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Epidemiology of ascites fluid infections in patients with cirrhosis in Queensland, Australia from 2008 to 2017

A population-based study

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Abstract

Spontaneous bacterial peritonitis (SBP), a common infection in patients with cirrhosis and ascites, is associated with high morbidity and mortality. The aim of this study was to investigate changes in the epidemiology of ascites fluid infections over time in an Australian population, including patient demographics, trends in mortality, length of hospital stay and the nature and antibiotic resistance profile of causative organisms.

An observational descriptive population-based epidemiological study of patients with cirrhosis admitted to public hospitals in Queensland during 2008–2017 was performed, linking demographic/clinical and microbiology data.

Among 103,165 hospital admissions of patients with cirrhosis, ascites was present in 16,550 and in 60% (9977) a sample of ascitic fluid was tested. SBP was diagnosed in 770 admissions (neutrophil count >250/ml) and bacterascites in 552 (neutrophil count <250/ml with positive culture). The number of admissions with an ascites fluid infection increased by 76% from 2008 to 2017, paralleling an 84% increase in cirrhosis admissions over the same timeframe. Patients with SBP had a longer hospital stay (median 15.7 vs 8.3 days for patients without SBP, $P < .001$) and higher in-hospital mortality, although this decreased from 39.5% in 2008 to 2010 to 24.8% in 2015 to 2017 ($P < .001$). Common Gram-positive isolates included coagulase negative staphylococci (37.9%), viridans group streptococci (12.1%), and *Staphylococcus aureus* (7.2%). Common Gram-negative isolates included *Escherichia coli* (13.0%), *Klebsiella pneumoniae* (3.1%) and *Enterobacter cloacae* (2.6%). The prevalence of resistance to any tested antibiotic was <10%.

SBP remains associated with high in-hospital mortality and long hospital stay. Typical skin and bowel pathogens were common, therefore, empirical antibiotic therapy should target these pathogens. This study provides valuable evidence informing infection management strategies in this vulnerable patient population.

Abbreviations: CoNS = coagulase negative staphylococci, PMN = polymorphonuclear, SBP = spontaneous bacterial peritonitis.

Keywords: antibiotic resistance, ascites, cirrhosis, gram negative, gram positive, infection, liver disease

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The data that support the findings of this study are available from a third party, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are available from the authors upon reasonable request and with permission of the third party.

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1. Introduction

Ascites is the commonest complication in patients with decompensated cirrhosis.[1] Spontaneous bacterial peritonitis (SBP) is a common infection, present in 10% to 30% of hospitalised patients with ascites, and is associated with significant morbidity and mortality.[2] SBP is defined as the spontaneous infection of ascitic fluid (AF) in the absence of a secondary intra-abdominal focus and its pathogenesis is related to several endogenous factors such as gut bacterial dysbiosis, mucosal barrier dysfunction, bacterial translocation and cirrhosis associated immune dysfunction.[3–6] Due to the high rate of culture negativity, reportedly up to 60%, SBP is diagnosed based on the AF polymorphonuclear (PMN) count. AF PMN count ≥250 cells/mm^3 is diagnosed as SBP.[2,7] Among AF samples with a PMN count of <250 cells/mm^3, culture-positive samples are considered a variant of SBP, termed bacterascites.[2] It is believed that these patients are in the early stage of infection, as studies have showed that bacterascites has the potential to evolve into SBP,[8,9] or in the resolving stage of SBP.

Due to the association with gut microbes, the most common causative organisms of SBP were thought to be the enterobacterales group of bacteria, hence the recommendation of third generation cephalosporins (TGC) as the empirical antibiotic treatment.[7,10,11] However, interventions such as large volume paracentesis, transjugular intrahepatic portosystemic shunts, use of proton pump inhibitors, selective intestinal decontamination with long term prophylactic antibiotics and frequent hospitalizations have reportedly contributed to a change in the epidemiology of SBP infections worldwide during the past 20 years.[12–14] Concerns about the increasing incidence of infections due to Gram-positive organisms, increasing r esistance to TGC and increasing multidrug resistant (MDR) organisms in SBP infections leading to treatment failure have been raised.[12,15,16] Interestingly, the evolving epidemiology of SBP is reported to vary according to geographical location, emphasizing the importance of ascertaining the local epidemiology when treating patients with SBP.[14,16,17]

In this population-based data linkage study, we evaluated the epidemiology of SBP and bacterascites in public hospitals in Queensland, Australia, from 2008 to 2017. Our objective was to examine the trends in the available clinical characteristics and demographics of patients with cirrhosis who developed infections compared to those without, and trends in mortality and length of hospital stay and the nature and antibiotic resistance profile of causative organisms associated with episodes of infection.

