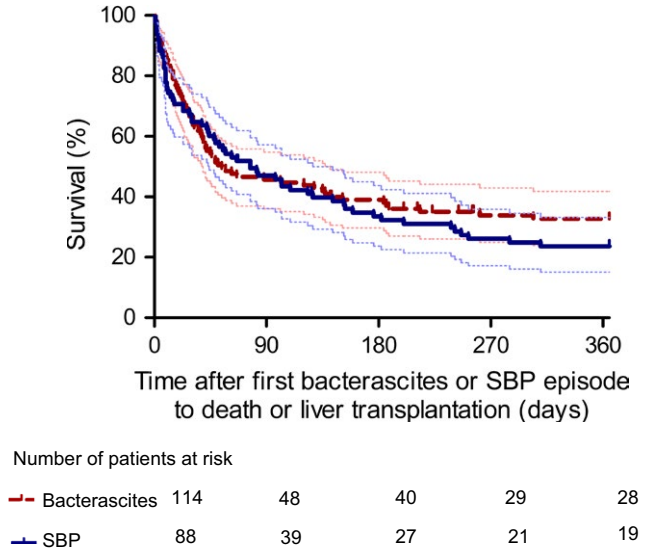

FIGURE 3 Comparable cumulative survival curves shown for 114 patients with bacterascites (red solid line) and 88 patients with SBP (blue solid line) (log-rank test $P = 0.3973$). The dashed lines with corresponding colours display the 95% confidence interval

TABLE 3 Independent predictive factors of 114 bacterascites patients predicting 3-month mortality (58 events) identified by multivariable Cox-regression analysis

	HR	95% CI	*P*-value
MELD score (per point)	1.099	1.082-1.156	<0.001
Hepatic encephalopathy			
None (reference)	1		0.002
West Haven grade 1-2	1.411	0.697-2.856	
West Haven grade 3-4	3.209	1.614-6.381	

CI, confidence interval; HR, hazard ratio; MELD, model for end-stage liver disease.

including age, gender distribution, and liver disease severity scores of SBP were comparable to those identified in our patient population with bacterascites. In addition, the cumulative mortality rate in our bacterascites cohort (1-month: 36%; 6-month: 62%; 1-year: 66%) also appears comparable to that reported for SBP (1-month: 13%-49%; 6-month: 52%-59%: 1-year: 49%-70%).

4 | DISCUSSION

Bacterascites is an infectious complication occurring in patients with advanced or end-stage liver disease, and is associated with a high short-term mortality risk. Bacterascites tends to persist, or to evolve to SBP, in a significant proportion of cases. Further, our findings indicate that bacterascites diagnosed in in-hospital patients has great similarities to SBP. In particular, patients with bacterascites and SBP present with a similar degree of liver insufficiency and have a comparable poor prognosis.

In our cohort, 78% of patients showed clinical symptoms of infection, which is reasonably similar to the rates of 66%-71% in previously published studies.[4,6] Although it is generally accepted that SBP is frequently accompanied by clinical symptoms, a proportion of 13%-32% patients with SBP has been reported to be asymptomatic.[6]

With the results of this study, it is difficult to clearly elucidate the underlying pathogenesis of bacterascites. Gram-positive bacteria were frequently isolated in bacterascites, which is in line with findings from other bacterascites series.[2,5-7] However, only a minority of episodes of bacterascites was considered to be due to exogenous contamination. In many cases, patients showed evident symptoms of infection, had a concomitant positive blood culture, or there were evidence of a porte d'entrée from the skin through an inserted line or catheter. It could be hypothesized that Gram-positive bacteria are less virulent or less likely to induce an inflammatory host reaction,

