Spontaneous Bacterial Peritonitis by *Burkholderia cepacia* Complex: A Rare, Difficult to Treat Infection in Decompensated Cirrhotic Patients

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Introduction: *Burkholderia cepacia* complex (Bcc) is non-fermenting Gram-negative bacillus and has been rarely reported to cause spontaneous bacterial peritonitis (SBP) in decompensated cirrhosis. **Objective:** This study was done to evaluate the clinical presentation of cirrhotic patients with SBP due to Bcc and to determine its impact on clinical outcome. **Methods:** This is a retrospective, observational study conducted during the period from 1st January 2013 through 31st March 2015. Medical records and microbiology laboratory files were reviewed to identify all cases of Bcc associated SBP among patients hospitalized at the liver intensive care unit and analyzed. **Results:** During the study period, out of 252 SBP patients, 11 (4.3%) patients with a positive ascitic fluid culture for Bcc were identified. Pain abdomen was the predominant symptom present in 9 (81%) patients followed by hepatic encephalopathy in 7 (63%) patients. Acute kidney injury (AKI) was universally present, seen in 6 (54%) patients at the time of presentation and 4 (36%) patients developed AKI during hospital stay. The mean CTP score was 11.2 ± 1.1 (10–13), and the mean MELD was 24.3 ± 5.9 (14–35). The mean SOFA and APACHE II score at presentation were 11 ± 4.2 (4–18) and 19.4 ± 5.2 (11–28), respectively. A total of 8 (72%) patients (6-ACLF, 2-NASH) succumbed to the illness during hospitalization due to severe sepsis and multiorgan dysfunction and 3 (27%) patients are doing well on follow-up after 3 months. **Conclusion:** SBP caused by Bcc has been rarely reported in cirrhotic patients. This organism is intrinsically resistant to third generation cephalosporins, which are the initial antibiotic of choice for SBP patients, hence associated with multi organ failure and high mortality rates.

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Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication of decompensated cirrhosis.¹ The incidence of SBP in cirrhosis with ascites varies from 10 to 30% in hospitalized patients.² In spite of widespread use of antibiotics, the mortality rate following an episode of SBP is about 10–46%.^{3,4} The efficacy of traditionally recommended therapy has been low in nosocomial infections (up to 40%), and multi-resistance has been observed in up to 22% of isolated bacteria in nosocomial SBP.⁵ *Burkholderia cepacia* complex (Bcc) is non-fermenting Gram-negative bacillus and has been reported to cause

infections such as bacteremia (in patients with indwelling catheters), meningitis, urinary tract infections (UTIs), septic arthritis, peritonitis (in patients undergoing peritoneal dialysis)⁶ and respiratory tract infections (especially in patients with cystic fibrosis and chronic granulomatous disease).⁷ Owing to high intrinsic resistance and being one of the most antimicrobial-resistant organisms encountered in the clinical laboratory, these infections can prove very difficult to treat and, in some cases, result in death.^{8,9} However, SBP in cirrhotic patients by Bcc is rarely reported and only few case reports are available in the literature.¹⁰ In fact a recent retrospective study of 306 pathogenic bacteria from 288 cases of SBP from China had no mention of Bcc suggesting rarity of SBP caused by Bcc.¹¹

Keywords: cirrhosis, infection, spontaneous bacterial peritonitis

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Abbreviations: AKI: acute kidney injury; APACHE II: Acute Physiology and Chronic Health Evaluation (APACHE); APASL: Asia Pacific Association for the Study of Liver; Bcc: *Burkholderia cepacia* complex; CSLI: The Clinical and Laboratory Standards Institute; CTP: Child Turcotte Pugh Score; HCV: Hepatitis C virus; ICU: intensive care unit; NASH: non-alcoholic steatohepatitis; PGIMER: Postgraduate Institute of Medical Education and Research; UTI: urinary tract infection; SBP: spontaneous bacterial infection; SIRS: systemic inflammatory response syndrome; SOFA: The Sequential Organ Failure Assessment