2. Patients and methods

A population-based cohort study of all people treated in hospital with cirrhosis in Queensland during 2008 to 2017 was conducted. The details of the identification of the cohort have been described previously.[18] Briefly, data relating to all patients discharged from Queensland public and private hospitals during 2008 to 2017 with a principal or other diagnosis of cirrhosis, or related complications or procedures, and/or who died during 2008–2017 with a principal or other cause of death of cirrhosis or related complications, were obtained from the Queensland Hospital Admitted Patient Data Collection. The study cohort ('parent cohort') was identified via a comprehensive list of ICD-10 diagnosis and procedure codes provided to the Statistical Analysis Linkage Unit. Criteria for selection of cirrhosis admissions have been described previously.[19] Briefly, a patient with cirrhosis was defined by hospitalization that included at least one ICD-10-AM code for cirrhosis (K70.3, K74.4, K74.5, K74.6), hepatocellular carcinoma (C22.0), alcoholic hepatic failure (K70.4), hepatic failure unspecified (K72.9), varices (I85.0, I85.9, I98.3, I98.2, I86.4) or portal hypertension (K76.6) as primary or other diagnosis. Patients with portal hypertension related to primary thrombophilia (D68.5, D68.6) and schistosomiasis (K77.0, B65.1, B65.9) were classified as non-cirrhotic. The accuracy of this algorithm for identification of patients with cirrhosis has been reported to have a 76% negative predictive value and 88% positive predictive value.[19] Admissions where the patient's age was <20 years, residential location was unknown, interstate or overseas, and admissions to private hospitals (due to the lack of centralised microbiology data collection) were excluded. A total of 12,423 individual patients with cirrhosis (103,165 hospital admissions) were included in the analyses.

Microbiology and cell-count data collected from AF samples during each admission was extracted through a state-wide pathology database (AUSLAB) utilised by all Queensland Health (public) hospitals and related to the parent cohort. A total of 9,977 AF results from eligible admissions of patients with cirrhosis were obtained. For admissions with multiple samples, if an admission had a positive culture for one sample and a negative culture for another, we have considered the patient to have a positive culture for that admission.

2.1. Measurements

Clinical and socio-demographic information and information about hospital discharge for all hospital episodes of care were obtained from Queensland Hospital Admitted Patient Data Collection. Patients' residential postcodes were used to determine area-based index of relative socioeconomic disadvantage score[20] and remoteness of residence.[21] Comorbidity burden was determined using the Charlson Comorbidity Index[22] using validated coding algorithms.[23] Patients were then categorised into groups with no known co-morbidity (Charlson score = 0) and at least one comorbidity (Charlson score ≥ 1). Patient age data were provide by 5-year age groups (capped at 75 years). Length of hospital stay was calculated by adding all days the patient was admitted during one admission (capped at 30 days).

2.2. Classification of ascitic fluid infection and microorganisms

An AF sample was considered SBP-positive if the PMN count was ≥250 cells/mm^3 and negative if the PMN count was <250 cells/mm^3. In traumatic taps PMN count was corrected to the red blood cell count (250 red cells:1 PMN). AF samples with a PMN count <250 cells/mm^3 and a positive culture were classified as bacterascites.

2.3. Data analysis

Analyses were conducted using Stata/SE (Version 16; Stata Corporation, College Station, TX) and JMP Pro 14.1.0 (SAS Institute, Cary, NC). Categorical variables were presented as numbers and percentages and the Chi-square test was used to compare groups. All p values were two-sided. Complete case analysis was used (ie admissions with no missing data).

In-hospital mortality (in-hospital deaths divided by hospital admissions) was calculated for the first (2008–2010) and last (2015–2017) two years of the study period, to gain insight into changes over time, and overall. Multivariable logistic regression was used to examine factors that were independently associated with in-hospital mortality. The final multivariable model was determined based on the results of the bivariable analysis, our previous analyses of this patient cohort that examined relationships and dependencies among variables and their association with in-hospital mortality,[24] as well as the clinical relevance of variables. The final model included age group, presence of diabetes, alcohol as a cofactor, and presence of cirrhosis-related complications, namely ascites, hepatic encephalopathy, hepatorenal syndrome and variceal bleeding. Results are presented as odds ratios (OR) with 95% confidence interval (CI).

2.4. Ethics approval

The study was approved by the Human Research Ethics Committees of Queensland Health (HREC/17/QPAH/23; HREC/2018/QMS/43571) and QIMR Berghofer Medical Research Institute (P3506).

