



ISSN:2456-9739

Available Online at <http://www.bjbr.org>

## BRITISH JOURNAL OF BIO-MEDICAL RESEARCH

Cross Ref DOI: <https://doi.org/10.24942/bjbr.2018.334> Volume 02, Issue 05, Sept -October 2018

### Research Article

## A Study of Infections Precipitating Hepatic Encephalopathy in Decompensated Chronic Liver Disease

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#### ARTICLE INFO

##### Article History:

Received on 10<sup>th</sup> Sept 2018  
Peer Reviewed on 23<sup>th</sup> Sept 2018  
Revised on 07<sup>th</sup> October 2018  
Published on 28<sup>th</sup> October 2018

##### Keywords:

Hepatic encephalopathy,  
precipitating factors, septicemia,  
urinary tract infections

#### ABSTRACT

**Introduction:** Hepatic encephalopathy includes a range of neurologic and neuropsychiatric impairments in patients with a chronic liver disease. There are a number of potential precipitating factors contributing to Hepatic Encephalopathy. In this study we analyzed infections, one of the major precipitating factors, aiming to clarify the differences in the main infection sites and the common organisms causing it

**Materials and Methods:** Fifty Patients with chronic liver disease fulfilling the inclusion criteria were included in the study. Various patients' details, biochemical tests, total counts and pan cultures were collected and analyzed. Modified West Haven criteria were used for grading hepatic encephalopathy.

**Results:** The various infections precipitating encephalopathy were septicemia (30%), urinary tract infections (40%), spontaneous bacterial peritonitis (10%), respiratory tract infections (14%) and cellulitis (6%). Only 50% of patients showed increased WBC counts. 28 % of patients had gram positive infections, 72% of patients had gram-negative infections. E. coli was the most prevalent pathogenic bacteria identified in septicemia, peritoneum and urinary tract infections in these patients

**Conclusion:** In this study, it is found that urinary tract infection is the most common among several infections associated with hepatic encephalopathy. E.coli is the major etiological organism precipitating infection. The WBC counts were not elevated in all patients with infection probably due to immune dysfunction related to liver disease and hypersplenism.

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## INTRODUCTION

Hepatic encephalopathy (HE) is an umbrella term which includes a range of neurologic and neuropsychiatric impairments in patients with significant liver disease <sup>[1-4]</sup>. The World Congress of Gastroenterology (WCOG) in Vienna classified HE into types A, B and C depending on the nature of hepatic disturbances or dysfunctions <sup>[2]</sup>. Type A that was related to Acute Liver Failure; Type B was related to portosystemic shunts; Type C was related to Chronic Liver Disease or cirrhosis. Out of these 3 types, Type C was the frequently occurring and it has been divided as persistent encephalopathy, and episodic encephalopathy, and also the minimal HE. <sup>[5]</sup>

There are a number of potential precipitating factors contributing to HE in patients with end-stage liver disease. The most common precipitating factor is gastrointestinal bleeding, which leads to increased production of proteins and, consequently, increased production of nitrogenous products, particularly ammonia, in the gut. There are a few Indian studies that have analyzed the precipitating factors of hepatic encephalopathy in chronic liver disease. <sup>[6, 7, 8]</sup> Gastrointestinal bleeding was the major precipitating factor in all these studies.

The other precipitating factors in the development of HE include infections, electrolyte imbalance, renal failure and excessive diuretic use. Infections in cirrhotic patients have often been known to precipitate bouts of overt HE. Covert HE is seen to first appear after the elevation of acute inflammatory markers in blood. In the majority of cases, HE is caused by a single precipitating factor.

Bacterial infections represent one of the most common reasons for hepatic failure as well as occurrence of hepatic complications in these patients. Bacterial infection is a main cause of mortality in cirrhotic patients with HE. <sup>[9]</sup> Bacterial infections make a series of altered functions of the immune system which aggravate the hepatic damage. In a majority of cases, infections resulted from gram-negative

bacteria that originated from the intestines; gram-positive bacterial infections were also commonly encountered in patients who were hospitalized.

