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ORIGINAL ARTICLE

Factors Predicting the Recurrence of Spontaneous Bacterial Peritonitis in Patients with Cirrhosis

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ABSTRACT

Objective: To evaluate the frequency of recurrence of spontaneous bacterial peritonitis (SBP) in patients with end stage liver disease and the factors responsible for it.

Study Design: Descriptive study.

Place and Duration of Study: The Aga Khan University Hospital, Karachi, from November 2008 till November 2009.

Methodology: Patients with cirrhosis who were admitted at AKUH with diagnosis of SBP during the study period were included. Any episode of SBP after resolution of the first index case of SBP within one year was considered as recurrence.

Results: Out of 238 cirrhotic patients, 157 (66%) had single, while 81 (34%) had recurrent episodes of SBP. History of using proton pump inhibitors (PPI) and diuretics was found in 113 (47.5%) and 139 (58.4%) patients respectively. Only 58 (24.4%) patients were on prophylactic antibiotic therapy. Univariate analysis revealed that the female gender (52%), and presence of porto-systemic encephalopathy (PSE, 31%) were statistically significant (p=0.03) among those who had recurrent SBP. On multivariate analysis bilirubin level of > 1.0 mg (OR=7.03; 95%CI=1.55-32), protective factor of hepatitis B (OR 0.31; 95%CI=0.13-0.70) and presence of urinary tract infection (UTI) (OR=2.24; 95%CI=0.99-5.09) were significant in patients with recurrent SBP.

Conclusion: Recurrent SBP was noticed in 34% patients. Serum bilirubin level of > 1.0 mg, protective factor of HBV and presence of UTI were significant factors present in patients with recurrent SBP.

Key words: *Cirrhosis. Spontaneous bacterial peritonitis. Bilirubin. Urinary tract infection. HBV.*

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is one of the most common and life threatening complications of cirrhosis which is characterized by the infection of ascitic fluid in the absence of a concurrent intra-abdominal source of infection (e.g. intra-abdominal abscesses, intestinal perforation, cholecystitis or acute pancreatitis).[1] It can occur in 10-30% of cirrhotic patients with ascites,[2,3] having an in-hospital mortality rate of around 30 to 50%.[4] The risk of SBP recurrence is around 70% per year.[3] There is around 10% probability of developing SBP in patients with end stage liver disease and ascites over a period of one year.[5]

Altered host immune system and translocation of the bacteria from the gut to the extra intestinal sites are thought to be the basis for SBP.[6] Long-term prophylaxis with antibiotics like quinolones (Norfloxacin, 400 mg per day orally) has reduced the recurrence rate.[1] However, emergence of quinolone resistant organisms has lowered its use.[7]

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Internationally published data shows that increased serum bilirubin levels,[8] derangement in serum creatinine, presence of hyponatremia,[9] and the use of proton pump inhibitors (PPI)[10] are the risk factors associated with SBP. However, there is insufficient regional and no local data on factors responsible for the recurrence of SBP.

Therefore, the aim of this study was to determine the factors predicting the recurrence of SBP in cirrhotic patients with ascites.

METHODOLOGY

Cirrhotic patients admitted with the diagnosis of SBP at The Aga Khan University Hospital (AKUH), Karachi, from November 2008 to November 2009 were studied. The term SBP refers to the presence of more than 250 neutrophils in ascitic fluid in the setting of cirrhosis, and in the absence of bowel or peritoneal perforation.[11]

Any episode of SBP after resolution of the first index case of SBP within one year was considered as recurrence.[4,12]

The data of adult patients, more than 15 years of age, admitted with the diagnosis of SBP during the study period, was included. Patients in whom the improvement of SBP was not documented (repeat ascitic tap 48 hours after the treatment was started) at the time of discharge or those who were lost to follow-up during the

study period were excluded. Similarly, patients with chronic liver disease who were admitted with ascites secondary to tuberculosis or malignancy were also excluded.

Demographic data of patients was obtained from AKUH during the study period through a pre-designed questionnaire. The data included age, gender, etiology of cirrhosis; co-morbids like diabetes, chronic kidney disease (CKD) were noted. History of presenting complains like fever, abdominal pain, constipation, diarrhea, nausea, vomiting, history of gastrointestinal bleed or PSE was also recorded.