3. Results

3.1. Ascites patient cohort and sociodemographic factors

During the study period of 2008–2017 there were 103,165 admissions for 12,423 unique patients with cirrhosis (Fig. 1). For 25,371 admissions (24.6%) cirrhosis was the reason for the admission (based on diagnosis and procedure codes previously described).[24] A total of 16,550 of all admissions had an AF sample taken for analysis (n = 9977) and/or an ICD-10 code for ascites (n = 15,432), indicating they were investigated for ascites, whether or not cirrhosis was the reason for admission (Fig. 1). Patients who were admitted for reasons other cirrhosis were included in this study because we aimed to identify infections and outcomes in all patients with cirrhosis. 1,118 (6.8%) admissions involved microbiological analysis of an AF sample for a patient who did not have an ICD code for ascites. The majority of admissions with ascites were male patients (72%) in the over 50 age group (79%). Sixty-one percent of admissions were of patients who resided in major cities, and there was a trend towards increased admissions from socioeconomically disadvantaged areas (Table 1). Indigenous Australians were overrepresented among admissions. Alcohol was identified as the aetiology or a co-factor in the majority of admissions (64%), followed by cryptogenic (24.8%) and chronic HCV infection (24.4%) (Fig. 2). It was not possible to distinguish primary diagnoses and co-factors from the linked data.

3.2. Prevalence and characteristics of admissions for SBP and bacterascites

Of the 9,977 admissions in which an AF sample was sent to the microbiology laboratory, PMN count was available for 8,147 (82%) (Fig. 1). The reason for the lack of PMN data for some samples is unknown, since we did not have access to patients' medical records or any further information in this data linkage study. 770 admissions (9.5%) were considered as having an episode of SBP (PMN $\geq$250 cells/mm^3), which included 279 admissions with a positive culture (36% of SBP-positive episodes). Among the admissions with a PMN count <250 cells/mm^3, a positive culture (bacterascites) was present in 552 admissions. In 1,830 admissions without a PMN count (18%), 265 had a positive culture (Fig. 3A). These samples were considered only for the purposes of describing the organisms cultured from AF.

The number of admissions with a diagnosis of cirrhosis increased over the study period, from 1842 in 2008 to 3,396 in 2017 (1.84-fold), along with a 1.76-fold increase in the number of AF infections (SBP or bacterascites), from 88 to 155, respectively (Fig. 3B). Admission through the emergency department was the commonest mode of referral, accounting for 61% of the total admissions with ascites. A quarter of admissions were for a single day, likely for large-volume paracentesis, and 50% of patients had a hospital stay less than 5 days (Table 2). The median duration of hospital stay in SBP-positive admissions was longer than SBP-negative admissions (15.7 vs 8.3 days, $P < .001$, Fig. 3C). Among the SBP-positive admissions, the length of stay in culture-positive admissions

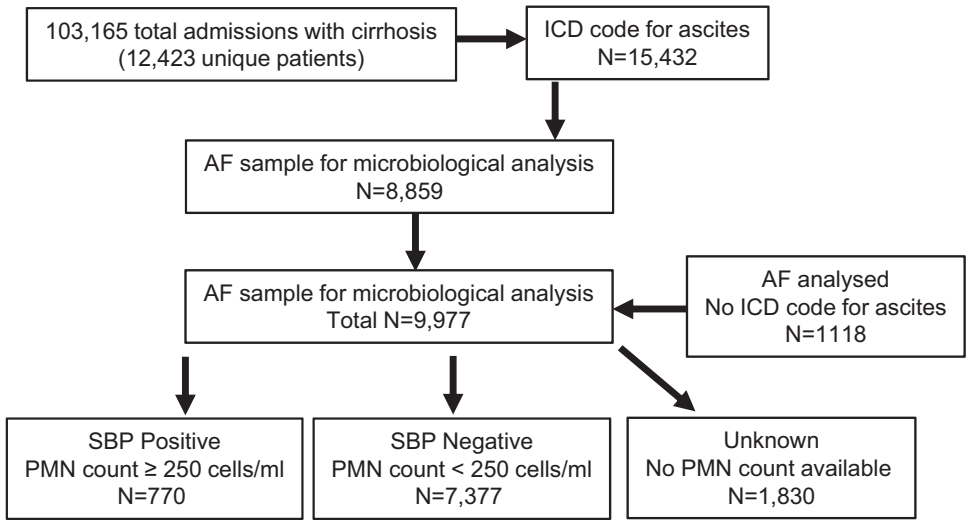

Figure 1. Summary of study cohort.

Table 1

Sociodemographic factors of patients with cirrhosis with and without ascites.

