

# Spectrum of Bacterial Infection among Chronic Liver Disease Patients: An Obstacle for Patients Safety

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## ABSTRACT

**Introduction:** The risk of infections is enormous among patients with cirrhosis. Studies have demonstrated that with each passing year, hospitals are confronted with an increasing number of bacterial infections among cirrhosis patients. The purpose of this work was to study the spectrum of bacterial infections among cirrhosis patients admitted in a tertiary care hospital of a South East Asian country.

**Material and methods:** In this hospital based study, we reviewed the case records of all consecutive cirrhosis patients admitted, between April 2019 to December 2019. All patients who had a positive culture report from any body site/ fluid were considered to have a definitive bacterial infection.

**Results:** In the present study, a total of 114 consecutive cirrhosis patients were included. Out of 114 cases, 31 cases i.e. 27.19% had culture positive bacterial infection of various sites. The most common etiology of cirrhosis was alcohol seen in 75.43 %. The most common infections were Urinary tract Infection (38.70%) followed by Spontaneous Bacteremia (22.58%) and SBP (16.12%). Majority of the bacterial organism identified were Gram Negative Cocci (Klebsiella species & E. Coli). Gram positive organism were implicated for spontaneous bacteremia in 42.86 % cases.

**Conclusion:** UTI , Spontaneous bacteremia and SBP are the most common site of infection among cirrhotic patients. Most prevalent organisms causing bacterial infections among cirrhosis patients are Gram Negative cocci. Gram positive bacteremia (spontaneous) is on the rise probably due to frequent instrumentations and repeated hospital admissions (nosocomial).

**Keywords:** Bacterial Infections, Spontaneous Bacterial Peritonitis , Spontaneous Bacteremia , Urinary Tract Infection, Liver Cirrhosis , Gram Negative Organism

## INTRODUCTION

Chronic Liver Disease (CLD) remains one of the frequent indication of admission in gastroenterology department in India.<sup>1</sup> The commonest indication for LT remains cirrhosis in India . Without a transplant, patients with decompensated chronic liver disease have a 5 years survival rate of <10%. The need for liver transplantation (LT) in India is estimated to be around 25,000 LT per year.<sup>2</sup> This need is growing with each passing year. A large denominator of population is unable to access LT due to various reasons including cost and donor availability.<sup>3</sup> Majority of the liver transplant being done in India are living donor liver transplant (LDLT). Also it is estimated that only 10 % of the need of LT is being fulfilled in India due to scarcity of donor liver.<sup>4</sup> So a towering number of CLD patients who actually needs

LT don't get it. This subset of patients eventually succumbs to death. Few specific common causes of death among CLD patients include Gastro Intestinal bleed , peritonitis , infections and renal injury.<sup>5</sup>

The risk of infection is enormous in patients with CLD . The reason for heightened risk of infection is multifactorial. Increased intestinal permeability leading to pathological bacterial translocation , depressed innate and adaptive immunity are the two important reasons. Early diagnosis of bacterial infection is essential but difficult as signs and symptoms are non specific and mimics other non infectious causes and / liver function deterioration. For example tachycardia could be due to hyperdynamic circulation and tachypnea due to hyperventilation secondary to tense ascitis or this could represent SIRS in a CLD patient with bacterial infection.<sup>6</sup>

Not just elevated risk of bacterial infection but a high prevalence of infection with Multi Drug Resistance (MDR) bacteria has also been reported in patients with CLD. Infection by MDR bacteria is associated with a higher incidence of shock , new organ failures and higher In- hospital mortality rates.<sup>7</sup>

Good clinical acumen , appropriate use of empirical antibiotics and rapid de-escalation of antibiotics when not indicated are to key to treat infection among cirrhotic population and at the same time to prevent the spread of antimicrobial resistance.<sup>8</sup>

Studies have demonstrated that with each passing year, hospitals are confronting with an increasing number of bacterial infections among CLD patients.<sup>9</sup>

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**How to cite this article:** Amit Soni, Shavi Nagpal. Spectrum of bacterial infection among chronic liver disease patients: an obstacle for patients safety. International Journal of Contemporary Medical Research 2022;9(11):K1-K4.



The purpose of this study was to study the spectrum of bacterial infections among CLD patients admitted in a tertiary care hospital.

## MATERIAL AND METHODS

In this hospital based study, we reviewed the case records of all consecutive patients admitted, between April 2019 and December 2019, in the Department of Gastroenterology, of a tertiary care center in Northern India. A total of 114 consecutive patients (>18 years) were identified. All the details of patients were collected including Patients Age, Sex, Date of admission, Date of discharge, Diagnosis of patient including etiology, various Co morbidities and Addictions. Information regarding laboratory parameters including Complete blood counts( CBC), Liver function tests (LFT), Blood urea, Serum creatinine, Serum electrolytes, INR, fasting blood sugar, Chest x ray, Urine routine / microscopy, Ultrasound abdomen, Ascitic fluid analysis (tlc, dlc, protein and albumin), Blood, Urine & Ascitic fluid culture results were recorded. Any other site specific culture eg Sputum, Skin to detect bacterial infection if done were also recorded. Patients with complete work up and a definite diagnosis were included in the study. Child-Pugh scoring (CTP SCORE) and Model for End stage Liver Disease (MELD) was also recorded for all patients. The study protocol conformed to the ethical guidelines and was approved by the institutional review board.

