Original Article

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Burden and Impact of Multidrug Resistance Infection on Outcome of the Patients with Decompensated Liver Disease in a Tertiary Care Institute

Microbiology Section

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ABSTRACT

Introduction: Cirrhosis-Associated Immune Dysfunction (CAID) increases the risk of development of infection which progresses to sepsis and death. Most common infection associated with liver cirrhosis patients are Spontaneous Bacterial Peritonitis (SBP) and Urinary Tract Infections (UTI), together they make up about two thirds of these infections, while the remainder belongs to infections of the skin and soft tissue, bacteremia and other infections. There are increasing numbers of Multidrug Resistant Strains (MDRs) emerging especially in the hospital setting.

Aim: To assess the prevalence of bacterial infection, MDR pattern among the isolates, infection status in correlation with Child-Turcotte-Pugh (CTP) score, survival rate and mortality rate.

Materials and Methods: This retrospective study includes 359 consecutive hospitalised cirrhotic patients from August 2017-July 2018. Based on the clinical examination, laboratory findings and culture positivity, the bacterial infections were diagnosed accordingly.

Results: The prevalence of bacterial infection was 29.80%. The most common infections were UTI (51.56%) followed by Blood Stream Infection (BSI) (24.21%), SBP (14.06%) and Skin and soft tissue infections (7.03%). The most common isolates were *Escherichia coli*, *Staphylococcus* spp, *Klebsiella* spp, *Enterococus* spp, and among Fungi were *Candida* spp. Among bacterial isolates 55.9% turned out to be MDR. The mortality rate was high (61.1%) among the patients with infection and patients with CTP-C (≥10 points) with multiple infections which showed significantly higher mortality rate. Based on the source and development of infection, majority were under community-acquired infections (39.84%) followed by nosocomial (38.29%) and healthcare associated (21.87%). A higher MDR (68.18%) among nosocomial infections were observed.

Conclusion: Increased trend of MDR in nosocomial and healthcare associated infections, shows increased failure rates of empirical antibiotic treatment and necessitates the implementation of Antibiotic stewardship programs. Infections acts as precipitating factor for liver function deterioration thereby increases the chance of mortality. So, the patients with cirrhosis should be carefully monitored for infections.

Keywords: Antibiotic resistance, Bacteria, Liver cirrhosis

INTRODUCTION

Patients with liver cirrhosis are highly prone to infections compared to general population, and those patients presenting with decompensated liver disease are highly vulnerable to infection compared to patients presented with compensated liver disease [1,2]. Patients with decompensated liver disease have a high risk of developing infection with abnormal bacterial translocation and immune dysfunction which might lead to sepsis and death. Infections are often progressed to liver failure which can precipitate GI Bleed, hepatic encephalopathy, Hepato-Renal syndrome and acute exacerbation of chronic liver failure [3,4]. Prevalence of bacterial infection ranges from 21-25% in US population, 38.15% in European population [5,6]. There is scarcity and only limited study on bacterial infections in cirrhosis of liver from India, where the prevalence ranges from 30-54% [7,8]. Infection present on admission or developed during hospitalisation of the patients with cirrhosis liver are accountable for higher mortality outcome in more than 50% of patients [5]. The fundamental cause behind the mortality might be due to the translocation of bacteria from the site of infection to other distinct organ i.e., the spread from intestinal lumen to the mesenteric lymph nodes, there by presence in portal and systemic circulation followed by existence of portosystemic shunts and damaged functions of reticuloendothelial system which may lead to decreased immune reaction and reduction in the removal of bacteria and endotoxins from the portal circulation [6].

Several literature and clinical data shows that bacterial infections predominantly develops in patients with advanced liver cirrhosis especially patients with high CTP score, patients with bleeding associated with esophageal varices, patients with low levels of protein in ascites and also those who had previous episodes of SBP [9]. Bacterial infections are also enhanced by some invasive diagnostic and therapeutic procedures, and also during placing of Blakemore probe to prevent bleeding from oesophageal varices, while placing urinary catheters before or after surgery, like central venous or subclavian catheters, sometimes ascites paracentesis and also alcoholism, malnutrition, immunosuppressive drugs, proton pump inhibitors therapy also enhances the risk of progression of infection [10]. Most common infection associated with liver cirrhosis patients are SBP and UTI, together they make up about two thirds of these infections while the remainder belongs to infections of the skin and soft tissue, bacteremia and other infections [11]. Among various pathogenic organism, the patients with liver cirrhosis are mostly presented with *Escherichia coli*, *Klebsiella* spp, *Enterobacter* spp. and *Pseudomonas aeruginosa*, as well as *Staphylococcus aureus*.