	Without ascites N = 86,615	With ascites N = 16,550	*P*-value
Gender			
Male	59,385 (68.6%)	11,974 (72.4%)	<.001
Female	27,230 (31.4%)	4576 (27.6%)	
Age			
20–39 yr	7,573 (8.7%)	812 (4.9%)	<.001
40–49 yr	13,349 (15.4%)	2696 (16.3%)	
50–59 yr	23,859 (27.5%)	5967 (36.1%)	
60–69 yr	22,687 (26.2%)	4278 (25.8%)	
70 years and over	19,147 (22.1%)	2797 (16.9%)	
Rurality of residence			
Major city	49,517 (57.2%)	10,053 (60.7%)	<.001
Inner regional	16,073 (18.6%)	3302 (20.0%)	
Outer regional	16,136 (18.6%)	2776 (16.8%)	
Remote/very remote	4889 (5.6%)	419 (2.5%)	
Socioeconomic advantage and disadvantage			
Q1 most affluent	9925 (11.5%)	2219 (13.4%)	<.001
Q2	14,750 (17.0%)	2713 (16.4%)	
Q3	14,476 (16.7%)	3076 (18.6%)	
Q4	20,123 (23.2%)	3788 (22.9%)	
Q5 most disadvantaged	27,341 (31.6%)	4754 (28.7%)	
Country of birth			
Australia	64,161 (74.2%)	12,396 (75.1%)	.024
Overseas	22,254 (25.8%)	4113 (24.9%)	
Indigenous status			
Indigenous	17,630 (20.4%)	1620 (9.8%)	<.001
Non-Indigenous	68,976 (79.6%)	14,923 (90.2%)	

Data presented as number (%). *P* – value by Chi square test.

were significantly longer than culture-negative admissions (median 18.6 days vs 14 days, $P < .001$). There was a significantly longer hospital stay in bacterascites admissions compared to SBP-negative, culture-negative admissions (median 13.3 days vs 8.2 days, $P = <.001$). Overall, the presence of an AF infection (SBP or bacterascites) was associated with a significantly longer hospital stay compared to the absence of AF infection (median 15.7 days vs 8.2 days, $P = <.001$).

3.3. Comorbidities and complications of cirrhosis other than ascites

Comorbid conditions were present in 33.7% of the admissions with an AF sample sent to the laboratory, with a higher proportion of patients with SBP having comorbidities (44.2% vs 32.6% for patients without SBP; $P < .001$). Diabetes was present in 21.5% of all admissions (25.3% in SBP-positive vs 21.1% in SBP-negative admissions; $P = .006$; Table 2). Variceal bleeding was the commonest complication of cirrhosis other than ascites and was present in 16.5% of all admissions. The prevalence of variceal bleeding, hepatic encephalopathy, and hepatorenal syndrome were significantly higher in admissions with SBP (all $P < .001$).

3.4. In-hospital mortality

The in–hospital mortality rate among SBP-positive admissions was significantly higher compared to SBP-negative admissions (28.6% (95%CI 25.4–31.8) vs 7.8% (95%CI 7.2–8.4), $P < .001$). Following adjustment for age-group and clinical factors (diabetes, alcohol as presumed aetiology, hepatic encephalopathy, variceal bleeding, hepatorenal syndrome, and hepatocellular carcinoma), in-hospital mortality was 4.28 times more likely in SBP-positive admissions (adjusted OR = 4.28, 95%CI 3.52–5.20).

A significant reduction in the in-hospital mortality rate was observed in the last 3 years (2015–2017) compared to the first 3 years (2008–2010) of the study (Fig. 3D) among SBP positive admissions (39.5% vs 24.8%, respectively; $P = .001$). In–hospital mortality rate was higher in culture-positive SBP admissions (37.6% 95%CI 31.9–43.3, $P < .001$) compared to culture-negative SBP admissions (23.4% 95%CI 19.7–27.1, $P < .001$). There was no significant change in proportion of culture-positive versus -negative admissions over the study period (data not shown).

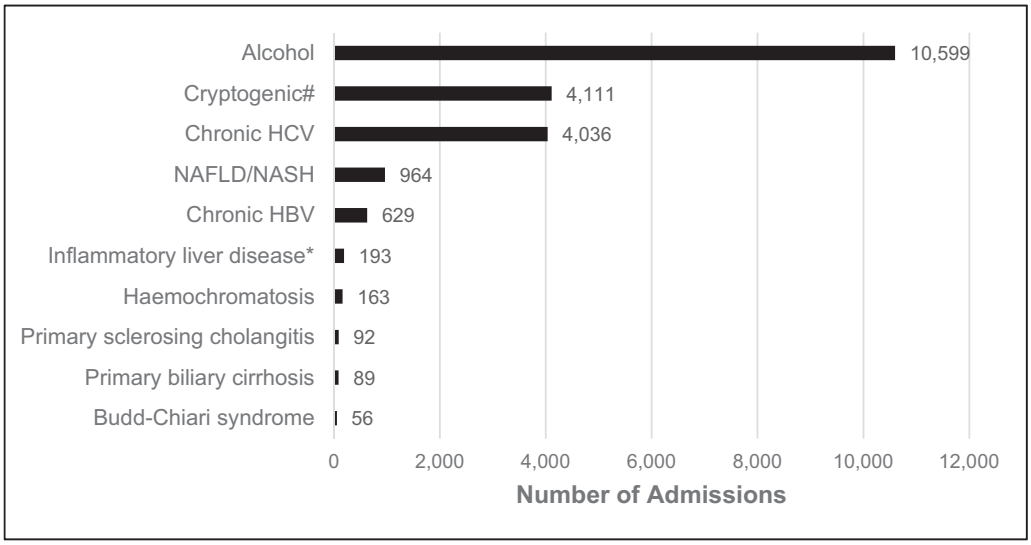

Figure 2. Aetiology of cirrhosis for ascites cohort (16,550 admissions). Number of admissions with listed ICD codes as primary diagnosis or co-factor (for etiologies with >50 admissions over the study period). Admissions may be associated with more than one code. *ICD K769, K753, K759, #ICD K746.