Laboratory parameters included in the questionnaire were total bilirubin, serum albumin, prothrombin time, platelet count, serum creatinine, random blood sugar and serum sodium. Presence of hepatitis B surface antigen (HBsAg) and hepatitis C virus (HCV) antibodies by micro enzyme immunoassay (MEIA), history of alcohol intake, serum sodium and serum alpha fetoprotein were also documented.

Ascitic fluid analysis at the time of admission as well as repeat analysis done after 48 hours was also noted with culture and sensitivities report of both.

In drug history, patients who were on PPIs, diuretics and prophylactic antibiotics were also noted. Child turcotte pugh (CTP) score and model for end stage liver disease (MELD) score at the time of admission was calculated and documented in the questionnaire. Length of hospital stay and mortality were also parameters included in the questionnaire.

Mortality was defined as patients who died due to complications of SBP during that index admission.

A descriptive analysis was done for demographic and clinical features and results are presented as mean ± standard deviation for quantitative variables and number (percentage) for qualitative variables. Differences in proportions for recurrence of SBP in cirrhotic patients with ascites were assessed by using the chi-square test or Fisher's exact test where appropriate. For contrasts of continuous variables, independent sample t-test was used to assess the difference of means.

All significant factors on univariate analysis were considered for inclusion in the multivariable logistic model. All analyses were conducted by using the Statistical Package for Social Sciences (SPSS version 16.0). All p-values were two-sided and considered as statistically significant if < 0.05.

RESULTS

Three hundred and fifty patients were recruited during one year out of which 41 were excluded due to no documentation of SBP improvement at the time they were discharged. Seventy-one were excluded because they were lost to follow-up. Two hundred and thirty eight cirrhotic patients were enrolled in the study out of whom 157 (66%) had single episode of SBP, while 81 (34%) had recurrent episodes.

One hundred and thirty seven (57.6%) of the cirrhotic patients admitted were males, while the female patients numbered up to 101 (42.4%). The mean age was 50.47±12 years with the majority of population being < 55 years i.e. 160 (67.2%).

Table I: Demographic, clinical, ultrasonological and endoscopic characteristics among all the study patients (n=238).

Characteristics	Single admission n = 157 (66%)	Recurrent admission n = 81 (34%)	p-value
Age (years)	51 ± 13.31	50 ± 8.88	0.30
Age			
< 55 years	100 (63.7%)	60 (74.1%)	0.10
> 55 years	57 (36.3%)	21 (25.9%)	
Gender			
Male	98 (62.4%)	39 (48.1%)	0.03
Female	59 (37.6%)	42 (51.9%)	
Fever	80 (51%)	51 (63%)	0.08
Abdominal pain	85 (54.1%)	54 (66.7%)	0.06
CRF	29 (18.5%)	9 (11.1%)	0.14
PSE	72 (45.9%)	25 (30.9%)	0.03
Prothrombin time			
< 12 sec	13 (8.3%)	2 (2.5%)	0.08
> 12 sec (abnormal)	144 (91.7%)	79 (97.5%)	
Bilirubin count			
< 1.0 mg	20 (12.7%)	2 (2.5%)	0.01
> 1.0 mg (abnormal)	137 (87.3%)	79 (97.5%)	
Serum creatinine			
< 1.2 mg	74 (47.1%)	50 (61.7%)	0.03
> 1.2 mg (abnormal)	83 (52.9%)	31 (38.3%)	
MELD score			
< 15	34 (21.7%)	21 (25.9%)	0.46
> 15 (abnormal)	123 (78.3%)	60 (74.1%)	
Child Class			
B	50 (31.8%)	17 (21%)	0.08
C	107 (68.2%)	64 (79%)	
PPI used	75 (47.8%)	38 (46.9%)	0.9
Diuretic used	85 (54.1%)	54 (66.7%)	0.06
Prophylactic antibiotics	38 (24.2%)	20 (24.7%)	0.93
Large volume paracentesis	52 (33.1%)	33 (40.7%)	0.24
Esophageal varices	22 (14%)	19 (23.5%)	0.07
HCV CLD	87 (55.4%)	58 (71.6%)	0.01
HBV CLD	39 (24.8%)	9 (11.1%)	0.01
HBV+HDV CLD	15 (9.6%)	4 (4.9%)	0.21
ALD	7 (4.5%)	8 (9.9%)	0.10
DM	41 (26.1%)	31 (38.3%)	0.05
UTI	19 (12.1%)	16 (19.8%)	0.11
Non B non C CLD	30 (19.1%)	11 (13.6%)	0.28
Hepatocellular carcinoma	38 (24.2%)	11 (13.6%)	0.05
Mortality	31 (19.7%)	3 (3.7%)	0.001
Length of hospital stay	6.55 ± 5.11	5.07 ± 2.51	0.003
< 5 days	87 (55.4%)	56 (69.1%)	0.04
> 5 days	70 (44.6%)	25 (30.9%)	

