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Original Research Article

Bacterial infections in Indian cirrhotic patients: a prospective study

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ABSTRACT

Background: Bacterial infections (BI) are more prevalent in liver cirrhosis (LC), high among hospitalized patients. The aim of this study was to explore the epidemiological pattern of BI in hospitalized patients with LC, and identification the causative agents. Objective of the study was evaluation of therapeutic/empirical approaches for these infections.
Methods: Inputs from the body fluid analysis and culture reports were recorded. The Child Pugh score (CPS) was used to assess the severity of liver disease. Antibiotic treatment strategy was analysed, prescribed antibiotics were checked for contraindications using Lexicomp software.
Results: Of 60 enrolled patients, four had mixed infection and 55% were culture positive. There was a male preponderance (83.3%). BI was more frequent in those aged 51-60 years (38.3%) and >60 years (35%). Higher proportion of patients (60%) belonged to class C of CPS followed by class B (31.7%). The most common causative organisms identified were *E. coli* (28.5%), *K. pneumonia* (14.2%), *Enterococcus spp* (11.4 %) and less common were *K. oxytoca*, *Coagulase-negative staphylococci*, *Staphylococcus aureus*, *gram-positive cocci*, *gram-negative cocci*, *P. aeruginosa*, *S. hemolyticus*, *ß-hemolytic streptococcus spp*. Majority of the subjects had spontaneous bacterial peritonitis (36.7%) followed by urinary tract infection (21%), lower respiratory tract infection (18.3%), sepsis (13.3%), cellulitis (3.3%) and acute gastroenteritis (1.7%). Cephalosporin (61.7%), rifaximin (51.7%), penicillin and β lactamase inhibitors (36.7%) were the common prescribed antimicrobials.
Conclusions: There is a positive association between the risk of BI and severity of liver damage.

Keywords: Bacterial infection, Child pugh score, Liver cirrhosis, Spontaneous bacterial peritonitis

INTRODUCTION

Compromised immune status, along with structural and hemodynamic abnormalities in the patients with liver cirrhosis increases the risk and make them highly vulnerable to bacterial infections (BI).[1] BI are more prevalent in liver cirrhosis; 4-5 times higher and severe than that of patients without cirrhosis, high among hospitalized patients (25%-47%).[2-4] Preveden has reported a prevalence of BI in cirrhotic patients to be 38.15%.[5] It is one of the major causes for sepsis, systemic inflammation and organ failure; brain being the frequent target (55.7%) followed by kidney (15.1%); circulatory (17.6%) and respiratory failure (15.8%) further make it critical.[6] CANONIC study has noted renal failure as the most frequent organ failure, brain damage being second in the list and the incidence of circulatory (16.8%) and respiratory (9.2%) failure in the list.[7] High mortality at one month and at one year is 4 times higher in patients with cirrhosis.

With a rising global trend in infections in cirrhotic patients, increase in associated morbidity, mortality can be expected, which is preventable and controllable with meticulous management. Emergence of drug resistance which high globally (40%) and highest in India (70%), calls for early empirical antibiotic therapy.[8]

Cirrhosis is listed as the 10th most common cause of death globally. In advanced cirrhosis, BI is more common and a major cause of mortality. In cirrhotic patients, once the infection develops, it causes further damage and leads to more severe complications such as septic shock, hepatic encephalopathy, chronic liver failure, multi-organ failure and finally death. Severity of cirrhosis and rate of survival are assessed using the Child Turcotte Pugh (CTP) introduced by Child, Turcotte and Pugh. It helps to predict the life expectancy in patients with cirrhosis and in the management.

Urinary tract infections (UTI) (23-41%) and spontaneous bacterial peritonitis (SBP) (20-35%) are the most common infections in cirrhotic patients; pneumonia (8-14%), spontaneous bacteraemia (8-21%), and skin and soft tissues infections (SSTIs, 6-13%), though less frequent, may cause significant and can prove fatal.