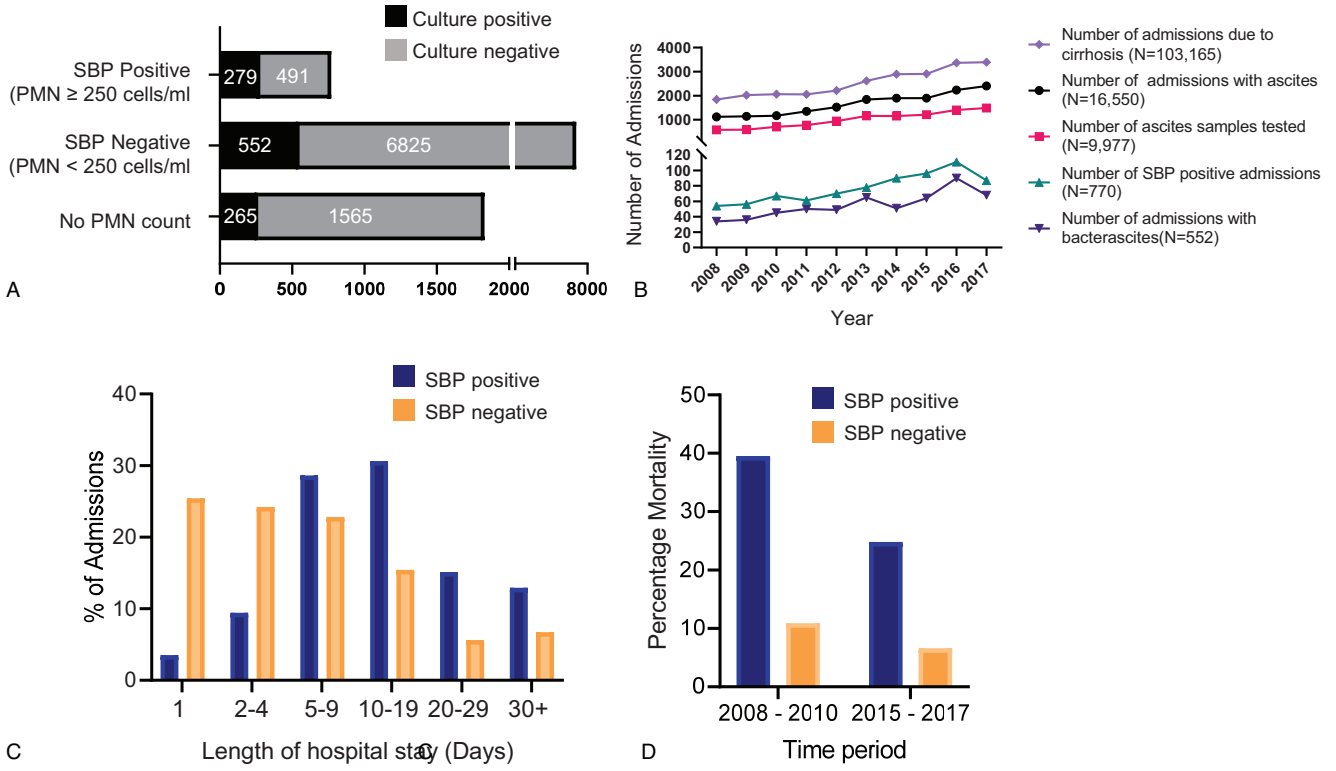

Figure 3. Ascites admissions, infection rate and outcomes. A. Classification of admissions with an ascitic fluid sample based on the neutrophil (PMN) count and culture positivity. B. Proportions of total cirrhosis admissions with ascites, ascites fluid samples, SBP and bacterascites per study year. C. Length of hospital stay and D. In–hospital mortality in SBP-positive and -negative admissions.

Table 2

Diabetes, cirrhosis related complications, length of stay and in hospital mortality in spontaneous bacterial peritonitis (SBP) positive and negative infections.