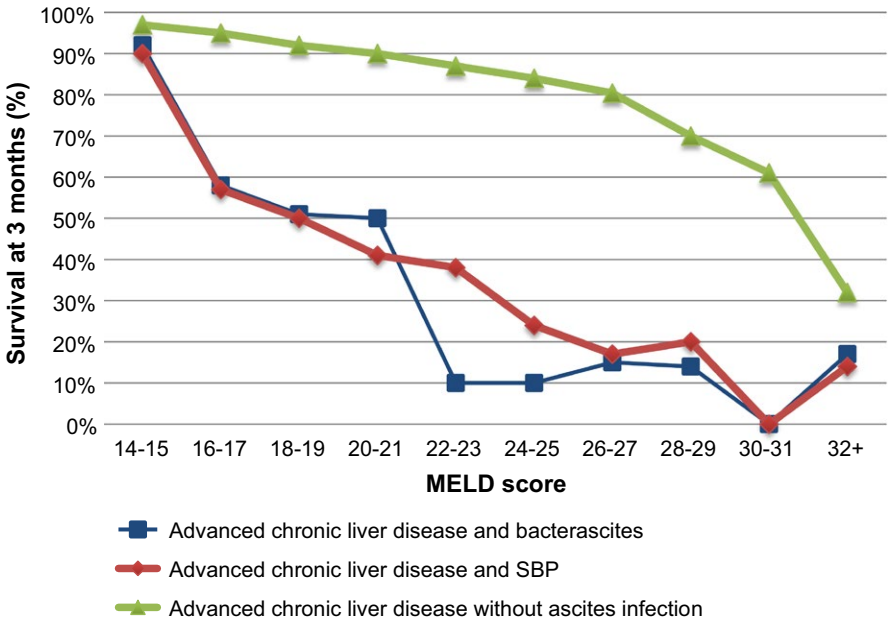

FIGURE 4 The figure shows a MELD score-dependent relation for the 3-month survival after bacterascites diagnosis of 114 patients (blue line). The survival of 88 patients with SBP (red line) and advanced chronic liver disease without ascites infection (green line) are plotted for comparison

TABLE 4 Overview of observational studies assessing the clinical characteristics and mortality rates of patients with SBP in comparison with our present study with bacterascites patients

Author, year (corresponding number in reference list)	Number of patients	Male gender (%)	Mean age	CP class A/B/C (%) or mean CP score	Mean MELD	1-month or in-hospital mortality	6-month mortality	1-year mortality
Toledo, (1993) ([15])	185	64%	56	1/22/74	-	44%	-	-
Follo, (1994) ([16])	197	63%	55	-	-	24%	-	-
Navasa, (1998) ([17])	52	63%	64	10.5	-	23%	-	-
Thuluvath, (2001) ([18])	348	57%	58	-	-	33%	-	-
Soylu, (2005) ([19])	87	71%	53	0/10/90	-	26%	-	-
Song, (2006) ([20])	106	79%	55	0/28/72	-	33%	59%	-
Nobre, (2008) ([21])	73	77%	62	0/23/77	23	37%	-	-
Cheong, (2009) ([22])	236	70%	57	10.6	-	49%	-	-
Terg, (2009) ([23])	127	-	-	-	18	17%	-	-
Kim, (2010) ([24])	130	68%	52	10.7	-	13%	52%	70%
Tsung, (2013) ([25])	95	74%	59	2/31/67	-	39%	55%	63%
Tandon, (2013) ([26])	184	66%	55	-	20	27%	-	-
Cho, (2014) ([27])	336	77%	61	10.9	22	38%	-	
Lim, (2014) ([28])	75	88%	59	11.0	19	25%	-	-
Hassan, (2015) ([29])	100	68%	57	0/15/85	18	22%	-	-
Balaraju, (2017) ([30])	150	86%	48	5/21/74	22	31%	59%	-
Oey, (2017) ([10])	95	62%	54	5/35/60	21	33%	-	49%
Present study	114	62%	63	24/50/26	20	36%	62%	66%

CP, Child-Pugh; MELD, model for end-stage liver disease.

which has been previously postulated in studies analysing patients with bacteremia.[31,32] Furthermore, traumatic paracentesis were highly unlikely to explain any cases of bacterascites in our cohort. In all polymicrobial bacteracites, a maximum of three different organisms were cultured and not the variety of bowel flora expected after perforation.[33] Thus, it is more likely bacterascites is an actual colonization of ascites, either behaving as a different form of peritonitis or with a large probability of evolving into a classic infection.

