Comparative Study of Community Acquired and Nosocomial Spontaneous Bacterial Peritonitis and its Variants in 150 Patients

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Background: **Nosocomial acquisition of spontaneous bacterial peritonitis (SBP) is debated as having a different microbial etiology and prognosis. Identification of clinical, laboratory predictors of mortality and appropriate empirical antimicrobial selection is necessary to prevent early mortality and morbidity. We aimed to find the clinical and bacteriological profile in nosocomial and community acquired SBP and its variants, and the predictors of mortality.** ***Material and methods:*** **One hundred and fifty patients with 162 discrete episodes of different types of SBP were analyzed. Relevant clinical and laboratory data were analyzed. SBP was diagnosed according to standard criteria and classified as community acquired if the infection detected within 48 h of admission and as nosocomial after 48 h of admission to the hospital.** ***Results:*** **Eighty seven percent had community acquired SBP (CSBP), 13% had nosocomial SBP (NSBP). Patients of NSBP were older, had more episodes of GI bleed and higher previous episodes of encephalopathy. Patients who died were older, had worse encephalopathy. NSBP had higher one month mortality. Age, serum sodium, encephalopathy and NSBP predicted mortality. Culture positivity was 22.22%.** ***Escherichia coli*** **was the commonest organism isolated. There was no difference in the bacteriological profile between CSBP and NSBP.** ***E. coli*** **showed up to 48% resistance to third generation cephalosporins. Overall sensitivity to aminoglycosides was more than 75%.** ***Conclusions:*** **Overall mortality was 59%. NSBP had significantly high one month mortality. Age, serum sodium, encephalopathy and NSBP were predictors of mortality. Bacteriological profile was similar between CSBP and NSBP. (J Clin Exp Hepatol 2017;7:215–221)**

Spontaneous bacterial peritonitis (SBP) is a frequent and severe complication of cirrhotic ascites.[1] SBP is the most common infection in cirrhotics (25%) followed by urinary tract infection (20%) and pneumonia (15%).[2]

SBP is a landmark event in the natural history of cirrhosis of liver with more than 50% mortality at one year.[3] Proper identification and treatment of SBP reduces in hospital and short term mortality significantly.[4]

Enteric gram negative bacilli are the commonest organisms isolated in ascitic fluid of patients with SBP. However there is increased incidence of gram positive organisms isolated in hospitalized patients with cirrhosis.[5] Studies done to assess the importance of acquisition site in prognosis of SBP have shown conflicting results. This study was done to compare the clinical, profile in CSBP and NSBP, predictors of mortality and to find out difference if any in the bacteriological profile between the two groups.

MATERIAL AND METHODS

This is a prospective study done from June 2010 to August 2012. Patients with SBP and its variants admitted to Department of Gastroenterology and Hepatology, St Johns medical college hospital, Bangalore were studied. The study was approved by institutional ethical review board (IERB). An informed written consent was obtained from all the patients. All patients under went detailed clinical examination, laboratory study and abdominal imaging. Ascitic fluid was collected from all the patients during admission at bedside and analyzed for total leukocyte count, differential count along with protein, albumin, glucose, amylase and 10 ml of ascitic fluid was injected into the BACTEC bottle at the bedside for culture and sensitivity. Diagnosis of cirrhosis was made based on clinical, radiological and endoscopic findings.

Past history of SBP, encephalopathy and GI bleed were recorded. Risk factors like EGD, diagnostic paracentesis, therapeutic paracentesis in the preceding one month of admission were noted.

SBP was defined as an ascitic fluid PMN count > 250 with or without positive culture. Patients with ascitic fluid

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Abbreviations: CNNA: culture negative neutrocytic ascites; HCV: Hepatitis C virus; SBP: spontaneous bacterial peritonitis
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PMN count > 250 and negative culture were labeled as culture negative neutrocytic ascites (CNNA), were grouped with culture positives for analysis. Patients with positive culture and PMN count <250 were labeled as Monomicrobial bacterascites and were excluded from final analysis. SBP was considered community acquired if the infection was detected within 48 h of admission and as nosocomial if it was detected after 48 h after admission to the hospital.[6–8] All the patients were followed up for 6 months from the date of admission, those went against medical advice were called by telephone to determine the status after discharge.

