Original Article

Shifting microorganism incidence in cirrhotic patients with ascites: a 5-year retrospective cross-sectional analysis

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Background: Historically, microbiologic studies in spontaneous bacterial peritonitis have shown a predominance of gram-negative bacteria. In recent years, the incidence of gram-positive and multi-drug resistant bacteria has become a rising concern. The aims of this study were to identify the incidence and antimicrobial susceptibility patterns of microorganisms in hospitalized cirrhosis patients with ascitic fluid absolute polymorphonuclear count ≥250 cells/mm^3.

Methods: A retrospective cross-sectional study was performed in 88 patients with a culture of ascites fluid and discharge diagnosis of spontaneous bacterial peritonitis from 2013–2018 in a single academic hospital in north central Florida, USA. The incidence and antimicrobial susceptibility patterns of microorganisms in blood and ascitic fluid cultures were measured.

Results: Spontaneous bacterial peritonitis and culture negative neutrocytic ascites were found in 25% and 75% of patients, respectively. Overall, the incidence of gram-positive bacteria was higher than gram-negative bacteria in spontaneous bacterial peritonitis patients (50% *vs.* 34.6%). A year over year increasing incidence of gram-positive bacteria was observed. Moreover, multi-drug resistant bacteria were found in 13.6% of included spontaneous bacterial peritonitis patients.

Conclusions: The microbiologic incidence of spontaneous bacterial peritonitis and culture negative neutrocytic ascites patients shifted over the 5-year study period towards a predominance of gram-positive bacteria over gram-negative bacteria. Multi-drug resistant bacteria are more commonly cultured in patients with hospital acquisition of spontaneous bacterial peritonitis.

Keywords: Ascites; drug resistance; multiple; liver cirrhosis; peritonitis

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Introduction

Spontaneous bacterial peritonitis (SBP) is the most common infection in patients with cirrhosis (1). The incidence of SBP has been reported to be 7–30% of hospitalized cirrhotic patients with ascites (2). SBP portends a poor prognosis with 30-day and 1-year mortality incidence reported to be 30% and up to 63%, respectively (2,3). The diagnosis of SBP is confirmed when there is a positive ascitic fluid culture and an elevated ascitic fluid absolute polymorphonuclear (PMN) count ≥250 cells/mm^3 without an evident intra-abdominal, surgically treatable source of infection (4). Culture-negative neutrocytic ascites (CNNA) refers to patients who meet the PMN count criterion but have negative ascitic fluid cultures (4). Both SBP and CNNA should be treated with empiric antibiotic therapy (4).

Typically, SBP is predominantly caused by enteric gram-

negative bacteria (2,5,6). However, notable trends have shifted toward gram-positive bacteria and multi-drug resistant (MDR) bacteria worldwide (2,6,7). A recently published epidemiologic study completed in 46 centers worldwide in cirrhotic patients with infections, including 27% with SBP, reported a microbial incidence of 57% gram-negative bacteria, 38% gram-positive bacteria, and 4% fungal cultures (1). SBP was the most common site of infection in 31% of cirrhosis patients in North and South America (1). Regional differences in microbial incidence in cirrhosis are remarkable. For example, Piano *et al.* reported 70% gram-negative bacteria in Asia, but only 54–59% in other regions (1). Meanwhile, the MDR incidence was 50% of patients in Asia, but only 27–35% in other regions (1). Moreover, within the Asian continent, the microbial incidence in cirrhotic patients varies significantly among the countries. One recent study conducted in China reported gram-negative bacteria in 73.9% of SBP patients (7). Meanwhile, two other studies in Japan and Korea showed a lower incidence with 50–55% of cirrhosis patients infected with gram-negative bacteria (8,9). In middle east countries, two studies in Iran and Pakistan consistently showed a 60–70% incidence of gram-negative bacteria and a 30% incidence of gram-positive bacteria (10,11). Nigeria showed an incidence of gram-negative and gram-positive bacteria to be 66.7% and 33%, respectively (12). A cohort study in Brazil found the incidence of MDR bacteria to be 46.9% in cirrhotic patients with SBP (13). It is clear from various recent reports worldwide, that there are important regional differences in microbial incidences and resistance patterns. Current clinical practice guidelines make recommendations for empiric therapy largely based on accumulated microbiologic data from epidemiologic and clinical efficacy studies. The American Association for the Study of Liver Diseases (AASLD) recommends cefotaxime or similar third generation cephalosporin for suspected SBP to empirically cover the historically most common gram-negative organisms (4). Patients with previous exposure to systemic antibiotics or antibiotic prophylaxis for SBP might require more broad-spectrum antibiotic coverage. In the United States, the trend of bacterial etiology in SBP remains unclear while the concern regarding MDR bacteria has risen. In a review by Fiore *et al.*, the reported incidence of gram-positive bacteria in SBP in North America was 57.1–73.9% (6). This incidence was higher than the incidence found in the Piano *et al.* epidemiologic study (1). A single site study in Connecticut showed that 54% of infections in cirrhosis patients during 2009–2010 were caused by gram-negative bacteria and 44% caused by gram-positive bacteria (14). The most common resistant bacteria were extended spectrum beta-lactamase (ESBL) producers (27%) followed by quinolone-resistant gram-negative rods (21%) (14). Due to known regional differences in microbial incidence and recent reports of shifting bacterial etiology in SBP, it is of utmost importance for clinicians to know their regional or local microbial incidence in order to select the most appropriate empiric antibiotic therapy (4). To that end, it was the objective of our study to identify the microbial incidence in cirrhotic patients with SBP in our tertiary care center. We present the following article in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/dmr-20-11).

