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Factors Predicting Failure of 3rd Generation Cephalosporins in Treatment of Spontaneous Bacterial Peritonitis- A Retrospective Observational Study

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Abstract
Background: *Spontaneous bacterial peritonitis (SBP) is the most prevalent bacterial infection in patients with cirrhosis. Cefotaxim has been considered the first choice of empirical antibiotic for the treatment of SBP. Studies from different parts of world have reported significant rates of resistance to third-generation cephalosporins. Patients not responding to 3rd generation cephalosporins require longer duration of treatment with higher spectrum antibiotics which will prolong the hospital stay and more financial constrains for the patients*
Objective: *To find Factors predicting failure of 3rd generation cephalosporins in treatment of SBP in decompensated cirrhosis patients*
Methods: *Retrospective Observational study by data collection of all patients admitted with cirrhosis and SBP who were started on cefotaxim from januvary 2015 to januvary 2016 in department of medical gastroenterology govt medical college Trivandrum were done. Multivariate logistic regression was used to determine independent predictors of third-generation cephalosporin resistance*
Results*: 168 patients met the criteria for study inclusion. 120 (71.42%) patients responded to cephalosporin therapy. 48 (28.57%) were non responders. Alcoholic liver disease 113(67%), NASH 36 (21%), Hep B infection 26 (15%) were predominant cause of decompensated cirrhosis. 58(48.3%) responders and 22 (44%) non responders were on norflox prophylaxis. H/o recent broad spectrum antibiotic usage was found in 24 (20%) responders and 17(35.41%) non responders. On multivariate analysis MELD >19 p0.001, OR 4.37 (95% CI 2.12-9.00), presence of hepatic encephalopathy p0.014, OR 2.53 (95% CI 1.2-5.3) and recent antibiotic usage p 0.01, OR 2.44 (95% CI 1.365-5.854) emerged as significant risk factor for resistance to 3rd generation cephalosporins*
Conclusion: *High MELD score, presence of encephalopthy and recent broad spectrum antibiotic usage emerged as significant risk factor for resistance to 3rd generation cephalosporins. These group of patients with SBP should receive empirical treatment with higher antibiotics during admission*
Keywords: *SBP, Cefotaxim, Response.*

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is the most prevalent bacterial infection in patients with cirrhosis. SBP occurs in 10%–35% of patients with liver cirrhosis with ascites, with an in hospital mortality rates ranging from 20% to 40% and 1 and 2 years mortality rate after an episode of SBP is 50-70% and 70-75% respectively[1]. 3rd generation cephalosporins has been considered the first choice of empirical antibiotics in treatment of SBP[2]. Cefotaxime, given intravenously at a dose of 4-8 g/d for a minimum duration of 5 days is the treatment regimen. With this regimen, resolution of SBP is achieved in approximately 90% of patients and 30-d survival is at least 80%[3]. Studies from different part of world have reported significant resistance to third-generation cephalosporins[4]. Patients who are not responding to 3 rd generation cephalosporins requires longer duration of treatment with higher spectrum antibiotics which will prolong the hospital stay and more financial constrains for the patients.

Resistance to 3rd generation cephalosporin is associated with increased short term mortality independent of MELD score[5]. Factors which will predict resistance to cephalosporin can help in starting higher antibiotics during admission

According to EASL clinical practice guideline 2010 [2] SBP is defined as ascitic fluid absolute polymorphonuclear cell counts ≥250 cells/mm. Classified into two types culture positive SBP and culture neg SBP. According to AASLD 2012 guidelines culture positivity was mandatory for diagnosis of SBP and culture neg SBP were called culture neg neutrocytic ascites.(CNNA)[6]. Culture positivity was found in 10-40% patients only and there is delay in getting culture results. Symptoms and mortality rate in patients with culture neg SBP are similar to the course of disease in patients with diagnosed with culture positive SBP[7]. Both are identical from the clinical point of view and therapeutic approach. Appropriate and prompt antibiotic treatment is must for cure of SBP and we cannot wait till culture reports available as it will cause progression of liver disease and increase mortality. Empirical antibiotic therapy with 3rd generation cephalosporins will be started as soon as diagnosis of SBP is made. There are recommendations regarding treatment of nosocomial SBP (infection occurring 48 hours after hospital admission) with carbapenem and glycopeptide[8]. Regarding health care related infection (defined as those diagnosed within the first 48 h after hospital admission in patients who had contact with the health care system in the previous three months) and community acquired SBP treatment should be considered according to gut bacterial flora and resistant pattern in that particular area.