Increasing numbers of MDR particularly in the hospital-acquired bacterial infections are emerging [12]. Though there are several drugs available to decrease the severity of infection, still there is high mortality due to infection in patients with cirrhosis. In order to attain effective treatment outcome of bacterial infections, early

identification of infection should be taken in to account. Clinical examination and determination of the acute phase inflammatory markers, such as C-Reactive Protein (CRP) and Procalcitonin (PCT), may raise suspicion of the presence of a bacterial infection [9,13]. As there is scarcity on epidemiological data of bacterial infections in cirrhotic patients from our region, therefore the present study was aimed to evaluate the type and aetiology of bacterial infections and drug resistance pattern in correlation with survival and mortality rate among the hospitalised cirrhotic patients in a tertiary care center.

MATERIALS AND METHODS

This retrospective study included 359 patients with DCLD admitted in our tertiary care unit, over a period of one year from August 2017 to July 2018. The diagnosis of hepatic cirrhosis was based on clinical, biochemical, echographic findings. Patient with HIV, evidence of hepatocellular carcinoma or other solid tumours, patients taking any immunosuppressant drugs were excluded from the study.

Following are the diagnosis standards followed to identify the infections: i) Community-acquired infections are defined as infections manifesting and diagnosed within 48 hours of admission in patients without any previous encounter with healthcare; ii) Nosocomial infections are infections that have been caught in a hospital and are potentially caused by organisms that are resistant to antibiotics; iii) Health Care-Associated Infection (HCAI) can affect patients in any type of setting where they receive care and can also appear after discharge.

Data Collection

Basic demographic characteristics, clinical or histological of all aetiology, diagnostics test results, Child-Pugh Score, Infection data and their distribution, source and site of infection, drug sensitivity test results, empirical antibiotic regimens and appropriate biochemical and microbiological investigation were collected.

Culture and Drug Sensitivity

Urine samples for culture and sensitivity were collected and plated on CLED (Cystine Lactose Electrolyte Deficient), blood samples were incubated in BHI broth at 37°C for 5 days, respiratory specimen were cultured in Crystal Violet Blood Agar and pus samples were collected from skin and soft tissue infections, plated in Mannitol Salt Agar with Oxacillin and Blood Agar. Ascitic fluid were collected and inoculated in BHI broth at bedside and then sent for culture. After 24 hours of incubation, Gram's stain was done from the growth. The cultures were identified by standard procedures and antibiotic susceptibility test for recommended drugs (as per CLSI guidelines 2016) [14], performed by using Kirby Bauer Disc Diffusion and Minimum Inhibitory Concentration (MIC) method. MRSA and MRCONS was detected by inoculation in mannitol salt agar with oxacillin. Extended-Spectrum β-Lactamase (ESBL) were initially screened by phenotypic method and later confirmed by the enzyme production as per Clinical and Laboratory Standards Institute guidelines (CLSI-2016). The antibiotics used were: Azithromycin (15 µg), Erythromycin (30 µg), Ciprofloxacin (5 µg), Imipenem (30 µg), Gentamycin (10 µg), Ceftriaxone (30 µg), Nitrofurantoin (50 µg), Cefuroxime (30 µg), Ampicillin (10 µg), and Amoxicillin/Clavulanic acid (20/10 µg). Susceptibility/Resistance was interpreted using CLSI guidelines 2016.

STATISTICAL ANALYSIS

The data obtained were statistically analysed using SPSS 15.0. Data was presented as the mean±standard deviation for normal distributions and median and interquartile range for non-normal data. Continuous variables were analysed using the Student's t-test, depending on the normality of their distribution. Categorical values were analysed using the chi-square test. The $p<0.05$ was considered as statistically significant.