CI = Confidence Interval; CRF = Chronic Renal Failure; PSE = Porto-systemic Encephalopathy; GI = Gastro-Intestinal; MELD = Mean End Stage Liver Disease; PPI = Proton Pump Inhibitor; HCV CLD = Hepatitis C Virus Chronic Liver Disease; HBV CLD = Hepatitis B Virus Chronic Liver Disease; HDV CLD = Hepatitis D Virus Chronic Liver Disease; ALD = Alcoholic Liver Disease; DM = Diabetes Mellitus; UTI = Urinary Tract Infection.

The most common presenting complains were abdominal pain 139(58.4%) and fever (n=131, 55%). PSE was significantly seen in 97 (40.3%) patients. The most common cause of cirrhosis was found to be HCV related liver disease in 145 (60.9%) patients. While HBV (20.2%), hepatitis D (HDV) (8%), non B non C CLD (17.2%) and alcoholic liver disease (ALD) (6.3%) were the causes in rest of the patients (Table I). Seventy-two (30.3%) patients were found to have Diabetes as a co-morbid condition, 35 (14.7%) had concurrent UTI.

Radiological diagnosis of HCC was present in 49 (20.6%) of the patients. Use of medicine (PPI and diuretics) was found to be 113 (47.5%) and 139 (58.4%) respectively. Fifty eight (24.4%) patients were on prophylactic antibiotic therapy. The mean duration of hospital stay amongst patients was found out to be 6 ± 5 days. Most of the patient admissions lasted less than 5 days (n=143, 60.1%). The total mortality amongst patients was 34 (14.3%).

Table II: Univariate analysis for factors predicting recurrent spontaneous bacterial peritonitis.

Characteristic	Odd ratio (95% CI)	p-value
Age		
< 55 years	1.0	0.10
> 55 years	0.61 (0.33 - 1.11)	
Gender		
Female	1.0	
Male	0.55 (0.32 - 0.96)	0.03
Fever	1.63 (0.94-2.83)	0.07
Abdominal pain	1.69 (0.96-2.96)	0.06
CRF	0.55 (0.24-1.23)	0.14
PSE	0.52 (0.29-0.92)	0.03
Prothrombin time		
< 12 sec	1.0	0.10
> 12 sec (abnormal)	3.56 (0.78 - 16.20)	
Bilirubin count		
< 1.0 mg/dl	1.0	0.02
> 1.0 mg/dl (abnormal)	5.76 (1.31 - 25.32)	
Serum creatinine		
< 1.2 mg/dl	1.0	0.03
> 1.2 mg/dl (abnormal)	0.55 (0.32 - 0.95)	
Child class		
B	1.0	0.08
C	1.75 (0.93 - 3.30)	
Diuretic used	1.69 (0.96-2.96)	0.06
Esophageal varices	1.88 (0.94-3.72)	0.07
HCV CLD	2.02 (1.14-3.61)	0.01
HBV CLD	0.37 (0.17-0.82)	0.01
ALD	2.34 (0.82-6.72)	0.10
DM	1.75 (0.99-3.10)	0.05
UTI	1.78 (0.86-3.70)	0.11
Hepatocellular carcinoma	0.49 (0.23-1.02)	0.05
Mortality	0.15 (0.04-0.52)	0.003
Length of hospital stay		
< 5 days	1.0	0.02
> 5 days	0.90 (0.83 - 0.98)	

CI = Confidence Interval; CRF = Chronic Renal Failure; PSE = Porto-systemic Encephalopathy; HCV CLD = Hepatitis C Virus Chronic Liver Disease; HBV CLD = Hepatitis B Virus Chronic Liver Disease; ALD = Alcoholic Liver Disease; DM = Diabetes Mellitus; UTI = Urinary Tract Infection.