	Total n = 8,147	SBP positive n = 770	SBP negative n = 7377	*P*-value*
Charlson comorbidity category				
No comorbidity	5405 (66.3%)	430 (55.8%)	4975 (67.4%)	<.001
At least one comorbidity	2742 (33.7%)	340 (44.2%)	2402 (32.6%)	
Diabetes				
Not present	6399 (78.5%)	575 (74.7%)	5824 (78.9%)	
Present	1748 (21.5%)	195 (25.3%)	1553 (21.1%)	.006
Hepatorenal syndrome				
Not present	7749 (95.1%)	691 (89.7%)	7058 (95.7%)	
Present	398 (4.9%)	79 (10.3%)	319 (4.3%)	<.001
Hepatic encephalopathy				
Not present	7744 (95.1%)	704 (91.4%)	7040 (95.4%)	
Present	403 (4.9%)	66 (8.6%)	337 (4.6%)	<.001
Variceal bleeding				
Not present	6803 (83.5%)	590 (76.6%)	6213 (84.2%)	
Present	1344 (16.5%)	180 (23.4%)	1164 (15.8%)	<.001
Length of hospital stay				
1 d	1901 (23.3%)	27 (3.5%)	1874 (25.4%)	<.001
2–4 d	1854 (22.8%)	72 (9.4%)	1782 (24.2%)	
5–9 d	1903 (23.4%)	220 (28.6%)	1683 (22.8%)	
10–19 d	1371 (16.8%)	236 (30.6%)	1135 (15.4%)	
20–29 d	528 (6.5%)	116 (15.1%)	412 (5.6%)	
30+ d	590 (7.2%)	99 (12.9%)	491 (6.7%)	
In hospital mortality/live discharge				
In-hospital mortality	799 (9.8%)	220 (28.6%)	579 (7.8%)	<.001
Discharged alive	7348 (90.2%)	550 (71.4%)	6798 (92.2%)	

SBP. Data are presented as a percentage of the total admissions for the category. *P* value (Chi – square test) compares between SBP positive and negative admissions.

3.5. Organisms isolated in AF cultures

A positive culture was recorded in 1,096 admissions (11%). Overall, monomicrobial infections were present in 973 (88.8%) admissions. Considering all the bacterial cultures, coagulase negative staphylococci (CoNS) were isolated in 37.9% of admissions, with *Escherichia coli (E coli)* (12.9%) and viridans streptococci (12%) being the second and third most common bacteria isolated (Table 3). A small number of fungal infections were identified (58/1096, 5.3% infections), with *Candida albicans* (3.4%) and *Candida* non *albicans* species (1.9%). Among the culture-positive SBP episodes, monobacterial infections accounted for 91.4%, monofungal infections 4% and polymicrobial infections 4.6%. Gram negative bacteria (GNB) were present at a slightly higher frequency compared to Gram positive bacteria (GPB), (49.5% vs 45.7%) in monobacterial infections. The most frequently isolated GNB was *E coli* (31.4%), followed *by K pneumoniae* (6.8%), *E cloacae* (4.7%) and *P aeruginosa* (2.5%). The most frequently isolated GPB were CoNS (14.4%), *S aureus* (9.8%), viridans streptococci (11%) and enterococci (5.8%). Excluding CoNS episodes, considering the possibility of them being contaminants, the proportion of GNB infections was much higher than GPB infections (58% vs 37%) in the SBP culture-positive admissions.

In polybacterial SBP-positive infections, *E coli* (36%), viridans streptococci (27%) and CoNS (21.6%) were the commonest bacteria isolated. Similar to SBP, the majority of bacterascites episodes were monobacterial (88.4%). GPB accounted for 72% of episodes, predominantly CoNS (49%). GNB accounted for 9.4% of episodes with *E coli* (6.6%) being the most common. The profile of culture positive infections for which no PMN count was available was similar to that observed overall (Table 3).

3.6. Antibiotic resistance

Considering all positive cultures in our cohort, the prevalence of methicillin resistant *Staphylococcus aureus* (MRSA), vancomycin resistant enterococci (VRE) and extended spectrum beta-lactamase producing *E coli* was 1.37%, 0.91% and 0.82% respectively. A higher number of the MDR organisms were isolated in SBP-positive admissions compared to bacterascites and missing PMN count admissions (Table 3).

Frequently used empirical treatment for SBP includes antibiotics such as TGC and co-amoxiclav for community-acquired, and piperacillin–tazobactam, carbapenems and daptomycin for resistant or hospital-acquired infections.[7,10,11,25] Considering all GNB isolated in 20 or more admissions, the overall prevalence of ceftriaxone resistance was <10%, resistance to ciprofloxacin was 6.7% and co–trimoxazole 21.6%. The prevalence of ceftriaxone resistance was 8.5% among *E coli* isolates and 50% among *Enterobacter cloacae* isolates, whereas

Table 3

Frequency of commonly isolated gram positive and negative bacteria over the 10 year period (2008 – 2017).