Infection and sepsis are a major burden in the management of patients with liver cirrhosis. Its occurrence alters the natural course, precipitates hepatic encephalopathy and is associated with increased risk of mortality. Shawcross et al observed that infection is a frequent precipitating factor of HE in cirrhosis and also revealed an association between infection and systemic inflammation, but not ammonia, in cirrhotic patients who develop severe HE. <sup>[10]</sup>

A number of studies have focused on the infections precipitating HE, however, the sites of infection remain controversial. <sup>[11, 12]</sup> A study from China has analyzed infection as a precipitating factor for HE evaluating the sites of infection and etiology. <sup>[13]</sup> This present study was conducted aiming to clarify the differences in the main infection sites and the common organisms causing it in patients with the chronic liver disease. The findings may aid in the early diagnosis and prevention of HE and the identification of effective treatments.

## AIMS AND OBJECTIVES

To assess the spectrum of infections precipitating the hepatic encephalopathy in patients with decompensated chronic liver disease.

## MATERIALS AND METHODS

It is an observational type of study in which fifty patients with chronic liver disease admitted to a tertiary hospital in South India were included in the study. Patients with a diagnosis of chronic liver disease and hepatic encephalopathy with culture-proven infection were included. The diagnosis of the chronic liver disease was based on patient history, physical examination, liver imaging and laboratory findings. The study was initiated after obtaining permission from the

institutional ethics committee. The diagnosis of HE was made according to the recommendations of the working party of the 11th World Congress of Gastroenterology and the diagnosis of HE grades was based on the West Haven criteria.<sup>[2]</sup>

Data was collected through a pretested proforma which included patients details like age, sex, detailed past history, personal history, treatment history, clinical examination, diagnosis, and laboratory investigations which included liver function tests, complete blood counts, prothrombin time, renal functions, serology for hepatotropic viruses, ultrasound abdomen and serum ammonia. Blood for total counts and pan cultures were done in all cases prior to initiation of antibiotics. Pan cultures included blood, urine, ascitic fluid cultures and endotracheal aspirate culture in intubated

patients. Ascitic fluid was sent for culture in blood culture bottles during the admission.

Modified West Haven criteria were used for grading hepatic encephalopathy (HE) in all patients. Clinical findings and data on grades of hepatic encephalopathy were entered into proforma which was used. Special tests were used for diagnosing minimal hepatic encephalopathy (MHE). All analyses were done with SPSS software. Statistical analysis has been done for all variables. The data were expressed as mean +/- SD or the median, depending on their distribution. Value of  $p < 0.05$  is considered as statistically significant.

## RESULTS

### Social demographic characteristics

The social and demographic characteristics of the patients are shown in the tables below.

*Table 1: Sex distribution*

Sex	Number	Percentage
Male	44	88%
Female	06	12%

*Table 2: Age distribution*

Age (years)	Number	Percentage
<50	22	44%
50-60	19	38%
61-70	07	14%
>70	02	4%

The grades of HE according to the West Haven criteria were grade 1 in 11 patients (22%), grade 2 in 28 patients (56%), grade 3 in 11 patients (22%) and grade 4 none. In this study, out of the 50 patients, as determined by blood cell

analysis, 25 patients (50%) showed increased WBC counts; 22 patients (46%) showed normal WBC counts and 3 patients (6%) showed decreased WBC counts.

*Table 3: Etiology of liver cirrhosis*

<b>Etiological Disease</b>	<b>No of Patients</b>
Hepatitis B	3
Hepatitis C	3
Ethanol	35
NAFLD	4
Autoimmune Hepatitis	1
Wilson's	1
Etiology not certain	3

From the above Table.3 In terms of etiological factors of cirrhosis of the liver, out of 50 patients, 70 % were found to have ethanol consumption, Ethanol consumption is found to

be the most common aetiological factor of cirrhosis followed by non-alcoholic fatty liver disease (NAFLD) and others.