Epidemiology of liver infections varies globally.[9,10] Data on BI in liver cirrhosis in Indian patients is limited. Aim of the study was to explore the epidemiological pattern of BI in hospitalized adult Indian patients with cirrhosis of liver with determination of the causative agents. Objective of this study was evaluation of therapeutic/empirical approaches for infections as the objectives.

METHODS

This prospective observational study was carried out by the department of Pharmacy practice of a pharmacy college and pharmacology of a tertiary care teaching hospital, during October 2018 to March 2019, after obtaining the approval from the Institutional Ethics Committee, prospective participants were screened after obtaining a written informed consent.

Patients aged above 25 years, who were diagnosed with BI with chronic liver disease/cirrhosis with features of portal hypertension, ascites, variceal bleeding, hepatic encephalopathy, hepato-renal syndrome, type 2 diabetes mellitus, alcohol abuse, metabolic syndrome were included. Patients with auto-immune liver disease, inherited liver disorders, drug-induced liver disease, hepato-cellular carcinoma, hepatic injury caused by viral, fungal, and protozoan infection, haemolytic anaemia, pregnant and lactating women, heart failure, acute poisoning were excluded.

Details of relevant medical history, clinical and laboratory investigations, treatment history were obtained from the case records, treatment charts and prescriptions. Inputs from the body fluid analysis and culture reports for the identification of causative organisms and type of bacterial involved in the infection were recorded. CTP was used to assess the severity of the liver disease. Antibiotic treatment strategy was analyzed to document antibiotic prescribed for the corresponding infections. Prescribed antibiotics were checked for contraindications using the Lexicomp software.

Statistical analysis

Data was captured on Microsoft excel worksheets and edited for completeness. Descriptive statistics (frequency, percentage) was used; tables and figures were used as appropriate. Chi-square test was used to determine the association between BI and liver cirrhosis.

RESULTS

Data of 60 cirrhotic patients with infections, meeting the selection criteria were available for analysis. There were 50 (83.3%) males and 10 (16.6%) females (p=0.082).

The mean age±SD was 50.5±3.77 years. Twenty-eight (46.66%, female- 01, 3.57%) were alcoholics, four (6.66%, all males) were both alcoholic and smokers; twenty-eight (46.66%, males- 19, 67.86%, females- 09, 32.14%) were neither smokers nor alcoholics. There were 31 (62%) male patients who smoked tobacco and consumed alcohol but only one female patient (10%) was alcoholic.

The mean age of the patients was 50.5 years±3.77, higher for females (62 years±5.73). There were 41 (68.33%) patients aged >50 years (p= 0.910) (Table 1).

Thirty-six (60%) patients had co-existing illnesses, 23 (76.66%) with multiple co-morbidities; 13 (36.11%) patients had single co-existing illness, type 2 diabetes mellitus (n=09, 18%) and hypertension (n=04, 6.66%) (Table 2). Maximum number of co-morbidities was four. Diabetes mellitus and hypertension were the common co-morbidities. More number of males had associated comorbidities attributable to more number of male patients in this study. Type 2 diabetes mellitus is an independent factor of poor prognosis, a risk factor for increased complications and infections in particular.

Types of infection

SPB (n=22, 36.6%) and UTI (n=18, 30) we are the common infections, with *E. coli*, K. pneumoniae being the common isolates. Table 3 lists the infections and the common causative organisms that caused BI in our study population.

Causative organisms

There were 35 culture positives. *E. coli* (10, 28.5%) was the most common causative organism. The other predominant organisms involved in the infection were *K. pneumonia* (n=05, 14.2%), *Enterococcus spp* (n=04, 11.4%), *K. oxytoca*, *Coagulase-negative staphylococci* and *S. aureus* were isolated from three (8.5%) each, gram positive cocci (n=02, 5.7%) and *Citrobacter ferendii*, *gram-negative cocci*, *P. aeruginosa*, *S. hemolyticus*, *ß-hemolytic streptococcus spp*. isolated from one each.

CTP score

CTP score was calculated for all patients to predict the survival rate; thirty-six (60%) patients were in class C indicating one-year survival rate of 45%. Those in class B (19, 31.66%) and A (05, 8.3%) were less (p=0.0.630) (Table 4).