Methods

Design overview

We conducted a retrospective cross-sectional study at a 1,162-bed tertiary care academic medical center in Gainesville, Florida, USA. An integrated data repository was used to identify all adult patients admitted between 1 January 2013 and 28 February 2018 who had a culture of ascites fluid and a discharge diagnosis of SBP using ICD9 567.23 and ICD10 K65.2 codes. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the University of Florida Institutional Review Board (IRB201600349). Due to the retrospective nature of the study informed consent was not required.

Study participants

Manual review of electronic heath records was performed to collect demographic, microbiologic and other clinical data. Subjects were excluded if they had ascitic fluid PMN count <250 cell/mm^3, missing data, secondary peritonitis, peritoneal dialysis, and/or end-stage renal disease. We stratified all included patients into SBP and CNNA groups.

Definitions

SBP and CNNA patients were defined as having ascites fluid PMN count ≥250 cell/mm^3 with positive ascites fluid culture and without positive ascites fluid culture, respectively. Contaminated blood cultures were not included in the microbial incidence report. We defined

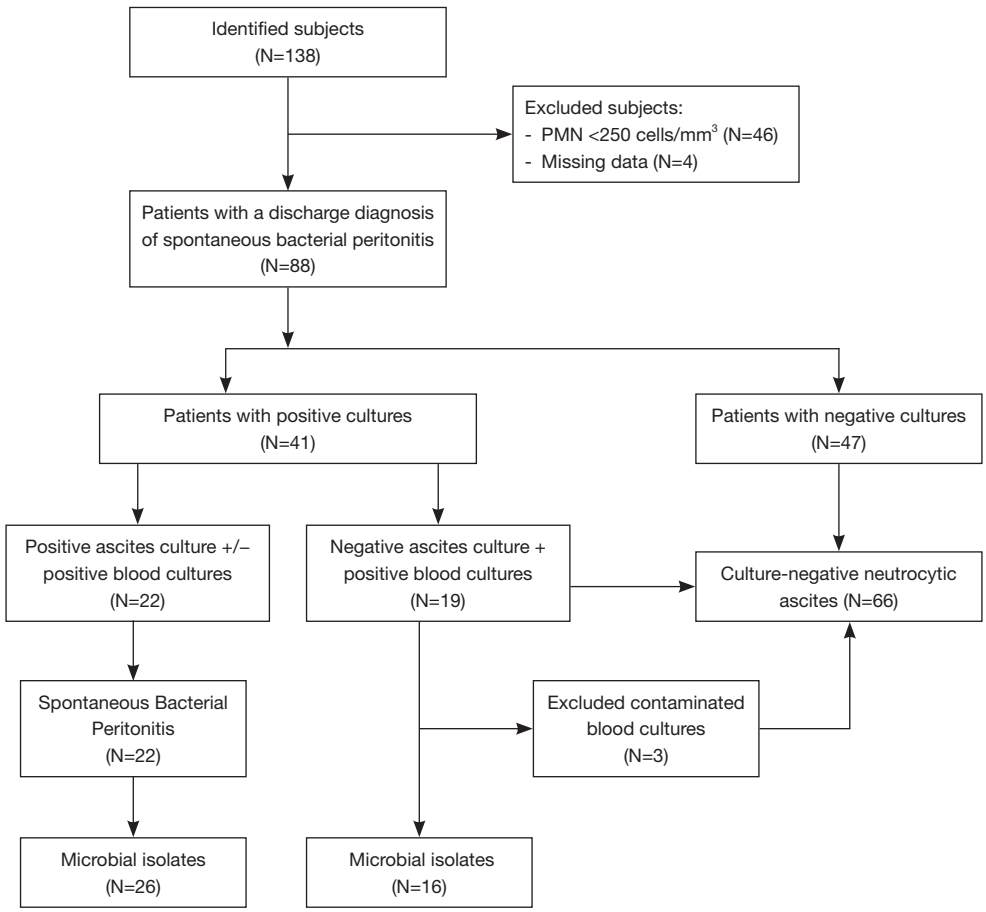

Figure 1 STROBE diagram. Total of 138 patients were identified by an integrated data repository. Fifty patients who met exclusion criteria were excluded and 88 patients were included in the analysis. After categorizing the included patients based on positive culture results, 22 patients met with criteria of SBP and 66 patients met with criteria of CNNA.

blood culture contamination as a single positive blood culture (i.e., one of four blood culture bottles) with common contaminant pathogens (e.g., coagulase negative *Staphylococcus spp*., or *Bacillus spp*.). MDR was defined by presence of non-susceptibility to at least one agent in three or more antimicrobial categories or identification of ESBL producing organisms, methicillin-resistant staphylococcus aureus (MRSA) and/or vancomycin-resistant enterococci (VRE) (15). Hospital-acquired SBP was defined as SBP diagnosed >48 hours from admission, while community-acquired SBP was defined as SBP diagnosed ≤48 hours from admission.