STATISTICAL ANALYSIS

Data were analyzed with statistical software StataIC-12. The results were reported as mean ± SD or Median (Range) for the continuous variables. The Student *t*-test or Wilcoxon rank sum and Chi-square test were used to compare quantitative data and qualitative variables. Logistic regression was done to assess the clinically and statistically significant factor associated with mortality separately after adjusted odds ratio was calculated. The *P*-value of <0.05 was considered statistically significant.

RESULTS

One hundred and fifty patients with 162 episodes of spontaneous bacterial peritonitis and its variants were studied among 706 patients of cirrhotic ascites. Incidence of SBP was 22.94%. Of the 162 episodes, 141 episodes (87.04%) were due to CSBP and 21 (12.96%) were secondary to NSBP. Mean age was 48.4 ± 14 and male to female ratio was 6:1.

One hundred and twenty six episodes (77.7%) were due to culture negative neutrocytic ascites (CNNA), rest were culture positive. Among them thirty three were due to spontaneous bacterial peritonitis and three episodes were due to Monomicrobial bacterascites.

Clinical characteristics, laboratory data, risk factors before an episode of SBP, past history and mortality comparing CSBP and NSBP are shown in Table 1.

Patients of NSBP were older, had more episodes of GI bleed, more episodes of vomiting and higher previous encephalopathy episodes compared to CSBP. Patients with CSBP presented with diarrhea more often than NSBP. Before an episode of SBP, endoscopic interventions and diagnostic paracentesis were more in NSBP compared to CSBP. Other risk factors were ERCP, ruptured urethra and pleural tap. Ascites was common in CSBP than NSBP. Few patients of NSBP developed ascites after admission and later showed SBP. CSBP had lower BMI in spite of more ascites compared to NSBP. Patients with NSBP had higher bilirubin compared to CSBP. Patients with NSBP had higher amount of alcohol use per day and higher cumulative dose compared to CSBP.

Etiologies for liver cirrhosis are depicted in Table 2. Ethanol was the commonest etiology followed by cryptogenic cirrhosis. Other etiologies were, Hepatitis B virus (HBV) in 8.6% (n = 14), Hepatitis C virus (HCV) in 4.3% (n = 7), Combination of HBV and ethanol in 2.4% (n = 4), Budd chairi syndrome in 3% (n = 5) and others in 4.3% (n = 7). There was no statistically significant difference between CSBP vs NSBP and culture positive vs culture negative with respect to etiology of cirrhosis.

Overall mortality was 59% at six months. Clinical characteristics, laboratory data, risk factors and past history comparing those who survived and died are shown in Table 3. Patients who died were older, had more renal impairment and had worse sensorium than those who survived. Patients who survived presented with fever more often than those who died. Patients who died had more endoscopic interventions, had higher number of patients with edema, encephalopathy, had higher bilirubin, creatinine, higher number of patients with CTP class C and lower serum sodium compared to those who survived. NSBP had significantly higher early mortality (less than one month) compared to CSBP. There was no statistically significant difference in mortality between culture positives and negatives.

Univariate and multivariate logistic regression of predictors of mortality are shown in Table 4. In univariate analysis age, serum sodium, serum creatinine, encephalopathy, bilirubin, NSBP, history of endoscopic procedure and AST predicted mortality. However on multivariate logistic regression age, serum sodium and encephalopathy predicted mortality.