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MATERIALS AND METHODS

Study Design and Population

A retrospective, observational study was conducted to evaluate the outcomes of cirrhotic patients with SBP due to Bcc and to determine its impact on clinical outcome. Microbiology laboratory files were reviewed to identify all cases of Bcc associated SBP with a positive result of an ascitic fluid culture among patients hospitalized at the Liver Intensive Care Unit (Post Graduate Institute of Medical Education & Research, Chandigarh, India) during the

period from 1st January, 2013 through 31st March, 2015. Patients with a culture positive for other organisms and those with secondary peritonitis were excluded from the study. We reviewed the medical records of the patients, and the following information was collected from patients: age, sex, cause of cirrhosis, Child–Pugh score, MELD score, APACHE II and SOFA score, initial symptoms at the time of presentation, gastrointestinal bleeding, presentation with septic shock, laboratory results, previous SBP history, and empirical antibiotic regimen. The primary outcome measure was in hospital mortality rate.

Definitions

SBP was defined by an ascitic fluid polymorph nuclear leukocyte count >250 cells/mm³ and/or positive culture result. Septic shock was defined as sepsis associated with evidence of organ hypo perfusion and a systolic blood pressure <90 mmHg or a requirement for the use of a vasopressor to maintain the blood pressure.

Laboratory Testing

The ascitic fluid specimens were obtained aseptically by paracentesis and inoculated into blood culture bottles at the bedside. Ascitic fluid samples were also sent to the microbiology laboratory for polymorph nuclear leukocyte counting, Gram staining, protein, sugar, serum ascitic albumin gradient and adenosine deaminase levels. The recovery of isolates from ascitic fluid was performed with the BACTEC system (BD Diagnostic Instrument Systems, Vendor city). Identification of isolates was performed by matrix-associated laser desorption and ionization – time of flight. (MALDI-TOF) Antibiotic susceptibility testing of isolates was performed by Kirby–Bauer disk diffusion method as per Clinical and Laboratory Standards Institute (CLSI) guidelines.¹²

RESULTS

Clinical Characteristics of Patients with Bcc SBP

During the study period, out of 252 SBP patients, 11 (4.3%) patients with a positive ascitic fluid culture for Bcc were identified. There was no clustering of cases except that three cases were diagnosed in 3 months, rest being evenly distributed over time. Among them, 8 (73%) patients had an ascitic fluid polymorph nuclear leukocyte count >250 cells/mm³, and 3 (27%) patients had monomicrobial non-neutrocytic bacteriascites. Therefore, a total of 11 patients with SBP due to Bcc were enrolled in the study. The clinical characteristics of the patients studied are given in Table 1. Pain abdomen was the predominant symptom present in 9 (81%) patients followed by hepatic encephalopathy in 7 (63%) patients, fever in 6 (54%) patients and GI bleeds in 2 (18%) patients. The presence of septic shock/SIRS was seen in 8 (72%) patients. Acute kidney injury

Table 1 The Clinical Characteristics of SBP Patients.

Parameter	n (%)
Presentation	
• Pain abdomen	9 (81%)
• Hepatic encephalopathy	7 (63%)
• Fever	6 (54%)
• GI bleed	2 (18%)
Septic shock/SIRS	8 (72%)
Acute kidney injury	10 (90%)
Associated infection	
• Pneumonia	1 (0.09%)
• UTI	1 (0.09%)
Prior history of hospitalization (30 days)	5 (45%)
Prior antibiotic use (7 days)	8 (73%)
• Quinolones	3 (27%)
• Third generation cephalosporins	5 (45%)
Prior history of SBP on secondary prophylaxis	4 (36%)

(AKI) was universally present, seen in 6 (54%) patients at the time of presentation to the hospital and 4 (36%) patients developed AKI during hospital stay. There were other associated infections in 2 (18%) patients, which included pneumonia in 1 patient and UTI in 1 patient. The history of prior hospitalization was found in 5 (45%) patients; broad-spectrum antibiotic usage due to various infections was observed in 8 (72%) patients and prior history of SBP on secondary prophylaxis was present in 4 (36%) patients. There was no history of similar Bcc infection isolates from other infections in the liver intensive care unit.