AIM

To find Factors predicting failure of 3rd generation cephalosporins in treatment of SBP in decompensated chronic liver disease patients.

METHODS

Retrospective observational study of patients with decompensated cirrhosis and SBP admitted in Medical college hospital Trivandrum in department of medical gastroenterology from January 2015 to January 2016 were included. Cirrhosis was diagnosed by compatible clinical presentation, radiology and laboratory markers. Diagnostic paracentesis was done using sterile 23G needle with 20 cc syringe under aseptic preparation. Ascitic fluid collected into ethylenediaminetetra acetic acid tubes. After centrifugation analysed for total and differential leukocyte count, total protein and albumin. For ascitic fluid culture beside inoculation of 10 ml ascitic fluid aseptically into blood culture bottles and direct inoculation on blood agar plate incorporated with 2% tween 80 were done. Positively flagged culture specimens were subcultured on chocolate agar and Mac conkey agar plates. Antibiotic susceptibility test was done on Mueller hinton agar by using disc diffusion method. SBP was defined according to EASL

2010 practice guidelines as ascitic fluid absolute polymorphonuclear cell counts ≥250 cells/mm^3.

Patients were started on cefotaxim, and response to antibiotics were assessed by clinical improvement and after 2 days with repeat ascitic fluid study showing 25% reduction in ascitic fluid polymorphonuclear cell count . Patients were divided into two group cefotaxim responders and cefotaxim non responders. Patients not responding to cefotaxim were switched over to piperacillin tazobactum or antibiotic based on culture sensitivity report. If still no response meropenem given. Local ethics approval was obtained for retrospective data collection. Hospital based electronic discharge data and case records were collected .The demographic, clinical, biochemical characteristics in cefotaxim responders and non responders were compared and analysed. Following information were collected age, sex, cause of cirrhosis, Child-Pugh score, MELD score, recent gastrointestinal bleeding, laboratory results, previous SBP history, h/o norflox prophylaxis, h/o broad spectrum antibiotic usage in past 90 days. Only one episode of SBP for each patient was included in the analysis. Patients received treatment with cefotaxim and intravenous albumin therapy if criteria for high-risk were met (serum creatinine >1mg/dl or blood urea nitrogen >30mg/dl or T bilirubin >4mg/dl), were included. Patients initially started on higher antibiotics for severe sepsis, secondary bacterial peritonitis, mixed ascites, nosocomial SBP were excluded from the study.

STATISTICAL ANALYSIS

Continuous variables were described by mean ± SD; Categorical variables were described by percentages. Association between study variables were assessed by t-test, Chi square test and Mann Whitney U test depending upon the nature of study variables. The logistic regression was done to identify the risk factors.

RESULTS

Total 168 patients met the criteria for study inclusion. All patients were started on cefotaxim. Out of these 168 patients 120 (71.42%) patients were responded to cefotaxim, 48 (28.57%) patients were non responders and in these patients cefotaxim was changed to higher antibiotics. 22 patients were initially started on higher antibiotics were excluded. 16 patients had repeat episode of SBP during that one year. Mean age was 48 years. 141 (84%) patients were male. Alcoholic liver disease 113(67%), NASH 36 (21%), Hep B infection 26 (15%) were predominant cause of decompensated cirrhosis. Alcoholic hepatitis were found in 46 (27%) patients.100 (83 %) Responders and 41 (85%) non responders were in CHILD C category. Hepatic encephalopathy was found in 23 (19%) cefotaxim responders and 18 (37%) non responders. Total 70 (41.66%) patients were taking quinolone prophylaxis 58 (48%) patients in responder group and 22 (44%) in non responder group. Out of 168 patients 41(24%) patients had h/o broad spectrum antibiotic usage in the past 90 days 24 (20%) in responder group and 17 (35%) non responder group. Previous episode of SBP were found in 47 (28%) patient, 32 (26%) in cefotaxim responder group and 15 (31%) in cefotaxim non responders. Clinical characteristics of patients are given in table 1 and table 2.

