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# PROFILE OF SPONTANEOUS BACTERIAL PERITONITIS AND HEPATITIS B DNA STATUS IN CHRONIC HEPATITIS B RELATED CIRRHOSIS.

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**Abstract**

**Background:** Activity of etiologic agent for chronic liver disease (CLD) has impact on treatment outcome of spontaneous bacterial peritonitis (SBP).

**Aims and objectives:** To study infection acquisition, antibiotics resistance pattern, treatment success and mortality with SBP in patients having chronic hepatitis B (CHB) related CLD in our region. These parameters were studied in context to detectable or non-detectable hepatitis B virus (HBV) deoxyribonucleic acid (DNA) status.

**Materials and Methods:** This observational prospective study was carried out in Super speciality Hospital; Srinagar: over period of two years in 2017. Patients with Ascites with CHB related CLD and were taken for studied. We studied serum HBV DNA, infection acquisition, antibiotics resistance pattern, treatment success and mortality in patients of CHB related CLD with SBP.

**Results:** Over 2 year's period, 246 patients were enrolled. Mean age of patients was 57.09 ± 13.90 years. Hepatitis B virus is a major etiological contributor to the burden of CLD amounting to 69 (28%) in Kashmir.SBP was present in 38 (55.06%) of chronic hepatitis B related CLD patients. Hepatitis B DNA was detectable in 71.05%. In this group 81.48% were cured. Mortality was 5 (18.51%)in patients with detectable HBV DNA and 1(9.09%)in non-detectable HBV DNA.

**Conclusion:** Our region CHB is the leading contributor of CLD. In this study trend towards better treatment outcome and less mortality was observed in patients with non-detectable HBV DNA in comparison to other group.

**Key words:** Etiologic, Chronic liver disease, Chronic Hepatitis B, Ascites and SBP.

**Introduction:**

Spontaneous Bacterial Peritonitis (SBP) is an infection of the previously sterile Ascitic Fluid (AF), without any apparent intraabdominal source of infection in patients of Chronic Liver Disease (CLD) [1]. It was first described by Conn and Fessel in patients with hepatic cirrhosis in 1906-1907 [2]. The prevalence of SBP varies from 1.5-3.5% in out-patients and 10-30% in hospitalized patients [3, 4]. Factors associated with SBP include age, history of SBP [4], gastrointestinal bleeding [4, 5]. Severity of liver dysfunction scores including the Child Turcotte Pugh (CTP) score or Model for End-Stage Liver Disease (MELD) score, neutrophil count, low protein concentration (< 1.5 g/ dl) in the ascitic fluid, and long term Proton Pump Inhibitors (PPIs) use has been reported as a predictive factor [6-11] for SBP. In hospital mortality for first episode of SBP is 10-50%depending on various risk factors [12, 13]. Recurrence rates are high, more than 70% within one year [14, 15].In cirrhosis disturbance in microcirculation of intestinal mucosa, results in a reduction of mucosal blood flow, intestinal bacterial overgrowth, impaired mucosal integrity [16-18] and deficiencies in local host immune defences are possible mechanisms for bacterial translocation [19,20]. Catheters and other equipment used during invasive procedures represent other possible sources of infection. The gold standard for diagnosis of SBP consists of count ≥ 250cells/ mm3 and/or a positive AF culture without any evidence of intra-abdominal infectious source. Culture negative SBP (CN-SBP) is defined as negative ascitic fluid culture with neutrophil count of ≥ 250 cells/ mm3 in ascitic fluid [21]. Culture positive SBP (CP-SBP)is seen in 35%-65% of SBP patients [22-26]. Enteric bacteria are the most common etiological agent [17]. Frequency of Multidrug Resistance (MDR), Extended drug resistance (XDR) and Pan drug resistance (PDR) bacteria in Hospital care associated SBP (HCA-SBP), Hospital Acquired SBP (HA-SBP)is 20%-35% [11, 27] and 4%-16% in Community-Acquired SBP (CA-SBP) [28].

**Aims and Objective:**

To study infection acquisition, antibiotics resistance pattern, treatment success and mortality with SBP in patients having chronic hepatitis B related CLD in our region. These parameters were studied in context to detectable or non-detectable HBV DNA status.