RESULTS

Infection Status among Patients with Liver Cirrhosis

Results obtained out of 359 patients, shows 29.80% culture positivity with 128 isolates were identified and is represented in [Table/Fig-1]. Among 128 isolates, 65.62% were Gram Negative Bacilli and 26.56% were Gram Positive cocci and remaining were fungal infections (7.8%) [Table/Fig-2]. Among Gram negative bacilli, *Escherichia coli* was the most common isolate and in Gram positive cocci, *Staphylococcus aureus* was the most common isolate. The most common infections were UTI (51%). The antibiotic resistance pattern among the bacterial isolates shows 55.9% were (MDR). When we categorise under specific resistance to antibiotic, we found 70.76% were ESBL, 37.50% were MRSA, 66.6% were MR-CONS and 8.3% were Vancomycin Resistant Enterococci (VRE) [Table/Fig-3]. Bacterial isolates were highly resistant (80%) to third generation cephalosporin, moderately resistant (60%) to Aminoglycosides and Fluroquinolones and least to carbapenams and glycopeptides. Based on the source and development of the infection, it is observed that community-acquired infections (39.84%) was most common among infection in the cirrhotic patient followed by nosocomial (38.29%) and healthcare associated (21.87%). Among the source of infection the rate of MDR was high in nosocomial infections (68.18%) compared to other infections [Table/Fig-4]. There was a significant difference in mean total count among the patients with cirrhosis and bacterial infection and patients without infection were observed. The results shows that 69.1% of infected cirrhotic shows more $>11\times10^3$ total count when compared to non infected patients [Table/Fig-5].

Source of infection	No. of infection/Culture positivity	Percentage
Urine	66	51.56%
Blood	31	24.21%
Ascitic fluid	18	14.06%
Skin and soft tissue	09	7.03%
Pleural fluid	04	3.12%

[Table/Fig-1]: Number of infection based on the source of isolates.

Isolates	No. of isolated organism	Type of bacteria	Percentage
Klebsiella spp	21	Gram negative bacteria	84 (65.62%)
Pseudomonas spp	09	Gram negative bacteria	
Escherichia coli	40	Gram negative bacteria	
Citrobacter spp	01	Gram negative bacteria	
Proteus spp	03	Gram negative bacteria	
Acinetobacter spp	10	Gram negative bacteria	
Staphylococcus spp	22	Gram positive bacteria	34 (26.56%)
Enterococcus spp	12	Gram positive bacteria	
Candida albicans/ non albicans	10	Fungal	10 (7.8%)

[Table/Fig-2]: Number of organisms isolated and type.

Distribution of drug resistance	Total among isolates	Percentage %
ESBL	46	70.76
MRSA	06	37.50
MRCONS	04	66.66
VRE	01	8.33

[Table/Fig-3]: Drug resistance pattern of the isolates.

The Baseline characteristics of our study population shows that, among 359 eligible patients 293 were male (81.61%) and 66 were female (18.38%), with the average age of 46.87±10.79 and 46.79±15.34 years of age respectively. Among 107 infected patient

Organism isolated	Community acquired	Health care associated	Nosocomial
Gram positive bacteria	11	9	14
Gram negative bacteria	35	19	30
Fungal	5	0	5
Total	51 (39.84%)	28 (21.8%)	49 (38.28%)
MDR	18 (39.13 %)	18 (64.28 %)	30 (68.18%)

[Table/Fig-4]: Distribution of isolated pathogens by source of infection and its multidrug resistance pattern.

Survival status of the patient	Infected	Non-infected	p-value
Expired TC count <4×10^3	4 (7.3%)	2 (5.7%)	0.04
4-11×10^3	13 (23.6%)	17 (48.6%)	
>11×10^3	38 (69.1%)	16 (45.7%)	
Discharged TC count <4×10^3	5 (9.6%)	29 (13.4%)	0.06
4-11×10^3	23 (44.2%)	125 (57.3%)	
>11×10^3	24 (46.2%)	63 (29.0%)	

[Table/Fig-5]: Correlation of total count in infected and non-infected cirrhotic patients and their survival status.

79 (73.8%) male and 28 (26.2%) female were identified. Among study group alcohol was the most frequent cause for liver cirrhosis, which was accounted for 73.3%. The in-hospital mortality was 25.06%, the mortality rate was higher in the patients with infection (61.11%) than in those without infection (38.8%). Correlation of CTP score with mortality of the patients shows that, CTP C has significant higher mortality (56.3%, p≤0.01) in infected patient when compared with non-infected cirrhotic patient [Table/Fig-6,7].