*Table 4: Infections precipitating hepatic encephalopathy*

<b>Infections precipitating Hepatic encephalopathy</b>	<b>Frequency</b>	<b>Percentage</b>
Septicemia	15	30%
Urinary Tract Infection	20	40%
Spontaneous Bacterial Peritonitis (SBP)	05	10%
Respiratory Tract Infection	07	14%
Cellulitis	03	06%

From the above Table.4, it is seen that urinary tract infections were the commonest infection precipitating hepatic encephalopathy in 40 % of patients followed by blood culture-proven septicemia. In terms of causative agents of septicemia, out of 15 patients who showed blood culture-proven sepsis, 7 patients (46.6%) had E.coli sepsis which was the most commonly isolated organism, 3 patients (20%) had Klebsiella sepsis, 1(6.6 %) patient had enterococcus sepsis, 1 patient each had

staphylococcal (6.6%), Pseudomonas sepsis (6.6 % ), myroides sepsis (6.6 %).

Out of 50 patients, 20 (40%) had Urinary tract infection as a precipitating factor. In terms of the causative agents for urinary tract infection, E.coli was the most commonly isolated organism in 09 (45%). Followed by klebsiella found in 05 (25%), Enterococcus in 03(15%), Staphylococcus in 02 (10%) and Candida albicans in 02 (10%).

Out of 50 patients, 5 had spontaneous bacterial peritonitis as precipitating factor, of which, 3 (60%) had E.coli which was the most commonly isolated organism, 1 patient (20 %) had Klebsiella, 1 patient (20%) had Sphingomonas paucimobilis. Out of 50 patients, 7 had respiratory tract infection as a precipitating factor. The causative agents for respiratory tract infection are Klebsiella 04 (57 %), Candida species seen in 01 (14.3 %), E.coli seen in 01 (14.3%) and Staphylococcus seen in 01 (14.3%).

3 out of 50 patients had skin infections – cellulitis as a precipitating factor. The causative agents were Streptococcus pyogenes in 01(33.33%), Staphylococcus aureus in 01(33.33%) and Pseudomonas aeruginosa in 01(33.33%). Out of 50 patients, 14 patients (28 %) had gram-positive infections, 36 patients (72%) had gram-negative infections.

## DISCUSSION

HE is a common complication of cirrhosis and it is the most common cause of mortality in cirrhotic patients.<sup>[14]</sup> HE may be induced by a variety of factors and the recognition of precipitating factors and their early removal is regarded as the primary approach for improving prognosis and reducing mortality.

In our study, out of total 128 patients with decompensated chronic liver disease with hepatic encephalopathy studied, 50 patients who met criteria of culture-proven sepsis were enrolled.

In our study 88% were males, 12% were females. This finding of male preponderance is consistent with other studies. The male predominant population in this study is likely due to the risk of chronic alcohol use as a cause of liver disease which was consistent with other studies.<sup>[15]</sup>

In our study, urinary tract infection was the most common infection precipitating hepatic encephalopathy. A previous study reported that spontaneous bacterial peritonitis (SBP) is currently the most frequent infection in cirrhosis.<sup>[11]</sup> Another study shows SBP and

UTI are more commonly occurring past skin infections, pneumonia, soft-tissue pathologies in cirrhosis patients.<sup>[16]</sup> Our result was not in accordance with the findings of previous studies where SBP was the primary precipitating factor. This may be due to differences in etiologies, Child-Pugh classes, regions and ethnic origins. Bacterial overgrowth, intestinal motility and barrier dysfunction were conducive to bacterial translocation leading to bacteremia. The mononuclear phagocyte system is suppressed and the ability of the liver to remove bacteria declines, leading to reductions in immunoglobulin, complement and albumin and ultimately results in ascites infection.<sup>[17]</sup>