Statistical analysis

MS Excel for Windows (2016; Microsoft Inc.) was used for descriptive statistical analyses of the data. Incidence proportions were calculated and reported for microbial incidences in ascites fluid culture, blood culture, MDR, and antimicrobial susceptibility of all identified bacterial isolates.

Results

Patient characteristics and microbiology

One-hundred thirty-eight subjects were identified and reviewed for eligibility. *Figure 1* describes the 88 patients that were included in the study. In the included patients, 22 (25%) had SBP and 66 (75%) had CNNA. Patient characteristics are delineated in *Table 1*. The mean age ± standard deviation of all included patients was 55.6± 11.8 years. The majority of patients were male (63.6%).

Table 1 Patient characteristics

Characteristics	Total (N=88)	SBP (N=22)	CNNA (N=66)
Age (years), mean (SD)	55.6 (11.8)	56.5 (12.5)	55.2 (11.7)
Male, N (%)	56 (63.6)	14 (63.6)	42 (63.6)
High risk of acute kidney injury[§], N (%)	69 (78.4)	20 (90.9)	49 (74.2)
Gastrointestinal bleed, N (%)	3 (3.4)	0 (0%)	3 (4.5)
Hepatic encephalopathy, N (%)	14 (15.9)	3 (13.6)	11 (16.7)
Diabetes, N (%)	20 (22.7)	5 (22.7)	15 (22.7)
Hepatocellular carcinoma, N (%)	6 (6.8)	3 (13.6)	3 (4.5)
Labs upon admission			
Creatinine (mg/dL)	1.84±1.9	2.31±2.1	1.67±1.8
Blood urea nitrogen (mg/dL)	32.86±29.4	40.0±25.8	30.34±30.2
Total bilirubin (mg/dL)	8.25±9.7	8.43±8.4	8.18±10.1
Length of hospital stay (days)	15±18.8	16.1±13.1	14.1±20.4
Antibiotics administered prior to paracentesis, N (%)	45 (51.1)	12 (54.5)	33 (50.0)

[§], high risk of acute kidney injury defined as polymorphonuclear cell count ≥250 plus serum creatinine >1 mg/dL, blood urea nitrogen >30 mg/dL OR total bilirubin >4 mg/dL. SBP, spontaneous bacterial peritonitis; CNNA, culture-negative neutrocytic ascites; SD, standard deviation; N, number of patients.