Ascitic fluid positive culture yield was 22.22% (36 patients). Thirty three had SBP (20.37%). Three patients had Monomicrobial bacterascites (1.8%). The type of organisms in CSBP and NSBP are shown in Table 5. *Escherichia coli* was the commonest organism isolated. *S. aureus* or MRSA was not isolated in any of the patients. Culture positivity in CSBP was 22.69% and in NSBP was 19.04% (P = 0.59). No significant difference noted in bacteriological profile of CSBP and NSBP. All patients (n = 3) with Monomicrobial bacterascites were CSBP, however they were excluded from final analysis. Even though small number of culture positives in NSBP and *E. coli* was the commonest organism isolated, 50% isolates were due to gram positives.

Antimicrobial susceptibility of common organisms are depicted in supplement 1. Alfa-hemolytic Streptococci showed 100% sensitivity to penicillin, gentamicin, vancomycin and Teicoplanin. Since the number of culture positives in NSBP group was small, intergroup comparison between CSBP and NSBP with respect to drug susceptibility and resistance was not possible. The resistance pattern of organisms to various drugs as follows. *E. coli* showed 75% resistance to ciprofloxacin, around 50% resistance to third generation cephalosporins. *Klebsiella* showed around

Table 1 Clinical, Laboratory Data, Past History, Risk Factors and Mortality in Comparison Between CSBP vs NSBP.

	CSBP *n* (%)	NSBP *n* (%)	*P* value
Symptom			
Ascites	130 (92.2)	13 (61.9)	0.001
Jaundice	59 (41.8)	12 (57.1)	0.18
Pain abdomen	60 (42.5)	11 (52.38)	0.39
GI bleed	37 (26.3)	6 (28.6)	0.01
Fever	50 (35.5)	9 (42.7)	0.22
Vomiting	13 (9.2)	5 (23.8)	0.04
Diarrhea	23 (16.3)	0 (0)	0.04
Renal impairment	34 (24.1)	3 (14.2)	0.41
Altered sensorium	37 (26.2)	8 (38)	0.29
Mean Age (years)	48	54	0.07
Past history			
SBP	19 (13.4)	3 (15)	0.73
GI bleed	29 (20.7)	6 (28.5)	0.41
Encephalopathy	13 (9.2)	5 (23.8)	0.04
Norfloxacin prophylaxis	18 (12.7)	3 (15)	0.7
Clinical signs			
Pallor	64 (45.7)	11 (52.4)	0.57
Edema	108 (76.6)	17 (80.95)	0.79
Septic shock	7 (4.9)	1 (4.7)	1
Hypothermia	2 (1.4)	1 (4.7)	0.34
Encephalopathy	47 (33.3)	7 (33.3)	1
Splenomegaly	38 (26.9)	3 (14.2)	0.28
Abdominal tenderness	28 (20)	4 (19)	1
BMI	22.9 ± 4.59 (mean ± SD)	25.5 ± 4.23 (mean ± SD)	0.01
Laboratory data			
PT seconds	21.5 ± 8.1	20.1 ± 5.9	0.47
INR	1.7 (0.9–10.1)	1.7 (1.1–3.0)	0.57
Creatinine (mg/dl)	1.2 (0.5–6.0)	1.3 (0.7–4.2)	0.56
Serum sodium (mEq/l)	128.7 ± 6.79	130.1 ± 6.77	0.34
Total bilirubin (mg/dl)	3.4 (0.2–41.3)	7.2 (0.5–34.04)	0.06
Albumin (g/dl)	1.85 ± 0.58	1.92 ± 0.47	0.58
CTP			
A	7 (5.1)	0 (0)	0.5
B	27 (19.7)	5 (25)	
C	103 (75.2)	15 (75)	
MELD score	21.68 ± 8.54	23.50 ± 8.93	0.38
Risk factor			
EGD	10 (7.1)	8 (38.1)	<0.001
Diagnostic paracentesis	17 (12.06)	12 (57.1)	<0.001
Others	3 (2.13)	0 (0)	1
Mortality			
In hospital	16 (22.2)	31 (43)	0.01
Discharge to 1 month	25 (34.8)	10 (62.5)	0.01
1 month to 6 months	31 (43)	1 (6.3)	0.01

Table 2 Common Etiologies of Liver Cirrhosis in CSBP vs NSBP and Culture Positive vs Culture Negative.