Characteristics	Infected patients N=107	Non infected N=252	p-value
Age <50 (years)	71 (66.4%)	163 (64.7%)	0.7
Age >50 (years)	36 (33.6%)	89 (35.3%)	
Female	28 (26.2%)	38 (15.1%)	0.01
Male	79 (73.8%)	214 (84.9%)	
Encephalopathy	60 (56%)	142 (56.3%)	0.5
Upper GI bleed	60 (56%)	117 (46.4%)	0.04
Ascites	74 (69.1%)	197 (78.17%)	0.04
Cellulitis	57 (53.2%)	85 (33.7%)	0.003
Laboratory parameters			
TC-10^3/µL	13119.16±7848.707	9910.71±8069.154	0.001
Platelet-10^5/µL	1.0±0.73	1.2±0.9	0.04
Creatinine-mg/dL	1.5±1.0	1.2±08	0.005
Billirubin-mg/dL	9.8±9.6	8.0±9.1	0.08
AST-U/L	194.30±247.06	96.34±121.74	0.001
ALT-U/L	154.63	69.42	0.001
SAP-U/L	109.05	121.89	0.20
TP-g/dL	5.9	6.0	0.46
Albumin-g/dL	3.2	2.7	0.001
INR	2.3	3.6	0.01

[Table/Fig-6]: Correlation of clinical characteristics among infected and non-infected cirrhotic patients.

DISCUSSION

The results obtained from our current study on infection and liver cirrhosis indicates that bacterial infections are often encountered in cirrhotic patients, these results are consistent with other similar type of studies published earlier. Our study reports that the prevalence of infection was 29.80% among infection in cirrhotic patients, a similar prevalence of 30% were also reported by Sahu MK et al., the study also shows that the infection are often asymptomatic [8]. Study conducted by Baijal R et al., also supports the same with similar prevalence [15]. On analysing the occurrence of sepsis in

Features	Expired (n=55)	Discharged (n=52)	p-value
Demographic features			
Male	44	35	0.1
Female	11	17	
Age<50 (years)	37	34	0.8
>50 (years)	18	18	
Child-pugh classification			
Class A	1	3	0.3
Class B	18	21	
Class C	36	28	
Initial presenting symptoms			
Altered sensorium	42	18	0.2
Upper GI bleed	47	13	<0.001
Ascites	52	22	0.9
Breathlessness	37	20	0.003
Cellulitis	45	27	0.002
Laboratory parameters			
TC-10^3/µL	14947.23±6747.5	10785.58±5222.8	<0.001
Creatinine-mg/dL	1.69±1.14	1.44±0.8	0.2
Total billirubin-mg/dL	11.70±11.3	7.9±6.8	0.04
AST-U/L	196.91±256.5	191±239.12	0.9
ALT-U/L	161.45±245.62	147±219.24	0.7
Albumin-g/dL	3.3±1.3	3.1±1.3	0.5
Etiological profile			
Alcoholic	46	36	0.81
Hepatitis B	4	7	
Hepatitis C	3	1	
Combined with Hepatitis B and C	1	1	
HBV+Alcohol	1	2	
Others	0	5	

[Table/Fig-7]: Comparison with survivors and non survivors among infected patients.

cirrhotic patients, a study by Arvaniti V et al., shows that the there is four times increase in the mortality with respect to the occurrence of sepsis and multi-organ dysfunction in patients with terminal liver cirrhosis [16] which correlates with our study. In connection to the lethal outcome our study shows 51.40% of patients with infection, which is consistent with available literature data. It is well known that increase in total count is directly proportional to the increased rate of infection, in our study there is significant change observed in total count when compared with non infected cirrhotics, the change in the total count were also correlated with mortality of infected patients, our study shows higher prevalence with infected mortality which is correlated with previous studies. Based on the literature the most common types of bacterial infections in cirrhotic patients are UTI, SBP and BSI followed by infections of the skin and soft tissue [5]. Based on the distribution among the types of bacterial infections and isolates, our study is reliable with the available literature and has been found that the most commonly occurring infections are UTI (51.56%), bacteraemia (24.21%), and others (24.21%). Preda CM et al., Fernandez J et al., and Lameirao Gomes C et al., also showed similar distribution of infections among cirrhotic patients but with different prevalence [17-19]. But study conducted by Xie Y et al., shows that among distribution of infection, the primary infection and majority were BSI, followed by SBP, lung infection, and UTI [20], which is not correlated with our study. When infection are classified based on CTP score majority were Class B and C. Similar distribution were observed in our study, where majority of patients classified as class C chronic liver disease with high mortality. With respect to SBP in our study