**Materials and Methods:**

This prospective observational study was conducted in Department of Gastroenterology and Hepatology, Super speciality hospital, Srinagar. It is a twenty seven bedded department with round the clock gastroenterology services. All patients of cirrhosis and ascites with possibility of SBP more than 10 years of age were recruited from out-patient Department of Gastroenterology and Hepatology, and medical emergency of government medical college; Srinagar over one year period. A predesigned structured Performa was used to record patient's demographics, clinical presentation and laboratory results.

**Exclusions:**

Etiology of ascites other than liver disease, recent antibiotics use(within two weeks), suspected or conformed intra-abdominal source of infection like surgery or trauma, children under 10 years of age and those who did not consented to participate.

Paracentesis (only diagnostic tap) was performed bedside with under mentioned protocol:

1. Performed using standard aseptic precaution for all study participants.
2. Twenty millilitre syringes with 20 G (gauge) needle used for ascitic fluid (AF) tap in left iliac fossa or midline below umbilicus at bedside.
3. Total 20 millilitres AF was collected from each patient.
4. Ten ml for AF detailed biochemical and cytological report.
5. Ten ml of AF inoculated in blood culture bottles at the bedside using aseptic technique and send for microbiology (for aerobic and anaerobic culture).
6. Blood sample (10 ml) was collected at same time to perform serum/plasma based blood work up as deemed necessary.
7. Serum HBV DNA quantitative levels.

Severity of liver disease was assessed by Child Turcotte Pugh (CTP) score. It depends on sum of these five variables patients are divided into three classes; A (score of 5-6), B (score of 7-9) and C (score of 10-15). Class A has 1 year survival of100% and 2 year survival of 90%. Class B has 1 year survival of 81%and 2 year survival of 57%. Class C has 1 year survival of 45 % and 2year survival of 35%.**[Table 1]**

**Table 1: Child Turcotte Pugh score**

| **Parameter** | **1** | **2** | **3** |
|---|---|---|---|
| Encephalopathy | None | Stage 1-2 | Stage 3-4 |
| Ascites | None | controlled | Poor control |
| Serum Bilirubin (mg/dl) | < 2 | 2-3 | ≥ 3 |
| Serum Albumin (gm./dl) | >3.5 | 3-3.5 | < 3 |
| Prothrombin time/ INR | 0-4 / < 1.7 | 5-6 / 1.7-2.3 | > 6 / > 2.3 |

Infections diagnosed on admission or within 2 days after admission were classified as HCA in patients with a prior contact with the healthcare environment (hospitalization or short-term-admission for at least 2 days in the previous 90 days, residence in a nursing home or a long-term care facility or chronic haemodialysis). The infection was considered CAwhen present at time of admission or developed within the first 2 days after hospitalization with no history as mentioned above in HCA andHA when the diagnosis was made thereafter [29, 30].
MDR was defined as non-susceptibility to at least one agent in3 or more antimicrobial categories. XDR was defined as non-susceptibility to at least one agent in all but 2or fewer antimicrobial categories and PDR as non-susceptibility to all currently available agents [31].

**Data analysis:**
Statistical analysis was conducted using SPSS ver. 16.0 for Windows (SPSS, Chicago, IL). Categorical variables were compared using the chi-square or Fisher's exact test where appropriate. Continuous data were compared using the t-test or the Mann-Whitney test, the Kruskal-Wallis test was used for multiple comparisons, when appropriate. Quantitative variables with a normal distribution were expressed as mean values± standard deviation and those with a non-normal distribution as median values (range). Significance level was two-sided and set to less than 0.05. Informed consent was obtained from all participants or their attendants.
This study was cleared by institution's review board.