	Total number of admissions (1096)		Admissions with Culture positive SBP (279)		Admissions with Bacterascites (552)		Admissions with no PMN count (265)	
Organism	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Escherichia coli	142	12.96	83	29.75	35	6.34	24	9.06
Klebsiella pneumoniae	34	3.10	20	7.17	7	1.27	7	2.64
Enterobacter cloacae	29	2.65	14	5.02	9	1.63	6	2.26
Pneudomonas aeruginosa	20	1.82	9	3.23	7	1.27	4	1.51
Klebsiella oxytoca	6	0.55	3	1.08	0	0.00	3	1.13
Citrobacter freundii	5	0.46	3	1.08	2	0.36	0	0.00
Acinetobacter baumannii	5	0.46	2	0.72	0	0.00	4	1.51
Stenotrophomonas malophilia	7	0.64	2	0.72	1	0.18	4	1.51
Serratia marcescens	6	0.55	6	2.15	0	0.00	0	0.00
TOTAL GNB	**249**	**22.72**	**142**	**50.90**	**61**	**11.05**	**52**	**19.62**
coagulase negative staphylococci	415	37.86	42	15.05	270	48.91	103	38.87
Staphylococcus aureus	79	7.21	28	10.04	37	6.70	14	5.28
Viridans streptococci	133	12.14	35	12.54	67	12.14	31	11.70
Streptococcus milleri group	20	1.82	11	3.94	4	0.72	5	1.89
Streptococcus pyogenes	4	0.36	2	0.72	0	0.00	2	0.75
Streptococcus pneumoniae	6	0.55	4	1.43	2	0.36	0	0.00
Streptococcus agalactiae	5	0.46	2	0.72	2	0.36	1	0.38
Enterococcus faecalis (vancomycin sensitive)	44	4.01	11	3.94	24	4.35	9	3.40
Enterococcus faecium (vancomycin sensitive)	30	2.74	10	3.58	15	2.72	5	1.89
TOTAL GPB	736	67.15	145	51.97	421	76.27	**170**	**64.15**
Candida albicans	37	3.38	16	5.73	13	2.36	8	3.02
Candida non albicans	21	1.92	12	4.30	5	0.91	4	1.51
TOTAL	**58**	**5.29**	**28**	**10.04**	**18**	**3.26**	**12**	**4.53**
MRSA	15	1.37	6	2.15	5	0.91	4	1.51
V. resistant *E faecalis*	0	0.00	0	0.00	0	0.00	0	0.00
V. resistant *E faecium*	10	0.91	4	1.43	4	0.72	2	0.75
ESBL *E coli*	9	0.82	7	2.51	1	0.18	1	0.38
CPE *E coli*	0	0.00	0	0.00	0	0.00	0	0.00
TOTAL MDR	**34**	**3.10**	**17**	**6.09**	**10**	**1.81**	**7**	**2.64**

Bacterascites: PMN count < 250 cells/ml. CPE *E coli* = carbapenemase-producing Enterobacterales, ESBL = extended spectrum beta lactamase, GNB = Gram negative bacteria, GPB = Gram positive bacteria, MRSA = methicillin resistant *Staphylococcus aureus*, PMN = Polymorphonuclear cell, SBP = spontaneous bacterial peritonitis (PMN count ≥ 250 cells/ml), V = vancomycin.

Table 4

Antibiotic resistance of Gram negative bacteria isolated during the study period. Cells are coloured from highest (red) to lowest (green) using a linear gradient.

Gram negatives N (Isolates)	Escherichia coli 143	Klebsiella pneumoniae 34	Enterobacter cloacae 28	Pseudomonas aeruginosa 20
Ampicillin	49.0%	97.0%	85.7%	
Amoxicillin/clavulanate	18.1%	3.0%	96.4%	
Ceftriaxone	8.5%	0.0%	50.0%	5.3%
Ceftazidime	9.6%	0.0%	50.0%	5.3%
Piperacillin - tazobactam	7.9%	18.1%	50.0%	15.8%
Ciprofloxacin	9.2%	3.0%	3.7%	0.0%
Trimethoprim/sulfamethoxazole	26.7%	3.0%	17.8%	
Meropenem	0.0%	0.0%	3.5%	0.0%

all *K pneumoniae* strains were sensitive to ceftriaxone (Table 4). There was no significant difference in the prevalence of TGC-resistant bacteria over time, but the majority of isolates were identified within the last 3 years (2015–2017) of the study. Carbapenem resistance was identified in only one isolate each of *E aerogenes* (1 of 2 isolates) and *E cloacae* (1 of 28 isolates) during the entire study duration. Among the isolated GPB, 25% of the 40 *Enterococcus faecium* isolates were resistant to vancomycin. Of the 42 CoNS isolates in SBP cultures, antibiotic sensitivity was determined in 18 isolates. Among them, all isolates were resistant to penicillin but sensitive to vancomycin. Of 15 CoNS isolates tested for ciprofloxacin, 60% demonstrated resistance (9/15). Eight out of 16 isolates (50%) tested for co-trimoxazole demonstrated resistance to it.