Univariate analysis revealed that age above 55 years, history of fever, abdominal pain, CRF, PSE, increased prothrombin time or serum bilirubin, worsening serum creatinine, advanced child class, used of diuretic and presence of esophageal varices or HCC were found to be statistically significant (Table II).

Using stepwise logistic regression age > 55 years (OR=0.45; 95%CI=0.23-0.88), bilirubin count > 1.0 mg/dl [(OR 7.03; 95%CI=1.55-32), protective factor of HBV (OR 0.31; 95%CI=0.13-0.70)] and presence of UTI [(OR=2.24; 95%CI=0.99-5.09) were found to be independently significant factors in patients having recurrent SBP (Table III).

Table III: Multivariate analysis for factors predicting recurrent spontaneous bacterial peritonitis.

Characteristics	Odd ratio (95% CI)	p-value
Age		
< 55 years	1.0	0.02
> 55 years	0.45 (0.23 - 0.88)	
Bilirubin count		
< 1.0 mg/dl	1.0	0.01
> 1.0 mg/dl (abnormal)	7.03 (1.55 - 32)	
HBV CLD		
No	1.0	0.005
Yes	0.31 (0.13 - 0.70)	
UTI		
No	1.0	0.05
Yes	2.24 (0.99 - 5.09)	
Mortality	0.12 (0.03-0.44)	0.001

CI = Confidence Interval; HBV CLD = Hepatitis B Virus Chronic Liver Disease; UTI = Urinary Tract Infection.

DISCUSSION

In this study, it was aimed to identify factors that predict the recurrence of SBP in patients with cirrhosis. A Spanish study by Tító *et al.* found serum bilirubin > 4 mg per dl, prothrombin activity ≤ 45% and protein concentration in ascitic fluid ≤ 1 gm per dl to be significantly ($p < 0.05$) associated with a high risk or re-currence of SBP on univariate analysis, but on multivariate analysis, only ascitic fluid protein concentration ($p = 0.005$) and prothrombin activity ($p = 0.009$) were found to be independent predictors of re-currence of SBP.[12] Both of which were not significant in this cohort but the significance of bilirubin as a predictor for recurrence was confirmed. Another study showed that serum creatinine and bilirubin are important predictors in determining renal failure, advanced liver disease and mortality.[13]

Diabetes mellitus as co-morbid was significant in patients having recurrence of SBP on univariate analysis, but not on multivariate analysis. The possible mechanism can be altered immunity and deficiencies in complement system with depressed functions of neutrophils and macrophages in patients with cirrhosis. It has been proven that cirrhotic patients with a lower

level of serum C3 and C4 are more prone to develop bacterial translocation.[15,16] A recent study also found association of proton pump inhibitor therapy with SBP,[17] but its use was not statistically significant in the present study population.

Patients with either single or recurrent episodes of SBP have no significant difference between their CTP or MELD scores. Although Hepatitis B related cirrhosis was found out to be a protective factor for recurrent SBP on multivariate analysis in this study, but this finding is explained by the fact that 71.8% of our study cohort included patients with Hepatitis C related cirrhosis.

Overall, this is the first study from Pakistan which would address the factors that are mainly responsible for the recurrence of SBP, but there remains a constraint of it being a single center study. There should be similar studies from other parts of the country and from South East Asia so that we are able to learn more related to this issue or similar factors which are largely responsible for this problem and, therefore, be able to adopt preventive measures and check repeated admission of patients.

CONCLUSION

Recurrent SBP was noticed in 34% patients with end stage liver disease or cirrhosis. Serum bilirubin level of > 1.0 mg [(OR 7.03; 95%CI=1.55-32), protective factor of HBV (OR 0.31; 95%CI=0.13-0.70)] and presence of UTI [(OR=2.24; 95%CI=0.99-5.09)] were significant factors associated with recurrent SBP.

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