**Results:**
Prevalence of SBP in CLD presenting at our centre was 38.09%. Mean age of patients was 59.09±12.90 years with minimum of 20 and maximum of 89. Male were 57.3% and females 42.7%. Most common clinical presentations were ascites 100% and hepatic encephalopathy 89%. Our data shows etiological profile different from rest of India.
CHB is the major etiological contributor to the burden of CLD amounting to 69(28%) followed by NAFLD 57(23%) in Kashmir. On one hand Alcoholic Liver Disease (ALD) is rare on other hand Recurrent Pyogenic Cholangitis (RPC) appears to be important etiologic factor in 9%.**[Table 2]**

**Table 2: Etiological profile of CLD in Study Group**

| **S. o.** | **Etiology** | **n** | **%** |
|---|---|---|---|
| **1** | Chronic Hepatitis B | 69 | 28.04 |
| **2** | Non Alcoholic Fatty Liver Disease | 57 | 23.17 |
| **3** | Chronic Hepatitis C | 42 | 17.03 |
| **4** | Cryptogenic Liver Disease | 33 | 13.41 |
| **5** | Recurrent Pyogenic Cholangitis | 21 | 8.53 |
| **6** | Non-cirrhotic Portal Fibrosis | 12 | 4.87 |

| | | | |
|---|---|---|---|
| **7** | Auto Immune Hepatitis | 9 | 3.65 |
| **8** | Alcoholic Liver Disease | 3 | 1.21 |
| | | 246 | |

We studied infection acquisition, antibiotics resistance pattern, treatment success and mortality in CHB with SBP with respect to Hepatitis B virus activity as assessed by presence or absence of detectable level of HBV DNA in serum of patient**. [Table 3]**

Out of 69 CHB related CLD patients, 38(55.07%) had SBP. CTP A, B, and C were 18.51%, 25.92% and 55.56% in patients with detectable HBV DNA respectively whereas CTP A, B, and C were 45.50%, 27.50% and 27.30% in patients with non-detectable HBV DNA respectively. Patients with detectable HBV DNA have more advanced liver disease compared to those with non-detectable HBV DNA. Patients with CP-SBP were 18(22%) and CN-SBP was 20(24%). CP-SBP patients with detectable HBV DNA were 15(55.55%) where as in CN-SBP it was 12(44.44%). Culture positivity rates were higher in patients with detectable HBV DNA. [Table 3]

CA-SBP, HCA-SBP, and HA-SBP was detected in 17(63%), 9(33.33%) and 1(3.70%) patients in patients with detectable HBV DNA respectively whereas CA-SBP, HCA-SBP was detected in 9(81.81%), 2(18.18%) and none in HA-SBP with non-detectable HBV DNA respectively. There was increased frequency of HA-SBP in patients with detectable HBV DNA.

DS-SBP was seen in 8(29.62%) and 2(18.18%) of patients with detectable HBV DNA and non-detectable HBV DNA respectively. MDR-SBP was seen in 6(22.22%) patients with detectable HBV DNA and 1(9.09%) in non-detectable HBV DNA respectively. There was one case (3.70%) of XDR-SBP in patients with detectable HBV DNA.

Cure rate of SBP in CHB related CLD was 32/38 (84.21%).Cure rate was 90% in patients with non-detectable HBV DNA whereas only 81.48% in patients with detectable HBV DNA. Mortality in CHB with SBP was 6/38(15.78%). Mortality was 5(18.51%) in patients with detectable HBV DNA whereas only 1(9.09%) in patients with non-detectable HBV DNA.

**TABLE-3: SBP IN CHRONIC HEPATITIS B RELATED CLD**

| **Chronic Hepatitis B with SBP (n=38)** | **HBV DNA Detectable 27(71.05%)** | **HBV DNA Not-Detectable 11(28.94%)** |
|---|---|---|
| **Child Class A (5)** | 3 (11.11%) | 2(18.18%) |
| **Child Class B (6)** | 5(18.51%) | 1(9.09%) |
| **Child Class C (27)** | 19(70.73%) | 8(72.72%) |
| **Culture Positive (18)** | 15(55.55%) | 3(27.27%) |
| **Culture Negative (20)** | 12(44.44%) | 8(72.72%) |
| **CA-SBP (26)** | 17(62.96%) | 9(81.81%) |
| **HCA-SBP (11)** | 9(33.33%) | 2(18.18%) |
| **HA-SBP (1)** | 1(3.70%) | 0(%) |
| **DS-SBP (10)** | 8(29.62%) | 2(18.18%) |
| **MDR-SBP (7)** | 6(22.22%) | 1(9.09%) |
| **XDR-SBP (1)** | 1(3.70%) | 0 |
| **Cured (32)** | 22(81.48%) | 10(90.90%) |
| **Death (6)** | 5(18.51%) | 1(9.09%) |

CA=community acquired, SBP=spontaneous bacterial peritonitis, HCA=hospital care associated, HA= hospital acquired, DS=drug sensitive, MDR=multi drug resistant, XDR= extended drug resistant, PDR=pan drug resistant.