Etiology of cirrhosis	CSBP *n* (%)	NSBP *n* (%)	*P* value	Culture positive *n* (%)	Culture negative *n* (%)	*P* value
Ethanol	85 (60.3)	10 (47.6)	0.27	25 (69.4)	70 (55.6)	0.18
Cryptogenic	24 (17)	4 (19)	0.76	6 (16.7)	22 (17.5)	1
HBV	11 (7.8)	3 (14.3)	0.39	2 (5.6)	12 (9.5)	0.73

HBV – Hepatitis B virus.

25% resistance to third generation cephalosporins. Non fermenting GNB showed around 50% resistance to third generation cephalosporins.

DISCUSSION

The incidence of SBP in our study of 162 episodes in 150 patients was 22.9%. CNNA was more common, and culture positivity was seen in 22.2%. Eighty seven percent had CSBP and 13% had NSBP. Patients with NSBP were older, had more episodes of GI bleed, higher previous episodes of encephalopathy, more diagnostic paracentesis and more endoscopic procedures compared to CSBP. Patients with NSBP had higher amount of alcohol intake compared to CSBP. Both the groups did not show any difference in previous episodes of SBP or patients on norfloxacin prophylaxis. Age, serum sodium and hepatic encephalopathy were the predictors of mortality in multivariate logistic regression. NSBP had significant high one month mortality and was a predictor of mortality in both univariate and multivariate analysis. *E. coli* was the common organism isolated in 58.3% patients. There was no statistically significant difference in bacteriological profile between CSBP and NSBP. Third generation cephalosporin resistance was noted in up to 48% for *E. coli*. Overall aminoglycoside sensitivity was seen in up to 75%.

There are limited studies comparing CSBP and NSBP from India. Mixed results are largely due to geographical differences in etiology with hepatitis B virus common in Asia and alcohol in the west, ethanol was the commonest etiology in our series which is similar to other Indian studies of SBP, however Indian studies comparing CSBP and NSBP are lacking.[7,8,10–12]

No clinical feature is unique to CSBP or NSBP. In study by Cheong et al. fever was more common in NSBP and abdominal pain was more common in CSBP, although there were no significant other differences.[7] Our study vomiting was more common in NSBP and diarrhea in CSBP. In our study patients who survived presented with more fever episodes than who died, underlining the fact that fever likely triggers more rapid analysis of ascitic fluid and hence early diagnosis and treatment.

Study by Kim et al., patients of NSBP had lower serum sodium compared to CSBP but there were no difference in CTP scores or mortality.[8] In our study we did not notice any difference in laboratory parameters between CSBP and NSBP except NSBP had higher bilirubin.

Patients with NSBP had more episodes of GI bleed and endoscopic interventions and higher prior diagnostic paracentesis compared to CSBP suggesting higher interventions contributing to NSBP. These interventions had valid indications including diagnostic and therapeutic. However there was no difference in the isolated bacteriological profile of organisms isolated between CSBP and NSBP.

Patients who died had severe liver dysfunction having more patients with CTP class C. which is a consistent predictor of mortality in all most all studies. In addition, we found older age, encephalopathy, low sodium was associated with higher mortality and NSBP had higher one month mortality. Another observation noted was that patients with NSBP had higher overall mortality than CSBP if gram positive organism was isolated more and there was no difference in mortality in studies where gram negative organism was isolated more.[7–10]