the occurrence of infection did not coincides with other available literatures, since the study was conducted in tertiary care center, the patients were admitted with pre-exposed to multiple doses of different antibiotics in various other hospital and also diagnostic paracentesis was not performed routinely in patients with ascites, here the study lack to rule out the exact status of infection among cirrhotic patients. It is well known that SBP often presents asymptomatically, so the diagnostic paracentesis should be done in case of occurrence of ascites [21,22]. Due to dysbiosis and increased chances of bacterial translocation, patients presenting with ascites and UGI Bleed are particularly prone to bacterial infections, which occur in about 45% of cases which correlated with our study (56.6%) [23]. In other words, more attention was paid to the treatment of liver cirrhosis and its decompensation than to the type of infection. The results of bacterial cultures in our study agree with literature data which also indicate that Gram-negative bacteria, especially *Escherichia coli* were predominant. According to recent data, approximately 65% of bacterial infections in patients with liver cirrhosis are caused by Gram-negative bacteria, in our study it correlates as 65.62% [24]. It is important to emphasise that results obtained from our study has similar outcome of GNB when compared with other studies ranging from 40-70% [2,17]. The most commonly reported Bacterial isolates were *Escherichia coli*, *Staphylococcus* spp, *Klebsiella* spp, *Enterococus* spp, and among Fungi were *Candida* spp which correlates with the literature. Among positive culture isolated 55.9% were MDR. When we categorise them under specific resistance to antibiotic, we have found 70.76% were ESBL, 37.50% were MRSA, 66.6% were MR-CONS and 8.3% were VRE. In depth analysis of drug resistance, bacterial isolates are observed to be highly resistant to third generation cephalosporin, moderately resistant to Aminoglycosides and Fluroquinolones and least resistant to carbapenams and glycopeptides. Fluroquinolones resistances among cirrhotic patients are due to oral Norfloxacin prophylaxis to prevent secondary SBP [7,12,25]. Based on the source and development of the infection, it is observed that community-acquired infections (39.84%) was most common among infection in the cirrhotic patient followed by nosocomial (38.29%) and healthcare associated (21.87%). Nosocomial infections had high MDR (68.18%) isolates compared to other infections. Study by Piano S et al., shows that 34% of MDR among worldwide, with high prevalence in developing countries like India (73%) [12,26]. Antibiotic prophylaxis in cirrhotics should be limited to patients who had gastrointestinal bleed, previous episode of SBP and low protein ascites [27]. This restricted prophylaxis will decrease the incidence of MDR. Reduced immune surveillance and inappropriate use of broad-spectrum antibiotics increases the risk of MDR bacterial infection, newer tools to detect the kind of infection will limit the use of broad-spectrum antibiotics and possibly reduce the incidence.

LIMITATION AND FUTURE RECOMMENDATIONS

With the limited resource and set up in the present study CRP and procalcitonin could not be performed, which are the markers of infection. All liver cirrhotic patients should be suspected for infection and evaluated accordingly, surveillance cultures should be taken to know about the MRSA carrier state. Antibiotic steward ship should be deployed vigilantly to prevent MDR. Infection control measures should be taken to prevent HAI and nosocomial infections.

CONCLUSION

Early diagnosis and prompt treatment of infections are very important for the management of patients with decompensated cirrhosis. Bacterial infection leads to rapid deterioration of liver functions in patients with cirrhosis and it is one of the most common precipitating causes of Acute-on-Chronic Liver Failure (ACLF). Therefore, they should be taken into consideration to introduce appropriate antibiotics that cover the most common pathogen as early as possible. Even before receiving the results of bacterial cultures, biomarkers of acute phase of inflammation, such as C-reactive protein and pro-calcitonin, must be analysed for the presence of bacterial infection. A detailed clinical examination and sampling material for bacteriological culture, may confirm the presence of bacterial infection and thus appropriate antibiotic therapy can be introduced on time. Since MDR organisms are alarming, definitive antimicrobial therapy should be taken into consideration for bacterial infections in patients with liver cirrhosis and their influence on mortality can be decreased, rising trend of nosocomial MDR necessitates the implementation of antibiotic stewardship programs, thus the duration of treatment can be shortened and treatment costs can be reduced.

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