In terms of causative agents, E.coli was the most commonly isolated infectious agent in blood culture-proven sepsis, urosepsis and spontaneous bacterial peritonitis. This was consistent with other studies which showed enteric gram-negative cocci to be the microorganisms most frequently isolated in SBP patients with hospital-acquired infections.<sup>[18]</sup> In this study, Out of 50 patients, gram-negative infections were found in 72% which were more common. This finding is more consistent with other studies. In our study, out of 50 patients on follow up, 6 patients died. Mortality rate found to be 12 % of the study population. The mortality rate is higher in infection with multi-drug resistant organisms in Cirrhosis than in non-cirrhosis patients.<sup>[18]</sup> The incidence of end-organ damage is more in the cirrhosis patients than in Non-cirrhosis patients.<sup>[17]</sup> Delay in diagnosis and starting treatment results in higher mortality in patients with unstable hemodynamic status.<sup>[17]</sup>

In this study, 50% showed increased WBC counts; other 50% patients showed either normal WBC counts or decreased WBC counts. But the neutrophil counts were significantly increased in all cases. Fewer patients with bacterial infection had a high WBC count which may be explained as due to immune dysfunction or hypersplenism. Therefore, doctors may not make a diagnosis on the basis of WBC count changes and left shift should be

observed in cirrhotic patients with complicated infectious diseases.

Patients with liver cirrhosis are abnormally susceptible to infection as a result of immunological deficits. The mechanisms of action include reduced hepatic production of complement (reduced C3 and C5 levels), impaired phagocytosis of Kupffer cells and clearance of inflammatory cytokines, and altered neutrophil chemotaxis.<sup>[19]</sup> In the liver, the function of reticuloendothelial cells is to remove bacteria from the blood. The activation of macrophages in cirrhosis is dysfunctional and the sterilization ability reduced, leading to a dysfunction of the reticuloendothelial system. Shawcross et al demonstrated that downregulation of HLA-DR expression on monocytes resulted in immunological deficits in decompensated liver cirrhosis.<sup>[20]</sup>

Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, may reduce hypokinesia and microglial activation, thereby restoring normal motor activity and cognitive function in rats with HE.<sup>[21, 22]</sup> These results may further support the role of inflammation in the induction of HE.

The impact of the systemic inflammatory response on ammonia-induced brain dysfunction was described in cirrhotic patients admitted to the hospital with infection.<sup>[23]</sup> The main source of inflammation in cirrhotics was infection and sepsis. Ammonia-induced deterioration in neuro-psychological dysfunction was prevented by antibiotics, supporting the notion of a synergy between ammonia and inflammation in the pathogenesis of HE. Merli et al. confirmed the presence of cognitive impairment (overt or subclinical) in 42% of cirrhotics without infection, in 79% with infection and in 90% with sepsis.<sup>[24]</sup> Hung et al. observed that infections increase the mortality of HE in cirrhotic patients, especially pneumonia and sepsis without specific focus.<sup>[25]</sup> Lastly, in the CANONIC study, a clear role for systemic inflammation was demonstrated in patients with advanced HE, which correlated with mortality.<sup>[26]</sup>

## CONCLUSION

1. In this study, urinary tract infection is the most common among several infections associated with hepatic encephalopathy.
2. E.coli is the major etiological organism precipitating infection in this study.
3. The WBC counts were not elevated in all patients with infection probably due to immune dysfunction and hypersplenism

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**How to cite this article:**

Santni Manickam, Anil Kumar Adla, Jayachandran Kuppusamy, Tolstoy Rajangam. *A Study of Infections Precipitating Hepatic Encephalopathy in Decompensated Chronic Liver Disease*. *Br J Bio Med Res*, Vol.02, Issue 05, Pg.544-551, September - October 2018. ISSN:2456-9739 Cross Ref DOI : <https://doi.org/10.24942/bjbmr.2018.334>

Source of Support: Nil

Conflict of Interest: None declared.

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