Campillo et al., described 70% NSBP were due to gram positive organisms, 24% from Methicillin resistant staph aureus (MRSA) infection. Mortality was higher in NSBP and especially with MRSA infection.[9] Our study showed that NSBP had significantly higher 30 days mortality compared to CSBP. NSBP itself was a predictor of mortality. In a similar study by Cheong et al., a third of whom had third generation cephalosporin resistance.[7] Some studies did not show difference in the mortality between CSBP and NSBP.[10]

E. coli was the commonest organism isolated in our study followed by *Klebsiella*, with resistance to third generation cephalosporin in up to 48%, which is similar to other studies.[7,10–12]

There is increased isolation of gram positive organisms in SBP in west, particularly in patients on quinolone prophylaxis.[13] There was no statistically significant difference noted between CSBP and NSBP in our study with respect to number of patients on norfloxacin prophylaxis, however they were seen in up to 15% patients and most of the infections were first episodes. This may explain gram negative predominance in our study.

A recent study from Italy showed a higher incidence of gram positive organisms (62%), with response to a combination of Meropenem and Daptomycin and a

Table 3 Clinical, Laboratory Data, Past History and Risk Factors in Comparison Between Survivors and Dead.

	Survived *n* (%)	Died *n* (%)	*P* value
Symptom			
Ascites	63 (85.1)	80 (90.9)	0.25
Jaundice	28 (37.8)	43 (48.9)	0.16
Pain abdomen	32 (43.2)	39 (44.3)	0.89
GI bleed	24 (32.4)	19 (21.6)	0.29
Fever	33 (44.6)	26 (29.6)	0.04
Vomiting	6 (8.1)	12 (13.6)	0.26
Diarrhea	11 (14.9)	12 (13.6)	0.82
Renal impairment	11 (14.9)	26 (29.5)	0.02
Altered sensorium	14 (18.9)	31 (35.2)	0.02
Mean Age (years)	45	51	0.002
Past history			
SBP	8 (11)	14 (15.9)	0.36
GI bleed	17 (23)	18 (20.7)	0.72
Encephalopathy	5 (6.8)	13 (14.9)	0.1
Norfloxacin prophylaxis	7 (9.4)	14 (15.9)	0.3
Clinical signs			
Pallor	40 (54.8)	77 (39.8)	0.47
Edema	52 (70.3)	73 (83)	0.05
Septic shock	1 (1.3)	7 (8)	0.07
Hypothermia	0 (0)	3 (3.4)	0.25
Encephalopathy	13 (17.6)	41 (57.6)	<0.001
Splenomegaly	19 (25.7)	22 (25)	0.92
Abdominal tenderness	14 (19.2)	18 (20.5)	0.84
BMI	23.10 ± 4.74 (mean ± SD)	23.52 ± 4.47 (mean ± SD)	0.54
Laboratory data			
PT seconds	20.05 ± 6.7	22.35 ± 8.7	0.06
INR	1.6 (0.9–10.1)	1.8 (1.1–5.8)	0.11
Creatinine (mg/dl)	1.2 (0.6–3.3)	1.35 (0.5–6.0)	0.02
Serum sodium (mEq/l)	131 ± 5	126.9 ± 7.4	<0.001
Total bilirubin (mg/dl)	3.25 (0.20–23.40)	4.30 (0.50–41.3)	0.009
Albumin (g/dl)	1.94 ± 0.64	1.79 ± 0.49	0.22
CTP			
A	6 (8.3)	1 (1.2)	0.02
B	18 (25)	14 (16.5)	0.02
C	48 (66.7)	70 (82.4)	0.02
MELD score	21.52 ± 8.9	22.23 ± 8.36	0.6
Risk factor			
EGD	4 (5.4)	14 (16.1)	0.04
Diagnostic paracentesis	9 (12.2)	20 (22.7)	0.08
Others	2 (2.7)	1 (1.1)	0.59

Table 4 Mortality Predictors in Univariate and Multivariate Regression.