TABLE 1 clinical characteristics of cefotaxim responders and cefotaxim non responders

	TOTAL 168	RESPONDERS 120	NONRESPONDERS 48	P VALUE
AGE(MEAN +SD)	48.47+10.4	49.93+11.2	47.37 +10.8	0.77
SEX MALE	141 (84%)	102 (85%)	39(81.25%)	0.80
ETIOLOGY ALCOHOL	113(67.26%)	79(65.83%)	34 (70.83%)	0.53
HEP B	26(15.47%)	18 (15%)	8 (16.66%)	0.78
ALCOHOLI HEPATITIS	46(27.38%)	30(25.83%)	16 (33.33%)	0.27
HEP C	13 (7.73%)	10 (9.0%)	3 (5.35%)	0.20
NASH	36(21.42%)	26 (21.66%)	10 (20.83%)	0.90
OTHER	15 (8.9%)	10(8.3%)	5 (10.41%)	0.62

TABLE 2 clinical characteristics of cefotaxim responders and cefotaxim non responders.

	Responders 120	Nonresponders 48	P value
CHILD B	20 (16.66%)	7 (17%)	0.73
CHILD C	100 (83.33)	41(85.41%)	0.73
TYPE 2 DM	36 (30%)	12 (25%)	0.52
VARICEAL BLEED	10 (8.3%)	3 (6.5%)	0.39
HE	24 (19.1%)	18 (37.5%)	0.01
HCC	7 (5.8%)	2 (4.1%)	0.66
Quinolone	58 (48.3%)	22 (44.6%)	0.641
Antibiotic use in past 90 days	24 (20%)	17 (35%)	0.03
Previous h/o SBP	32 (26.66%)	15 (31.25%)	0.27

Presence of hepatic encephalopathy and broad spectrum antibiotic usage in past 90 days were found to have significant association with p value <0.05

Laboratory parameters (table 3 and table 4) were compared between both groups. On univariate analysis high MELD score, elevated S creatinine, elevated PT INR were found to have significance in predicting cefotaxim response with a p value<0.05

TABLE 3 Laboratory characteristics in cefotaxim responders and cefotaxim non responders

	RESPONDERS 120 (MEAN+SD)	NONRESPONDERS 48 (MEAN+SD)	P VALUE
HB	9.88 +2.197	9.71+1.57	0.624
PLATELET COUNT	1.02+0.43	1.07+0.38	0.528
ANC	8485+5622	10100+6768	0.53
S Na	133+4.8	132.68+5.4	0.687
S creatinine	1.05+0.42	1.32+0.62	0.004
S albumin	2.59+0.48	2.55 +0.43	0.467
PT INR	1.84 + 0.37	1.99+0.35	0.02

TABLE 4 Laboratory characteristics in both groups

	RESPONDERS 120 MEAN+SD	NONRESPONDERS 48 (MEAN+SD)	P VALUE
BILIRUBIN	4.58+5.02	5.3+5.25	0.594
CTP	10.70+1.423	10.81+1.202	0.749
MELD	17.08+5.932	21.48+6.510	0.001
ANC in ascitic fluid	1820.55+2696	1129 +2048	0.373
Ascitic fluid protein	1.04+0.727	0.88+0.619	0.221
SAAG	2.01+0.360	2.12+0.425	0.32