Antibiotics were administered prior to paracentesis in 45 (51.1%) of the total patients. Of the 66 CNNA patients, 19 had a positive blood culture (three were deemed to be contaminated and were excluded from the blood culture microbial incidence report in *Table 2*. Thus, 16/66 (24.2%) of the CNNA patients had true positive blood cultures and were included in blood culture microbial incidence. *Table 2* lists the microbial pathogens identified. A total of 42 microbial isolates were cultured from 41 patients. Twenty-six microbial isolates were cultured from the ascitic fluid of the 22 patients with SBP, while 16 microbial isolates were cultured from the blood of the 66 patients with CNNA. Among the SBP patients, two had a polymicrobial infection in ascites fluid. One was positive for *Enterococcus faecalis and Escherichia coli + ESBL*. Another was positive for coagulase negative staphylococci (CoNS), *Candida albicans*, *Candida glabatra*, and *Candida tropicalis*.

Microbial incidence in ascitic fluid cultures of SBP patients

In SBP patients, the incidence of gram-positive bacteria and gram-negative bacteria were 50% and 34.6%, respectively. In ascites cultures, *Escherichia coli* was the most common gram-negative bacteria in 15.4% of isolates. *Enterococcus spp*., *Staphylococcus aureus*, and *Streptococcus spp*. were the most common gram-positive bacteria equally accounting for 15.4% of isolates each. Fungal pathogens were found in two patients accounting for 15.4% of isolates in ascites fluid. One patient with multiple isolates of *Candida spp*. in a single ascites culture and one patient with an isolate of *Candida glabrata* gave a resultant fungal peritonitis incidence of 9.1%. Of total positive ascites cultures, 73% were community-acquired while 27% were hospital-acquired.

Microbial incidence in blood cultures of CNNA patients

In positive blood cultures in CNNA patients, the incidence of gram-positive bacteria and gram-negative bacteria were 31.3% and 62.5%, respectively. In blood cultures, *Escherichia coli* was the most common gram-negative bacterium in 31.3% of isolates, while *Streptococcus spp* were the most common gram-positive bacteria in 18.8% of isolates. Of total positive blood cultures, 68.8% were community-acquired while 31.2% were hospital-acquired.

Annual microbial incidence with respective distributions of gram-negative and gram-positive bacteria incidence in the total cohort is depicted in *Figure 2*. We observed an increasing incidence of gram-positive bacteria over the 5-year study period from 33.3% in 2013 to 62.5% in 2017.