Antibiotic therapy in cirrhotic patients

Eleven different classes of antibiotics are prescribed to treat infections. Majority of the patients were treated with >1 class of antibiotic during hospitalization. The minimum duration of therapy with each antibiotic in a patient was about 3 days (range 3-7 days).

Cephalosporins (37, 61.7%), other antibiotics (rifaximin) (31, 51.7%), penicillin+ß-lactamase inhibitors (22, 36.7%), carbapenems (8, 13.3%), fluoroquinolones (6, 10%); three patients each received imidazole, lincomycin, oxazolidinone and one patient each received nitrofurans, glycopeptide inhibitors, macrolides.

None of the antibiotics prescribed in our study were contraindicated but certain drugs such as metronidazole, lincomycin and ceftriaxone had an advice to use with caution in patients with hepatic impairment. In our study they were absolutely indicated, and when prescribed, patients were monitored for any possible adverse effects.

Table 1: Age wise distribution of study population.

Age (years)	Total		Male		Female	
	N (%)	Mean age (years)±SD	N (%)	Mean age (years)±SD	N (%)	Mean age (years)±SD
<40	6 (10)	35±1.77	06	35±1.77	0	0
40-50	10 (16.6)	45±3.52	10	45±3.52	0	0
51-60	23 (38.3)	53±2.55	19	54±3.04	04	52±2.06
>60	21 (35)	69±7.23	15	66±5.07	06	72±9.39
Total	60	50.5 ±3.77	50	50 ±3.35	10	62±5.73

Table 2: Comorbidities in the study population.

Parameter	Gender N (%)		P value
	Male	Female	
Type 2 diabetes mellitus	9 (15)	0	0.076
Hypertension	4 (6.66)	0	0.179
Hypertension and type 2 diabetes mellitus	7 (11.6)	2 (3.33)	0.315
Hypertension, type 2 diabetes mellitus, hypoglycaemia	1 (1.66)	0	0.327
Hypertension, type 2 diabetes mellitus, chronic kidney disease and pulmonary edema	0	1(1.66)	0.014*
Type 2 diabetes mellitus, ischemic heart disease, acute kidney injury	0	1 (1.66)	0.014*
Ischemic heart disease, hypertension, vericose veins with eczema	1 (1.66)	0	0.327
Hypertension, type 2 diabetes mellitus, diabetic kidney disease, old cerebrovascular accident	1 1.66)	0	0.327
Hypertension, type 2 diabetes mellitus, cholelithiasis	1 (1.66)	0	0.327
Hepatic dysfunction	1 (1.66)	0	0.327
Grade 2 haemorrhoids	1 (1.66)	0	0.327
Alcohol dependence syndrome, lumbar spondylosis	1 (1.66)	0	0.327
Alcohol withdrawal syndrome with withdrawal seizures, hypertension, ischemic heart disease, anaemia	1 (1.66)	0	0.327
Coronary artery disease. myocardial infarction, type 2 diabetes mellitus	1 (1.66)	0	0.327
Multiple episodes of renal calculi	1 (1.66)	0	0.327
Undergone surgery for gastric ulcer and hernia	1 (1.66)	0	0.327
Urinary tract infection, type 2 diabetes mellitus	0	1 (1.66)	0.014*
Total	31 (51.66)	05 (8.33)	
No comorbidities	19 (31.66)	5 (8.33)	0.241

*statistically significant

Table 3: Bacterial infections in the study population.

Type of infection	N (%)	Isolates
Spontaneous bacterial peritonitis (SBP)	22 (36.6)	E coli, K. pneumonia, Enterococcus faecalis.
Urinary tract infection	18 (30)	*E. coli*, K. pneumonia, K. oxytoca, Citrobacter ferendii, Enterococcus aerogenus, Staph aureus
Respiratory tract infection	09 (15)	*E. coli*, K. pneumonia, Enterococcus faecalis, Staph aureus, Coagulase negative staphylococci, β-hemolytic streptococcus spp, gram-positive and gram-negative cocci
Sepsis	08 (13.3)	Staphy hemolyticus, P. aeruginosa, K. pneumonia, Coagulase negative staphylococci
Cellulitis	02 (3.3)	K. pneumonia, Coagulase negative staphylococci
Acute gastroenteritis	01 (1.6)	

Table 4: Comparison of risk category in different age groups and gender.