All patients were males with mean age of 59.5 ± 13.2 (40–80) years. The etiology of cirrhosis was alcohol in 7 (63%), nonalcoholic steatohepatitis (NASH) related in 3 (27%) and Hepatitis C virus (HCV) in 1 (0.09%) patient. Acute or chronic liver failure (APASL criterion)¹³ was found in 6 (54%) patients with alcohol cirrhosis, severe alcoholic hepatitis being the cause of acute deterioration in all patients. 7 (63%) patients had co morbidities including type 2 diabetes mellitus in 4 (36%) patients and past history of hypertension in 3 (27%) patients. Mean duration of stay in hospital before Bcc spontaneous bacterial infection was diagnosed 6.5 ± 7 (0–24) days. The severity of liver disease was assessed by using CTP & MELD score. The mean CTP score was 11.2 ± 1.1 (10–13), and the mean MELD was 24.3 ± 5.9 (14–35). SOFA and APACHE II scores were used for prognostication. The mean SOFA and APACHE II score at presentation were 11 ± 4.2 (4–18) and 19.4 ± 5.2 (11–28) respectively. The demographic characteristics of the patients are shown in Table 2.

The laboratory investigations revealed a mean total leukocyte count (TLC) of $18,873 \pm 11,592/\mu\text{L}$ (8000–49000) with predominant polymorph nuclear response

Table 2 The Demographic Characteristics of the Patients.

Parameter	Result in mean $\pm$ SD (min-max)
Age (years)	59.5 $\pm$ 13.2 (40–80)
Sex	
• Male (n)	11 (100%)
• Female (n)	0
Etiology of cirrhosis	
• Alcohol	7 (63%)
• NASH	3 (27%)
• HCV	1 (0.09%)
Hospital stay before SBP (days)	6.5 $\pm$ 7 (0–24)
CTP score (mean)	11.2 $\pm$ 1.1 (10–13)
CTP B	0
CTP C	11 (100%)
MELD score	24.3 $\pm$ 5.9 (14–35)
SOFA score	11 $\pm$ 4.2 (4–18)
APACHE II score	19.4 $\pm$ 5.2 (11–28)

at the time acquiring infection. 6 (54%) patients had AKI at presentation and 4 (36%) developed during hospital stay. The mean ascitic fluid cell count was $288 \pm 133.4/\text{mm}^3$ (100–560). Serum procalcitonin levels used as a biomarker of infection at presentation was raised in 9 (81.8%) patients with a mean value of 6.4 ± 7 ng/ml (0.2–22.6). None of the patients had blood culture positivity for any organism. The laboratory investigations of the enrolled patients are given in Table 3.

Table 3 Laboratory Investigations of Patients at the Time of SBP.

Parameter	Result in mean $\pm$ SD (min-max)
Hemoglobin (g/dL)	9.4 $\pm$ 2.2 (7.6–15.2)
TLC (μL)	18,873 $\pm$ 11,592 (8000–49000)
Platelets (μL)	63,909 $\pm$ 57,681 (12000–220000)
Urea (mg/dL)	123 $\pm$ 65.9 (40–236)
Creatinine (mg/dL)	2.4 $\pm$ 1 (1–4.2)
Na (mmol/L)	138.5 $\pm$ 5.5 (126–143)
Bilirubin (mg/dL)	11.9 $\pm$ 6.3 (1.7–19)
AST (U/L)	105.5 $\pm$ 90.8 (31–273)
ALT (U/L)	41.7 $\pm$ 27.2 (8–81)
Alkaline phosphatase (U/L)	147 $\pm$ 115.6 (37–479)
Albumin (g/dL)	3 $\pm$ 0.5 (2.3–3.9)
Procalcitonin (ng/ml)	6.4 $\pm$ 7 (0.2–22.6)
INR	2.4 $\pm$ 1.5 (1.5–6.7)
Ascitic fluid cell count (cells/ mm^3)	
At SBP diagnosis	288 $\pm$ 133.4 (100–560)

All Bcc isolates were sensitive to co-trimoxazole, and meropenem and resistant to ceftriaxone, ceftazidime, cefepime, cefotaxime, and colistin. All the patients were treated according to sensitivity pattern. Mean duration of total hospitalization was 17.45 ± 16 (3–60) days. 8 (72%) patients (6-ACLF, 2-NASH) succumbed to the illness during hospitalization due to severe sepsis and multiorgan dysfunction and 3 (27%) patients are doing well on follow-up after 3 months.