Table 2 Microbial incidence in positive cultures

Pathogen identified	Total n (%)			Ascites cultures n (%)			Blood cultures n (%)		
	Total (N=42)	Hospital acquired (N=12)	Community acquired (N=30)	Total (N=26)	Hospital acquired (N=7)	Community acquired (N=19)	Total (N=16)	Hospital acquired (N=5)	Community acquired (N=11)
Gram-negative bacteria	19 (45.2)	7 (58.3)	12 (40.0)	9 (34.6)	3 (42.9)	6 (31.6)	10 (62.5)	4 (80.0)	6 (54.5)
Enterobacter spp.	4 (9.5)	1 (8.3)	3 (10.0)	3 (11.5)	0 (0.0)	3 (15.8)	1 (6.3)	1 (20.0)	0 (0.0)
Escherichia coli	9 (21.4)	4 (33.3)	5 (16.7)	4 (15.4)	2 (28.6)	2 (10.5)	5 (31.3)	2 (40.0)	3 (27.3)
Escherichia coli ESBL	1	0	1	0	0	0	1	0	1
Klebsiella pneumoniae	3 (7.1)	2 (16.7)	1 (3.3)	1 (3.8)	1 (14.3)	0 (0.0)	2 (12.5)	1 (20.0)	1 (9.1)
Pasteurella multocida	1 (2.4)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (9.1)
Pseudomonas aeruginosa	1 (2.4)	0 (0.0)	1 (3.3)	1 (3.8)	0 (0.0)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Stenotrophomonas maltophilia	1 (2.4)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0 (0.0)	1 (9.1)
Gram-positive bacteria	18 (42.9)	5 (41.7)	13 (43.3)	13 (50.0)	4 (57.1)	9 (47.4)	5 (31.3)	1 (20.0)	4 (36.4)
Enterococcus spp.	4 (9.5)	3 (25.0)	1 (3.3)	4 (15.4)	3 (42.9)	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Vancomycin resistant *Enterococcus faecium*	2	2	0	2	2	0	0	0	0
Staphylococcus aureus	4 (9.5)	1 (8.3)	3 (10)	4 (15.4)	1 (14.3)	3 (15.8)	0 (0.0)	0 (0.0)	0(0.0)
Methicillin resistant *Staphylococcus aureus*	1	1	0	1	1	0	0	0	0
CoNS	3 (7.1)	0 (0.0)	3 (10)	1 (3.8)	0 (0.0)	1 (5.3)	2 (12.5)	0 (0.0)	2 (18.2)
Streptococcus spp.	7 (16.7)	1 (8.3)	6 (20)	4 (15.4)	0 (0.0)	4 (21.1)	3 (18.8)	1(20.0)	2 (18.2)
Fungal (Candida spp.)	5 (11.9)	0	5 (16.7)	4 (15.4)	0	4 (21.1)	1 (6.3)	0 (0.0)	1 (9.1)

ESBL, extended-spectrum beta-lactamase; spp, species; CoNS, coagulase-negative staphylococci.

MDR incidence

MDR bacteria were found in four of the 42 patients (9.5%) with positive cultures. Three of these patients had MDR in ascites fluid culture accounting for 13.6% of SBP patients. VRE was identified in two of these patients, and MRSA was identified in one patient. In positive blood cultures, MDR ESBL+ *Escherichia coli* was identified in one patient.

Antimicrobial susceptibility of identified bacterial pathogens

Table 3 shows the susceptibility rates of bacterial isolates from ascites and blood cultures. The susceptibility of *Escherichia coli* to ceftriaxone was 88.9%. In contrast, only 44.4% and 66.7% of isolated *Escherichia coli* were susceptible to fluoroquinolones and sulfamethoxazole/trimethoprim, respectively. The susceptibility of *Staphylococcus spp* and *Streptococcus spp*. to Vancomycin was 100%. The susceptibility of *Enterococcus spp*. to vancomycin was 50%, owing to the two VRE isolates cultured. However, these VRE isolates were both susceptible to linezolid.

Discussion

The relative proportions of SBP and CNNA observed in our study were similar to those reported by Kamani and colleagues in cirrhotic patients with ascitic fluid infection (11). Although *Escherichia coli* continues to be the most frequent cause of SBP, recent studies in various regions, including centers in North America, have found