## Discussion

SBP is considered among the worst complications in the natural history of chronic liver disease and an important cause of immediate and long term mortality among them and accounts for 10-40% of hospital admissions globally[32,33,34]. So far, the impact of prevalence of SBP has not been well

studied there are not well designed studies found in literature which could reflect, that the etiology has a significant impact on prevalence of SBP, type of SBP in terms of culture negativity and culture positivity. Further, literature is still unclear about the resistance patterns, microbiological spectrum, mortality trends in terms of etiology of CLD and SBP. The recent documentation of multidrug resistant bacteria causing SBP nonresponsive to recommended empirical antibiotics, and associated high mortality named as 'Difficult to treat SBP' remains a real challenge [35]. Here, in our study we tried to look into profile of SBP in hepatitis B related CLD and further, we looked into the impact of viral clearance on Culture positivity, CA-SBP,HCA-SBP,HA-SBP and drug resistance patterns-MDR,XDR and mortality.

The incidence of SBP in liver cirrhosis differs with regions globally, and chronic Hepatitis B is the most common etiological condition of liver cirrhosis in sub-Saharan Africa and some parts of Asia [35]. In our study, 38 patients out of 69 Hep-B related CLD developed SBP. Out of which 71.1% had presence of HBV-DNA and 28.9% had viral clearance. In our study culture positivity (55% VS 27%) was significantly higher in DNA detected group. The possible explanation for such a gradient remains in (1) malnutrition (2) unstable de-compensations and repeated hospitalization (3) immune exhaustion secondary to non-clearance of virus (4) Systemic manifestations of active viral replication (nephropathy) with further decrease in serum albumin, ACLF etc. In our study Child class was matching in both groups.

The European Association for the Study of Liver (EASL) has established a preventative treatment for SBP in cirrhosis based on therapeutic studies. It is essential to distinguish between the two types of infections (HA-SBP and CA-SBP) because the source of SBP has a significant impact on the patient's clinical outcomes [36, 37, and 38]. In our study, DNA detected group with CA-SBP was less prevalent as compared to DNA non-detected CA-SBP (62% VS 81%).The occurrence of HCA-SBP (33%VS13%), HA-SBP (4%VS0%) was higher in DNA detected group. Regarding microbial spectrum occurrence of MDR-SBP (22% VS 1.9%), XDR-SBP (3.7% VS 0%) was again higher in DNA detected group. Due to unstable de-compensations leading to frequent hospitalizations, day care visits, and empirical antibiotic use remains a valid explanation here.

In our study cure rate between two groups was 81% and 90% respectively.SPB has been associated with poor prognosis [14] and in spite of the progress made in its management and prevention, the rate of mortality among hospitalized patients was 37%(39), with one-year mortality rate estimated at up to 50% in some studies (39). Several factors have been reported to impact mortality in this cohort of patients. These include nosocomial infections, sepsis and septic shock, acute kidney injury (AKI) [24], and diagnosis as well as need for hospitalization among others. The renal dysfunction and the model for end-stage liver disease (MELD) are among the range of predictive algorithms that are suggested as predictors of mortality in hospitalized patients with cirrhosis and SBP [40].Regarding mortality, 18% patients in DNA detected group died despite hospitalization, antibiotics and management as per guidelines as compared to DNA non-detected group (9%).

**Conclusion:**

- All hepatitis B-related CLD with ascites should be evaluated for SBP whether symptomatic or asymptomatic.
- Their viral load should be checked routinely and during SBP events.
- Their antiviral resistance should be evaluated if needed.
- Their HCC status evaluated as per guidelines.
- Attempts to manage malnutrition should be maximized.
- Attempts to achieve viral clearance should be one of the primary goals.
- Judicious use of antibiotics in terms of difficult to manage SBP

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**Limitation of study:** Study population was small

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