DISCUSSION

An increased frequency of multidrug resistant bacterial SBP and infections by atypical organisms is being recognized now with use of prophylaxis and repeated hospitalization of the cirrhotic patients for ICU care. Difficult to treat SBP has been suggested for such nosocomial acquired SBP (indicated by previous ICU stay, previous antibiotic use, infection acquired by interventions in hospital) caused by organisms, which are resistant to the conventional antibiotics used for treating SBP.¹⁴ Such infections are problematic and are associated with greater mortality.¹⁵ Bcc is the name for a group or “complex” of bacteria that can be found in soil and water. Bcc poses little medical risk to healthy people, however, people who have certain health problems such as weakened immune systems or chronic lung diseases, and particularly cystic fibrosis may be more susceptible to infections. Bcc is a known cause of infections in hospitalized patients and it is intrinsically resistant to antimicrobial agents such as amino glycosides, first- and second-generation cephalosporins, antipseudomonal penicillins, and polymyxins. Bcc often develops resistance to β -lactams due to presence of inducible chromosomal β -lactamases and altered penicillin-binding proteins and efflux pumps in Bcc mediate resistance to chloramphenicol, trimethoprim, and fluoroquinolones. Even though the initial isolates are susceptible to trimethoprim-sulfamethoxazole and antipseudomonal β -lactams because of antimicrobial pressure these develop resistance very quickly. This phenomenon poses challenge to the clinicians in managing these patients.

CLSI 2010 guideline recommends cotrimoxazole, ceftazidime, minocycline, and meropenem for the treatment of Bcc infections in humans.^{8,16} The antimicrobial susceptibility profile of Post Graduate Institute of Medical Education & Research, Chandigarh, India (PGIMER) isolates revealed near complete resistance to fluoroquinolones and more than 50% resistance to carbapenems, the first-line therapeutics of choice against serious infections.^{17–19} Successful treatment using combinations of meropenem with ciprofloxacin and tobramycin has been reported, and doripenem appears to have therapeutically potential against Bcc.²⁰ All 50 clinical isolates of Bcc obtained from various specimens over the last 4 years in PGIMER were found susceptible to doripenem by E-test as per CLSI 2010

guidelines.²¹ Due to high intrinsic resistance and being one of the most antimicrobial-resistant organisms encountered in the clinical laboratory, these infections can prove very difficult to treat and, in some cases, result in death. However, SBP in cirrhotic patients by Bcc is rarely reported and only few case reports are available in the literature. This is the largest series of the culture positive Bcc SBP to be reported in literature. Most of these patients had history of prior hospitalization and use of antibiotics (quinolones and third generation cephalosporins) for treating infections within the last 4 weeks and history of secondary prophylaxis for SBP. This infection was more commonly seen in alcoholic cirrhosis, which might be explained by higher degree of neutrophil dysfunction and immune paralysis seen in alcoholic cirrhosis with acute on chronic liver failure like presentation. The association of such an infection can also be related to the severe liver disease in our patients requiring repeated hospitalization in ICU as illustrated by high CTP and MELD score. These patients also had severe sepsis and universal development of AKI at presentation or during the hospital stay. Most of the infections caused by Bcc reported in literature are resistant to third generation cephalosporins commonly used in patients with SBP. This is associated with high morbidity and mortality probably due to late detection of infection and development of multi-organ dysfunction. As has been shown in earlier studies serum procalcitonin was raised in all patients and might serve as a surrogate marker of infections in cirrhotic patients.²² APACHE II and SOFA scores can be used for prognostication in such patients admitted in intensive care units as previously seen.²³

CONCLUSION

SBP caused by Bcc has been rarely reported in cirrhotic patients. However infections caused by Bcc should be considered in patients requiring multiple admissions in ICU and repeated use of antibiotics. Critically sick ICU cirrhotic patients with SBP and non-response to conventional antibiotics should be evaluated for such difficult to treat organisms because of their associated high mortality.

AUTHOR'S CONTRIBUTIONS

Participated in research design: Y Chawla, RK Dhiman, V Singh. Performed data analysis: S Taneja, P Kumar. Wrote or contributed to the writing of the manuscript: A Duseja, V Gautam, P Kumar, S Taneja.

CONFLICTS OF INTEREST

The authors have none to declare.

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