Variable	Odds ratio	Confidence interval	*P* value
Univariate analysis			
Age	1.03	1.01–1.06	0.003
Serum sodium	0.89	0.85–0.95	0.00001
Serum creatinine	1.98	1.27–3.08	0.002
Total Bilirubin	1.08	1.02–1.13	0.004
AST	1.003	1.00–1.007	0.037
History of EGD	3.35	1.05–10.69	0.041
Hepatic encephalopathy	4.09	1.97–8.49	0.001
Nosocomial SBP	3.06	1.06–8.82	0.03
Multivariate regression			
Age	1.029	1.003–1.057	0.02
Serum sodium	0.92	0.866–0.977	0.007
Serum creatinine	1.169	0.69–1.972	0.559
Total bilirubin	1.055	0.966–1.118	0.06
History of EGD	2.9	0.81–10.36	0.1
Hepatic encephalopathy	2.73	1.19–6.29	0.01
Nosocomial SBP	2.53	0.71–9.00	0.15

recommendation was made to use it as an empirical treatment.[14] In our study Meropenem sensitivity to *E. coli* was seen in 66.6% and for Piperacillin tazobactum in 76%. Even though small numbers up to 50% of NSBP showed gram positives, larger study with more NSBP is required to suggest empirical gram positive cover in Indian patients. The variable antibiotic sensitivity calls empirical antibiotic choice to be made according to local sensitivity pattern.

Antimicrobial sensitivity of organisms are shown in supplement 1. *Klebsiella* spp. showed 25% resistance to third generation cephalosporins and quinolones in our study. All patients with CoNS (coagulase negative staphylococci) were sensitive to aminoglycosides in our study even though they showed variable resistance to other antibiotics. Overall Aminoglycoside sensitivity was seen in more than 75%. A study done by Puri et al., it was noticed that all patients with monomicrobial bacterascites were due to gram positive cocci, however we found gram negative predominance in the organisms isolated in monomicrobial bacterascites.[15]

Table 5 Number and Percentage of Organisms Isolated in CSBP and NSBP.

Organism	CSBP (*n* = 29) (%)	NSBP (*n* = 4) (%)
E. coli	17 (58.6)	2 (50)
Klebsiella spp.	4 (13.8)	0 (0)
Non-fermenting GNB	2 (6.9)	0 (0)
α-Hemolytic Streptococci	2 (6.9)	1 (25)
CoNS	3 (10.3)	1 (25)
Enterobacter spp.	1 (3.4)	0 (0)

P = 0.59.
GNB – gram negative bacilli.
CoNS – coagulase negative staphylococci.

Our study has several unique features like including a large number of patients of NSBP with alcoholic cirrhosis. There is a concern of NSBP with increasing interventions in hospitalized patients. Our study showed that apart from severe liver dysfunction which predict long term mortality, NSBP predict one month mortality. Awareness and proper early intervention lead to better survival. Enteric gram negatives like *E. coli* were still the commonly isolated organisms unlike the west where there is a trend of gram positive isolates. Since there is regional variation in bacteriological profile and sensitivity, empirical antibiotics to be chosen according to local sensitivity patterns. Limitations of our study included non-availability of species identification of non-fermenting gram-negative bacilli.

CONCLUSIONS

Patients of NSBP were older, had more episodes of GI bleed, endoscopic interventions and previous episodes of encephalopathy. Patients who died had worse liver function. Age, serum sodium, encephalopathy were predictors of mortality. Patients of NSBP had higher one month mortality, and itself was a predictor of mortality. CSBP and NSBP showed similar bacteriological profile. *E. coli* was

the common organism isolated in both. Third generation cephalosporin resistance was seen in 48%. Empirical antibiotics to be chosen according to local sensitivity pattern.

ETHICAL APPROVAL

This study was approved by Institutional ethical review board of St Johns Medical College Hospital, Bangalore.

CONFLICTS OF INTEREST

The authors have none to declare.

Appendix A. SUPPLEMENTARY DATA

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jceh.2017.03.005.

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