Age group (years)	Risk category						Total
	A		B		C		
	Male	Female	Male	Female	Male	Female	
<40	0	0	01	0	05	0	06
40-50	0	0	04	0	06	0	10
51-60	01	0	07	0	11	04	23
>60	03	01	05	02	07	03	21
Total	04	01	17	02	29	07	60

DISCUSSION

BI is common in patients with liver cirrhosis due to compromised immune status, altered gut status resulting in increased permeability and gut bacteria.[1] Hospitalization, further doubles the chances of infection in these patients. For this reason, we selected hospitalized cirrhotic patients with BI as our study cohort.

There is a male predominance (83%) in our study, which is well documented in literature.[6,11-12] Our patients were younger by a decade as previous reports stated a higher mean age (64.5±12.2 years and 61±13 years).[11-12] The patients in the age group of >50 years (44%) were the most vulnerable subgroup in our study, comparable with that reported by Yuan et al (55.7±13.3 years) and Andreu et al (64±13 years).[13,14] In our study, all females were aged > 51 years. Because of cultural and traditional values in this subcontinent, females do not indulge in alcoholism which is comparable with the study of Amin et al.[15]

Our study supports the presence of multiple co-morbidities as a common occurrence among cirrhotic patients; 3/5th (60%) of our patients had co-existing illnesses, and 76.66% had multiple co-morbidities; type 2 diabetes mellitus (18%) and hypertension (6.66%) were the most common co-morbidities. Maximum number of co-morbidities in our study cohort was four. More number of males had associated co-morbidities attributable to male preponderance. Type 2 diabetes mellitus is an independent factor of poor prognosis also a risk factor for increased complications and infections in particular.

UTI, SBP, Pneumonia, SSTI are the most common BI among cirrhotic patients.[5,16-19] The mortality rate of patients with SBP ranges from 10-50%.[20] Patients who survive the first episode of SBP have a 70% chance of recurrent infection. The first choice of antibiotics in treating SBP is third generation cephalosporins. Due to increased risk of nephrotoxicity, the drugs combined with aminoglycoside antibiotics are not used.[21] SBP (36.6%) was the most common type of infection in our study population, probably due to a contagion of pre-existing ascites by bacterial organisms of intestinal provenance which is supported by Conn et al.[22] Delay in antibiotic therapy increases the mortality during hospitalization (10-50%) and one-year mortality rate (31-93%).[23]

Urinary tract infections, the second common infections (20-40%), more common among women, with gram negative organisms (*E. coli*) as causative organism; pneumonia is the third most common infections (15-21%) in cirrhosis with a high mortality rate of 37-41% (8).[2,5,16,24,25]

Skin and soft tissue infection (SSTI) is seen in 2-11% of cirrhotic patients especially male alcoholics.[26] They are often recurrent, caused by gram positive and in few occasions translocated by gram-negative bacteria. Though mortality rate is comparatively less (20%), it has a potential to cause renal failure and hence, may increase the mortality. Cellulitis and erysipelas are the skin infections

that progress as a the result of bacterial entry through the skin barrier and lymphangitis of the lower terminus and the walls of the abdomen are the frequent soft tissue infections in cirrhotic patients.[27] Acute gastroenteritis (GE) occurs rarely in cirrhotic patient and the common organisms involved in the infection are *E. coli*, gram-negative fermenter bacilli and fungi. Other uncommon infections due to cirrhosis are endocarditis and meningitis.