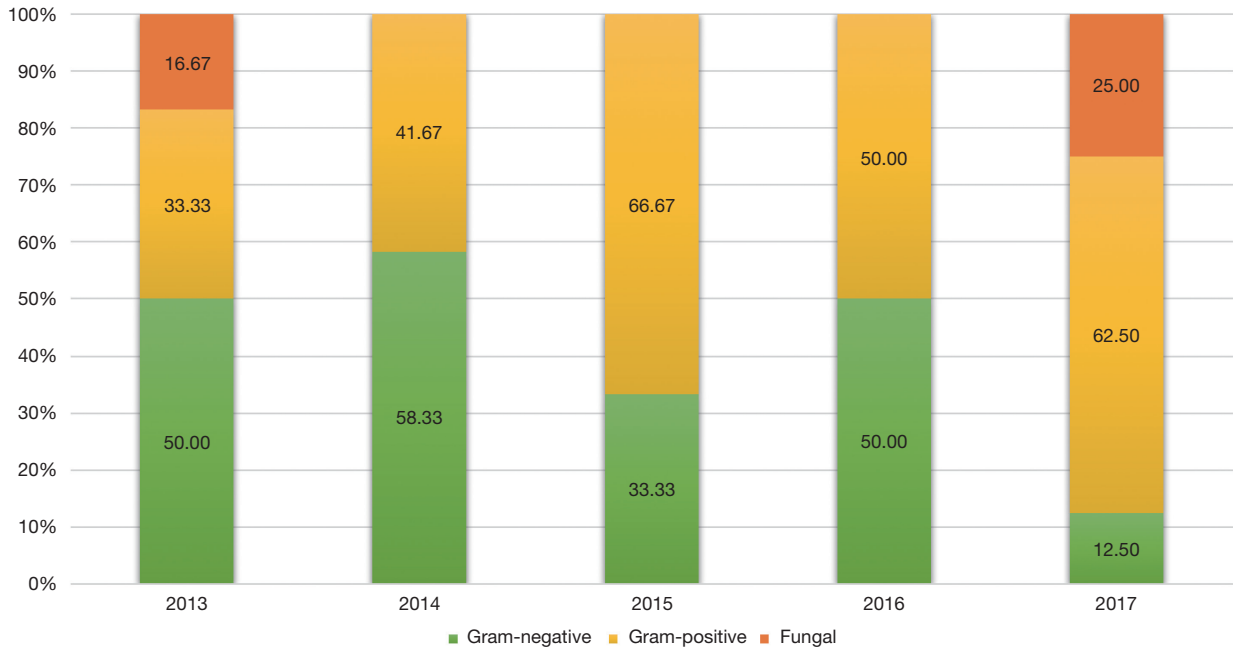

Figure 2 Annual microbiologic incidence. All positive cultures were analyzed in the 5-year time-series to calculate the percentage of gram-negative, gram-positive and fungal infections. Bacterial infection remained more common in cirrhosis patients with PMN ≥250 cell/mm^3. Gram-positive prevalence increased from 33.33% to 62.50% over the 5-year period, while gram-negative prevalence became less common in the most last year of the series.

an increasing incidence of gram-positive bacteria as the causative pathogens (2,6,11,14,16-18). The rising incidence of gram-positive bacteria we found in our study mirrors the incidences found in other North American centers (6,14). Specifically, we found gram-positive bacteria to be the most frequent cause of SBP accounting for the majority (50%) of microbial isolates cultured from ascites fluid of SBP patients during the 5-year study period. Subgroups showed a higher incidence of gram-positive bacteria in hospital-acquired SBP (57.1%) than community-acquired SBP (47.4%). *Streptococcus spp*. and *Enterococcus spp*. were the most frequently isolated pathogens in community-acquired SBP and hospital-acquired SBP, respectively. Two of the three *Enterococcal* isolates from hospital-acquired SBP patients were resistant to vancomycin (i.e., VRE). This finding was congruent with previous findings in Germany where *Streptococcus spp*. and *Enterococcus spp*. were the most common gram-positive bacteria in non-nosocomial SBP and nosocomial SBP, respectively (16). Interestingly, the gram-positive bacteria, *Enterococcus spp*., *Staphylococcus aureus*, and *Streptococcus spp*. each had equivalent incidence to the gram-negative bacteria, *Escherichia* coli (15.4 %) in the total SBP group. In our year over year analysis of the study period, a striking finding was the steadily increasing incidence of gram-positive bacteria from 33.3% in year 1 to 62.5% in year 5 equating to a relative increase of 87.5%. This growing incidence of gram-positive bacteria in cirrhotic patients with SBP is consistent with the findings of similar studies (2,6,17). Although identification and prediction of risk factors for gram-positive bacteria in SBP was not the aim of our study, it is worthy of discussion. In recent years, factors predicting risk for gram-positive bacteria in SBP have been elucidated. Namely, systemic antibiotic use within 30 days and a lower Sequential Organ Failure Assessment score have been found to be significantly associated with gram-positive bacterial infection in SBP patients (19). In particular, fluoroquinolone exposure has been shown to be associated with methicillin-resistant *Staphylococcus aureus* infection (20). Fungal isolates occur at a relatively high incidence in our study at 11.9% of isolates. However, of the five species of *Candida*, three unique species were isolated from a single ascites culture in one patient, one was isolated from the ascites culture of another patient and one was isolated from the blood culture of a CNNA patient. Therefore, the overall incidence of fungal infection was 3.4% (3/88) of patients in the total cohort, while the specific