4. Discussion

Cirrhosis and its complications are an increasing cause of morbidity and mortality, and burden on health resources, globally.[26] In Queensland, the number of admissions due to cirrhosis increased by 1.6-fold from 2008 to 2016.[24] Infections are common in patients with cirrhosis, reported in some studies to occur 4-fold more frequently than in the general population, and are a major determinant of prognosis.[1,27] Infections can precipitate decompensation and acute on chronic liver failure.[28] Multi-centre international studies have recently reported alarming longitudinal trends in infections in cirrhosis, with increasing prevalence of GPB and multidrug resistant infections, and increasing TGC and quinolone resistance among the gram negatives.[16,29] Experience differs from country to country, however, as local bacterial ecology and prescribing practice vary. Our analyses focused on ascites did not show a significant increase in ascitic fluid infections or antibiotic resistance during the study period in excess of the overall increased rate of admissions of patients with cirrhosis. We recently reported on the incidence of bacteremia, sepsis and antibiotic resistance to bloodstream infections in the same cohort analysed here.[30]

Infection in AF, including SBP and bacterascites, is one of the most common infections in patients with cirrhosis and is associated with 18% to 40% in-hospital mortality.[31] We observed a relatively high in–hospital mortality rate in SBP-positive (28%) compared to SBP-negative admissions, but report a significant decrease in in-hospital morality over the 10-year study period. This may reflect improved medical management of infections and their complications.

SBP diagnosis is based on AF PMN count due to the high rate of culture-negative infections, which may be due to dilution of bacteria with the large volume of AF in the initial stages of infection, patients already receiving antibiotics at the time of the diagnostic paracentesis or improper sample collection. A further consequence of culture-negative infection is the need for empirical antibiotic treatment, which has been suggested to contribute to the development of antibiotic resistance. The rate of culture-negative infection has been reported to be 40% to 60%.[2] In the current study, 64% of SBP episodes were culture-negative. During the 10-year period in our study, GNB and GPB were isolated at similar frequencies in monobacterial SBP infections. GPB were the predominant organisms identified in in bacterascites, as observed in previous similar studies.[8,32]

The frequent isolation of CoNS isolates in our cohort, especially in bacterascites, likely reflects skin contamination, highlighting the importance of rigorous hygiene practices to avoid contamination of AF samples. Nevertheless, given the immunocompromised state of these patients and repeated abdominal paracentesis, these organisms could potentially be pathogens in some patients.[33,34] This could be better analysed based on patients' symptoms and clinical status, which was not possible given the retrospective nature of this study.

The development of resistance to frequently used empirical antibiotics for treatment SBP, such as TGC and co-amoxiclav for community-acquired, and piperacillin–tazobactam, carbapenems and daptomycin for resistant or hospital-acquired infections, is a global concern.[7,10,11,25] The prevalence of MDR GNB was low in our cohort compared to Europe and Asian regions, which reported 16% to 50%.[25,35,36] This may, in part, be due to the strong public Antimicrobial Use and Resistance in Australia Surveillance System.[37] Ceftriaxone resistance was <10% among the GNB, though 18 resistant infections due to *E cloacae* and *P aeruginosa* were identified. As *P aeruginosa* is intrinsically resistant to ceftriaxone and *E cloacae* harbours a chromosomal AmpC gene, ceftriaxone monotherapy is not recommended for these organisms.[38] With respect to MDR GPB, while the prevalence of MRSA was comparatively low compared to other regions,[39] Vancomycin resistance among the *E faecium* isolates, which are frequently hospital acquired, was high (25%).[40–42] According to the latest report published by the Australian commission on safety and quality in health care, Australia is identified as having high prevalence of vancomycin-resistant *E faecium* compared to Europe.[37] Risk factors identified for enterococcal SBP include the use of SBP prophylaxis such as fluoroquinolones, co-trimoxazole or rifaximin,[43] recent history of gastrointestinal bleeding[44] and recent gastrointestinal endoscopy.[45]

The strength of this study is that it is a population-based analysis of patients from a large, diverse state in Australia, utilising linked clinical/sociodemographic and pathology data. As a retrospective study based on hospital admissions data, it is necessarily reliant on the quality of data coding, particularly in relation to diagnoses; which may vary from site-to-site and over time. Hospital admissions data does not provide sufficient detail to distinguish community- and hospital-acquired infections, or to examine potentially relevant clinical parameters, which would require detailed review of patient medical records. Finally, as the study utilised microbiology data from a database that is only used in the public health system we were only able to analyse public hospital admissions.

5. Conclusion

In contrast to international studies, we report no significant increase in ascitic fluid infections or multidrug resistance in patients with cirrhosis over the past decade and demonstrate a significant decrease in in-hospital mortality of patients with SBP over time. Regular assessment/review of the bacteria responsible for ascitic fluid infections and their antibiotic sensitivity is critical to ensure guidelines for empirical antibiotic therapy in patients with cirrhosis are current.

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