Infections caused by extended-spectrum β-lactamase-producing enterobacteriaceae (ESBL-E), methicillin-resistant staphylococcus aureus (MRSA) and enterococcus faecium are increasing in patients with cirrhosis, accounting to 34% of hospitalized patients, globally.[28] *Acinetobacter baumanni*, *Clostridium difficile* were not reported in our study. Gram negative bacilli are increasingly being common causative organisms. Infections reported in our study are in similar to the previous reports.[18,29]

There were 35 culture positives in our study. *E. coli* (28.5%) was the most common causative organism similar to the previous reports.[2,14,20,30] Peveden report culture positivity in 20.91% patients; gram negative bacteria, *E. coli* (71.87%) was the common isolate.[5] *E. coli* belongs to the phylum proteobacteria and is one of the predominant groups residing in the intestine. Due to dysbiosis and bacterial translocation caused by cirrhosis resulted in the *E. coli* being the more commonly isolated organism. The other predominant organisms in our patietns were *K. pneumonia*, *Enterococcus spp*, *K. oxytoca*, *Coagulase-negative staphylococci* and *S. aureus*. Results of our study are reflective of trend indicated by a global study.[20]

Piano et al have reported *E. coli* (28%), *K. pnemononiae* (14%), *enterococci* (12%), *S. aureus* (8%) as common causative organisms.[28] *P. aeruginosa* (3%), other gram positive (18%) and other gram-negative organisms (15%) contributed to the pool of infections.

There were nine cases (15%) of lower respiratory tract infections (LRTI) in our study which is comparable with Amin et al which had 12 cases of LRTI. In a previous study by Andreu et al no organisms were isolated from the respiratory tract.[14,15]

Eight cases (13%) of sepsis were identified in our study of whom 50% were culture-positive; in the remaining 50%, the diagnosis was ruled out based on the criteria of clinical signs and symptoms of the patients.

Cellulitis and erysipelas are the skin infections that progress due to the result of bacterial entry through the skin barrier and lymphangitis of the lower terminus and the walls of the abdomen are the frequent soft tissue infections in cirrhotic patients. Cellulitis was the most commonly reported dermatological infections observed in our study which is supported by Naqvi et al.[30] To date, there is only very few studies have assessed the risk factors for cellulitis. It was assumed that hepatic encephalopathy, hypoalbuminemia, and high CTP score play a vital role in the development of cellulitis in cirrhotic patients.

Acute GE is rare in cirrhotic patients with infections. In our study one case (1.6%) of acute GE was identified which was culture-negative.

CTP score was calculated for all patients to predict the survival rate; thirty-six (60%) patients were in class C indicating one-year survival rate of 45%. Those in class B (31.66%) and A (8.3%) were less. In contrast, Gomes et al have noted that 42.7% were in stage B, stage C (39.3%) and stage A (18%) were less frequent.[11]

Initial empiric antibiotic therapy consisting of broad-spectrum agents, later isolate adjusted therapy is followed routinely in the clinical practice globally and so in our hospital. It is crucial that empiric antibiotic therapy started at the earliest, to prevent the mortality in the first six hours of hospitalization.

The patients were advised to complete the course of an antibiotic which was prescribed during the time of hospitalization, even when the culture reports were negative, to prevent bacterial resistance. There were few severe infections where patients needed to be treated with an antibiotic(s) more than the recommended duration of therapy. Third generation cephalosporins are frequently used because they have a low risk of adverse events of superinfection and antibiotic-induced renal toxicity which is supported by Ghassemi et al.[21]

While prescribing antibiotic therapy, the physician has to be aware of the local epidemiology common causative organisms prevailing, severity and type of infection; safety of antimicrobials in cirrhosis, possible drug interactions, pharmacokinetics and pharmacodynamics of the agent, and its safety has to be considered and monitored.[9] It is noteworthy to remember that multidrug resistance is high globally (34%), being highest in Asia and India in particular, which is an additional reason for the use of appropriate antibiotic therapy to minimize treatment failure.[28]

CONCLUSION

Bacterial infections are common among cirrhotic patients. SPB and UTI are the common infections, with *E. coli*, *K. pneumoniae* being the common isolates. The risk of bacterial infections is high depending upon the severity of liver damage.

The choice of a particular antibiotic depends on the type of causative organism involved in the infection. To reduce the risk of drug induced hepato-toxicity, for better clinical outcomes, use of appropriate antibiotic therapy with dose adjustments and individualizing the dosage has to be considered.

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