Table 3 Susceptibility rates of bacterial isolates

	No. of isolates	Penicillin (%)					Meropenem	Cephalosporin (%)					Aminoglycosides (%)			Fluoroquinolone	Sulfamethoxazole/ Trimethoprim	Linezolid	Vancomycin
		Ampicillin	Ampicillin/ Sulbactam	Oxacillin	Penicillin	Piperacillin/ Tazobactam		Cefazolin	Cefepime	Cefoxitin	Ceftazidime	Ceftriaxone	Amikacin	Gentamicin	Tobramycin				
Gram-negative bacteria	19																		
Enterobacter spp.	4					50.0	100	0.0	100	0	50.0	50.0	100	100	100	100	100		
Escherichia coli	9	44.4	44.4			88.9	100	77.8	100	77.8	88.9	88.9	100	88.9	100	44.4	66.7		
Klebsiella pneumonia	3	0	100			100	100	100	100	100	100	100	100	100	100	100	100		
Pasteurella multocida	1	100				100	100		100		100	100	100	100	100	100	100		
Pseudomonas aeruginosa	1					100	100		100		100		100	100	100	100			
Stenotrophomonas maltophilia	1															100	100		
Gram-positive bacteria	18																		
Enterococcus spp.	4	50.0			50.0									75.0				100	50.0
Staphylococcus aureus	4			75.0	0.0											100	75.0	10	100
Staphylococcus coagulase negative	3			66.7	0.0									33.3		33.3	100	100	100
Streptococcus spp	7				42.9						42.9					14.3			100

spp, species.

incidence of spontaneous fungal peritonitis (SFP) was 9.1% (2/22) of patents in the positive ascites culture group. Our finding was in line with a recent systematic review reporting SFP in 7.8% of patients from six cohort studies (n=1,052), but higher than the incidence reported in a cohort study in Korea, which found a 3.6% incidence of SFP (21,22). Since SFP is relatively uncommon compared to SBP, the AASLD does not include antifungal therapy in the empiric treatment of cirrhotic patients with suspected peritonitis (4). Although SFP is uncommon, the 30-day mortality rate has been shown to be significantly higher than in SBP (73.3% *vs.* 28.7%; P=0.0007) (21). Prompt initiation of antifungal therapy is indicated when there is any evidence of SFP (21).

The incidence of gram-positive bacteria in blood cultures of our CNNA patients appears to be substantially lower (31.3%) than the incidence in ascites cultures of our SBP patients. This is partly due to three patients in our SBP group with gram-positive bacteria in ascites culture who also had the same gram-positive isolates in the blood who were only counted as SBP patients. Including these isolates in blood culture incidence would in effect increase the incidence of gram-positive bacteria in blood to 40%. Nonetheless, the gram-positive bacteria incidence in blood cultures is still lower than the 50% incidence observed in ascites cultures. The reasons for this disparity are not certain. One theorized explanation is due to blood cultures being performed more readily than ascites cultures (due to the timing and relative complexity of paracentesis). Consequently, blood cultures are more likely to be obtained before a dose of antibiotic as opposed to ascites cultures, which are more often delayed until after antibiotics are administered. Administration of broad-spectrum antibiotics 6 hours prior to paracentesis has been shown to result in no growth in 86% of previously positive ascites cultures (4). Considering that 51.1% of the patients in our study received one or more doses of antibiotics prior to paracentesis, it is likely that pre-paracentesis antibiotic administration increased the incidence of CNNA.

Our incidences of MDR organisms in the total cohort (9.5%) and SBP subgroup (13.6%) were lower than the incidences reported in Brazil (46.9%) and the Netherlands (32%) (13,18). Importantly, the 10-year interval cohort study in the Netherlands showed an increasing incidence of MDR from 25% in 2003–2005 to 32% in 2013–2014 (18). Hence, the rate of MDR in SBP appears to be increasing, which underscores the need to assess MDR risk factors in individual patients when selecting empiric antibiotic treatment. In Brazil, *Escherichia coli* had the highest prevalence of MDR in SBP-related cultures (13). In comparison, our study's MDR rates and the relative number of specific MDR species in our SBP patients were too small to guide decisions in selecting empiric MDR coverage. However, considering the overall MDR rates in our institution were similar to the rates in our study, it would appear that the probability of MDR organisms causing SBP in a cirrhosis patient at our institution is low. On the other hand, it should be noted that 75% of the MDR isolates in our study were from patients with hospital-acquired infection. Hospital-acquired (nosocomial origin) of infection is a known risk factor for MDR organisms (23). This further exemplifies the need for individualized MDR risk factor assessment.