Patients with incomplete medical records, any solid organ transplantation, any malignancy, pt with retroviral disease or on immunosuppressive medications were not included in this study.

All patients who had a positive culture report from any body site/ fluid were considered to have a definitive bacterial infection. These patients with positive culture report were considered to have bacterial infection in our study.

Further bacterial infection was differentiated between Community acquired and Nosocomial. Community acquired infection was defined when the infection was present at admission or within 48 hrs of admission. Nosocomial infection was defined when infection developed after 48 hrs of admission to hospital or when patient had infection at admission but was admitted somewhere else and transferred to our centre.

Results for continuous variables were expressed as means and standard deviation. Variables with non normal distribution were described by median. Categorical variables were expressed as percentages. Bivariate analysis was carried out using Pearson's coefficient of correlation. Odds Ratio (OR) was used to ascertain the strength of relationship between two variables. A p value of less than 0.05 was considered statistically significant. SPSS 23 software was used for statistical analysis.

## RESULTS

In the present study, a total of 114 consecutive CLD patients were included. Mean age of the patients was 50 ( $\pm$  13.81) years. The male to female ratio was 6.1: 1. Out of 114 cases,

31 cases i.e. 27.19% had culture positive bacterial infection of various sites.

The most common etiology of CLD was alcohol seen in 75.43%, followed by NASH [Non Alcoholic Steato Hepatitis] (15.78%). However there were various etiologies of cirrhosis as described in Table 1. 23 patients (20.17%) had more than one etiology for CLD. Coexistence of alcohol and NASH was the commonest among them, seen in 7 patient (6.14%). Majority of the patients were in Class C (57.90%) CTP Score, followed by class B (38.60%) & Class A (3.50%). Median score for MELD among CLD patients was 21. The Pearson's correlation coefficient between infection and MELD was moderately positive ( $r = .360$ ) and was significant at p value of 0.01 level. Also, the Pearson's correlation coefficient between infection and CTP score was also positive ( $r = .260$ ) and was significant at p value of 0.01 level.

The odds ratio (OD) was calculated for ascitis, renal failure, hepatic encephalopathy, gender and alcohol with respect to infections as the outcome. None of the odds ratio had significant p value.

The most common site of infections was Urinary tract followed by Blood. Table 2 depicts the percentage of site wise infection. The majority of bacterial organism identified were Gram Negative Cocci (Klebsiella species & E. Coli). Detail of organisms is described in Table 3. While gram negative bacteria constituted 91.66% of causative organism

Etiology of CLD	No. of patients (%)*
Alcohol	86 (75.43)
NASH	18 (15.78)
Hepatitis B	16 (14.03)
Hepatitis C	15 (13.15)
Others	4 (3.50)

**Table-1:** Etiology of chronic liver disease among patients (Total patients - 114)

Type of Infection	No. of patients (%)
Urinary tract infection	12 (38.70)
Spontaneous bacteremia	7 (22.58)
Spontaneous bacterial peritonitis (SBP)	5 (16.12)
Respiratory tract infection	4 (12.90)
Skin and soft tissue infection	3 (9.70)
Total	31 (100)

**Table-2:** Site of infection in chronic liver disease patients

Organism	Number
Escherichia Coli	10
Klebsiella species	10
Pseudomonas Aeruginosa	3
Citrobacter species	1
Streptococcus pyogenes	1
Staphylococcus Aureus	4
Enterococcus species	2
Total	31

**Table-3:** Identification of bacterial infection among chronic liver disease patients

for UTI, they were responsible for 57.14% of spontaneous bacteremia. Rest 42.86% were gram positive organism implicated for spontaneous bacteremia.

Community acquired infection constituted 71.4% while nosocomial included 28.6% bacterial infection.

## DISCUSSION

A Total of 114 chronic liver disease patients were included in this study. Of these, 31 patients (27.19%) had culture positive bacterial infection of various sites. Nearly similar result was shown by S Panigrahi et al, who demonstrated 23.32% of bacterial infection among CLD patients.<sup>10</sup> In a study by Sahu et al from India, 30 % of patients with cirrhosis were found to have bacterial infection.<sup>11</sup> In a study from Italy (Borzoi et al), bacterial infection was diagnosed in 34% cirrhotic patients.<sup>12</sup> Almost all studies have shown that one quarter to one third of CLD patients had or develop infection during their hospital stay. This number is huge and directly affects the prognosis of the patient.