Earlier reports have suggested bacterascites patients might have higher levels of bactericidal and opsonic activity, reflected by higher protein concentrations in ascites, preventing a full-blown inflammatory response.[4,34] Despite the fact that protein concentrations in ascites were measured on an irregular basis in our cohort, the mean protein level of 16 g/L does not indicate patients are deviant from SBP patients.[35,36]

Unexpectedly, female gender was one of the factors increasing the odds to receive antibiotic treatment for bacterascites. We found a correlation between female gender with autoimmune-related liver disease aetiology and immunosuppressant use. Female patients were more likely to have autoimmune hepatitis, primary biliary cirrhosis, or nonalcoholic steatohepatitis and more often used immunosuppressive medication. Possibly, the threshold to prescribe antibiotic treatment for bacterascites is lower in patients using immunosuppressive medication.

One of the goals of this study was to determine the clinical course of bacterascites. In two-thirds of the cases, the treating physician decided to initiate antibiotic treatment. However, in the 46 episodes not treated with antibiotics, 17% died before culture results were known. In the 26 untreated patients undergoing repeated paracentesis, 42% were diagnosed with either ongoing bacterascites or SBP.

The results of this study do not support the importance to distinguish clinically between symptomatic and asymptomatic bacterascites. The proportion of untreated bacterascites, which spontaneously resolved, was equal in symptomatic and asymptomatic patients. Furthermore, the presence of signs or symptoms of infection was not an independent predictor for mortality.

The rate of 25% MDR bacteria found in all bacterascites episodes was relatively high for the Netherlands, but it is in line with current international microbiologic SBP studies reporting MDR bacteria rates of 27%-67%.[37-39] The involvement of MDR bacteria in bacterascites was not associated independently with mortality in our study. Whether there is an independent association between MDR bacteria and a worse prognosis is still unclear with contrasting findings in studies regarding SBP.[10,20,22,40,41]

As shown in Figure 4, the prognosis after bacterascites is worse than the reported prognosis based on the MELD score, as developed in a large cohort of patients with advanced chronic liver disease.[11,12] The relatively high rate of short-term mortality suggests bacterascites is either directly endangering the patient or a symptom of a critical condition. Therefore, these data suggest that these patients should be medically supported by all available means including antibiotic treatment. Timely and appropriate antibiotic treatment, as has been proven effective in SBP, seems appropriate in bacterascites.[9] Taking in consideration that 27 of the 46 untreated cases of bacterascites in our cohort spontaneously resolved bacterascites, this clinical measure might induce a significant over-treatment. This study evidently does not prove that treating bacterascites in patients with spontaneously resolving infection will improve prognosis. Although we found age and MELD score important predictors for patients with a worse clinical course, it is clinically difficult to accurately distinguish these patients from patients resolving the infection spontaneously.

To the best of our knowledge, this is one of the first studies concentrating solely on bacterascites by analysing a large cohort of consecutive patients. Our cohort with 123 patients is substantially larger than previously reported cohorts including 18-48 patients.[2-7] One of the limitations of this study is that, because of the retrospective design, the natural course of bacterascites could not be optimally studied. For instance, it may well be that patients received antibiotic treatment while the bacterascites would have resolved spontaneously. It should also be pointed out that 14 patients had multiple bacterascites episodes, which could have led to a possible statistical bias, since a correlation between episodes of the same patient was ignored. Prospective studies would be necessary to further define the natural history of bacterascites and the optimal diagnostic and therapeutic strategy. Such studies could also confirm our finding that bacterascites carries a mortality risk comparable to that of SBP.

In conclusion, bacterascites is a complication of cirrhosis comparable to SBP with respect to clinical background and prognosis. Also considering that bacterascites seems to persist or to evolve into SBP in a substantial proportion of cases, with no clear differences in the course of symptomatic vs asymptomatic patients, our results may suggest that the (antibiotic) treatment strategy in bacterascites and SBP should be the same.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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