We present aggregate antimicrobial susceptibility rates of the cultured bacterial isolates in *Table 3* for illustrative and comparative purposes only. Current standards recommend aggregate susceptibility rates be used to guide empiric selection of antimicrobials only when 30 or more isolates of a species are tested (24). Our numbers of individual species isolates are too small to allow confident interpretation and clinical utility of our susceptibility data. Nonetheless, in comparison to our institution-wide antibiogram data during the years of our study, susceptibility rates for *Escherichia coli* isolates were substantially lower for antibiotics commonly used in the prophylaxis and treatment of SBP. Specifically, susceptibility rates of *Escherichia coli* to fluoroquinolones (44.4%), and sulfamethoxazole/trimethoprim (66.7%) were up to 20% lower than our institution susceptibility rates. Conversely, susceptibility rates of *Escherichia coli* to ceftriaxone (88.9%) and cefepime (100%) were high and comparable to our institution susceptibility rate. The majority of gram-positive bacterial isolates in our study demonstrated excellent susceptibility to vancomycin (100%) with the exception of the two VRE isolates. Clinical practice guidelines for management of infectious diseases recommend avoiding empiric use of antibiotics when resistance rates are known to be 20% or higher (25,26). Based on the high rate of *Escherichia coli* resistance to fluoroquinolones, ceftriaxone would be the prudent empiric choice to cover the likely susceptible gram-negative bacteria in SBP patients in our institution. For patients whom infection with resistant gram-negative bacteria (e.g., ESBL+ *Escherichia coli*) is a concern, a carbapenem, or cefepime would be empirically appropriate depending on severity of infection (13,27,28). Likewise, due to the high rate of

gram-positive bacteria observed in our cohort, it would also be prudent to add vancomycin to the empiric regimen. Once results of ascites fluid analysis and culture and susceptibilities are available, antibacterial spectrum should be narrowed (4).

In addition to the limitations discussed above, there were additional limitations in our study. First, our study participants were from a single academic hospital in Florida. As previously discussed, the regional differences in the microbiology of SBP limits generalizability to other centers and regions. Second, the proportion of patients receiving antibiotics prior to paracentesis could have affected the relative incidences of SBP and CNNA and the subsequent observed microbial incidences due to the effect on culture yield. Third, the retrospective design of our study might have introduced selection bias and additional confounders affecting the outcome. However, a study comparing prospective and retrospective data in patients with respiratory and gastrointestinal infection did not show a difference in the outcome (29). Finally, as this was designed to be a descriptive study, numerical differences were not tested for statistical significance. Despite the above limitations, our study has merit in that the data collected was from a large tertiary care center that admits patients from several surrounding counties within Florida. Furthermore, our data spans a 5-year interval improving the validity of our results.

Future research should aim to evaluate the regional differences in microbial incidence at multiple sites within the United States and validate risk factors for MDR in individual patients. Meanwhile, individual hospitals are encouraged to collect and analyse their local microbiologic data specifically in cirrhosis patients to optimize empiric antimicrobial selection.

In conclusion, the microbiologic incidence in SBP and CNNA patients in our large tertiary care center shifted over the 5-year study period towards a predominance of gram-positive bacteria over gram-negative bacteria. Our findings mirror the worldwide epidemiologic shift towards gram-positive bacteria as causative pathogens in SBP, albeit with important geographic differences. Although *Escherichia coli* continues to be the most isolated pathogen, empiric antibiotic treatment should sufficiently cover gram-positive bacteria. Empiric antibiotic selection should be individualized based on local microbial incidence, antimicrobial susceptibility rates and validated MDR risk factors in cirrhosis patients.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist, available at http://dx.doi.org/10.21037/dmr-20-11

Data Sharing Statement: Available at http://dx.doi.org/10.21037/dmr-20-11

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr-20-11). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and approved by the University of Florida Institutional Review Board (IRB201600349). Due to the retrospective nature of the study informed consent was not required.

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