Commonest site of infection in our study was found to be Urinary tract infections(38.70%) followed by spontaneous bacteremia (22.58%), while skin and soft tissue infections were among the least common site (9.70 %). Two studies from India suggested urinary tract infection as the commonest site for bacterial infection comprising 66.66% and 44.74% in each study respectively.<sup>10, 13</sup> In a recent study from Greece, commonest site for bacterial infection was spontaneous bacterial peritonitis (45%) followed by bacteremia (20%).<sup>14</sup> The reason for high prevalence of SBP in various studies can be explained by the fact that just ascitic fluid polymorphonuclear count  $\geq 250$  is considered as diagnostic of SBP, irrespective of whether culture is positive or not. While in our study we considered only culture positive cases. In a recent multicentre study, the commonest site of infection was SBP (27%) followed by UTI (22%) & Pneumonia (19%). Bacteremia comprises 8 % of all infections.<sup>7</sup> Urinary tract infection, Spontaneous bacteremia, SBP and respiratory tract infection are the commonest site for bacterial infections among CLD patients.

Gram negative (77.5%) were the commonest organism isolated in our study followed by gram positive (22.5%) bacteria. It is a well known fact that due to pathological bacterial translocation, gut bacteria cross intestinal mucosa and travel to blood / ascitis leading to frequent bacterial infection with gram negative organisms. Similar to our result, Study from Portugal had predominantly gram negative bacilli (60%) and 30-35% gram positive cocci.<sup>9</sup>

In a large multicentre (worldwide) study by Piano et al, Gram negative organism constituted 59% while gram positive accounted for 38 %.<sup>7</sup> In the same study, when Asian people were analyzed separately, almost 70 % cirrhotics had gram negative organism isolated from various sites causing infection.<sup>7</sup> Study by J Fernandez et al concluded that gram positive cocci constituted 53% of all bacterial infection in their study.<sup>15</sup> The author concluded that gram positive infection has increased among cirrhotics and linked it to high degree of instrumentation among them. Klebsiella (40%)

followed by E.coli (26.6%) were the commonest isolates in urinary tract in study by Girish kumar pati.<sup>13</sup> This spectrum is similar to what we found in our study.

In patients with spontaneous bacteremia, gram positive bacteria constituted 42.86%, which is higher when compared to other sites of infection eg UTI, where gram negative bacteria predominates. In a study by S Marciano, a similar trend was seen as gram positive bacteria were responsible for 52% of spontaneous bacteremia.<sup>16</sup> Gram positive organisms are frequently seen due to nosocomial infections/ instrumentation among cirrhotics.

In a study by M jain et al, 8.7% cirrhotics had skin infection and the organism were staphylococcus and E. coli.<sup>17</sup> In a similar study by A Sood et al, cellulitis was the commonest type of skin / soft tissue infection among cirrhotics.<sup>18</sup> Skin / soft tissue infection was the least common site of infection in our study too. The positive correlation between infection and MELD / CTP score is also an interesting finding, though the correlation is not very strong. Nonetheless, other studies have not demonstrated this correlation, rather they found correlation of MELD with mortality.<sup>19</sup>

Various studies done in India, other Asian countries and western world have revealed a male predominant trend among CLD patients as seen in our study.<sup>20</sup>

Majority studies from India and abroad have demonstrated alcohol as the main cause of cirrhosis.<sup>20</sup> NAFLD related cirrhosis constituted 15.78% of all etiology of CLD. Over past few decades NAFLD related cirrhosis has seen a rising trend worldwide. Few of the studies done in past from India reported no / small percentage of cirrhosis due to NAFLD while recent studies have shown a rising trend in India too.<sup>20</sup> <sup>21</sup> As predicted by few, NASH related cirrhosis is suppose to rise in coming years.

As per the author, the exact data on NAFLD is difficult to obtain, but it is likely a major driver of the increasing cirrhosis incidence, concordant with trends in obesity and metabolic syndrome.<sup>22</sup> In one nationwide study, author described that over past 3 decades the number of prevalent cases for decompensated cirrhosis due to NASH has more than tripled while it has doubled for compensated cirrhosis due to NASH.<sup>23</sup>

This study has limitations due to small sample size and hospital based observational work. Larger prospective studies can further ascertain the trend of infections and preventive measures can be taken to reduce it. Studies looking at the difference in susceptibility pattern of bacteria (in comparison to non CLD patients) will guide for better empirical treatment

## CONCLUSION

Bacterial infections are a frequent problem among CLD patients. UTI, Spontaneous bacteremia, SBP and respiratory tract infection are the common site of infection. Most prevalent organisms causing bacterial infections among CLD patients are Gram Negative cocci. Gram positive bacteremia (spontaneous) is also on rise probably due to frequent instrumentations and repeated hospital

admissions(nosocomial). With prompt diagnosis and effective management , morbidity and mortality related to infection can be curbed.

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**Source of Support:** Nil; **Conflict of Interest:** None

**Submitted:** 22-09-2022; **Accepted:** 06-10-2022; **Published:** 30-11-2022