ascitic fluid culture positivity were found in 16 patients , blood culture positivity were found in 20 patients.. Out of these 36 patients with culture positivity gram neg organisms were found in 26 (72.22%) patients, gram positive organisms were found in 10 (27.77%) patients. 22 (61%) patients had organisms sensitive to cefotaxim and 14 (38%) patients were cefotaxim resistant. There were no significant correlation between culture positivity and cefotaxim resistance with p value 0.12. Most common organism in cefotaxim responders were E coli followed by klebsiella, streptococcus pneumonia, acinetobactor. Common organism in cefotaxim resistant group were extended spectrum b lactase producing E coli, followed by enterococci, klebsiella, staph aureus, acinetobactor species. Pattern of culture sensitivity and organisms are given in table 5.

TABLE 5 Pattern of organisms in culture positive SBP

CULTURE POSITIVITY36(21.4%)	RESPONDERS 22 (61%)	NONRESPONDERS 14 (38.88%)
Escherichia coli	12	7
Klebsiella species	4	2
Streptococcus species	3	0
Enterococcus species	0	3
Streptococcus pneumonia	2	0
Staphylococcus aureus	1	1
Acinetobactor species	2	1
Salmonella typhimurium	1	0

On univariate analysis presence of hepatic encephalopathy (HE), broad spectrum antibiotic usage in the past 90 days, elevated PT INR, elevated S creatinine, high MELD score found to have significant association in predicting non response to cefotaxim therapy. MELD score, S creatinine and PT INR are highly correlated variables. MELD score was entered into multivariate analysis over S creatinine and PT INR to get an estimation of both liver and kidney function. Logistic regression analysis revealed broad spectrum antibiotic usage in the past 90 days, high MELD score (>19) and presence of hepatic encephalopathy were found to have significant predictive value in assessing non response to cefotaxim therapy.

TABLE 6 logistic regression analysis

	P value	ODDS ratio	95% CI
MELD>19	0.001	4.37	2.12-9.00
HE	0.014	2.53	1.2-5.3
RECENT ANTIBIOTIC USAGE	0.01	2.44	1.365-5.84

In hospital mortality was 9 (5.3%), 2 (1.6%) in cefotaxim responders and 7 (14.5%) in cefotaxim non responders. In responders cause of death was severe upper git bleed. In non responders cause of death was sepsis with multi organ dysfunction syndrome, hepatorenal syndrome. Cefotaxim non response was associated with increased in hospital mortaliy with a significant p value 0.005 with an odds ratio 10.07

DISCUSSION

Chronic liver disease is a state of various levels of immune dysfunction and immune paralysis referred to as cirrhosis associated immune dysfunction syndrome (CAIDS)[9]. Small intestinal bacterial over growth, increased intestinal permeability, translocation of gut bacteria, decreased phagocytic activity of macrophages, deteriorated humoral immunity, decreased ascitic fluid opsonin activity will cause infections by gram neg enteric bacteria, of which SBP, UTI, pneumonia, cellulites are the most common [10,11]. It is well established that 30% to 50% of cirrhotic patients either have bacterial infections when admitted to a hospital or acquire them during this period, and such infections are responsible for up to 25% of deaths in this patient population. These infections will cause deterioration of liver function and increased mortality if early diagnosis and prompt and adequate treatment not started. SBP is the most common infection in liver disease and empirical treatment is with 3rd generation cephalosporins as they are well tolerated and active against enterobacteria and non enterococcal streptococci. The effectiveness of cephalosporin has been questioned due to high prevalence of cefotaxim resistance in some part of the world due to frequent inadequate antibiotic exposure to these antibiotics by decompensate liver disease patients and frequent procedures in these patients. One retrospective study of two hundred and forty six episode of SBP revealed 3rd generation cephalosporin resistance of 21.5% (7.1% in community acquired SBP, 21.1% in health care related SBP, 40.9% in nosocomially acquired SBP)[12]. For nosocomial SBP empirical antibiotic treatment with carbapenem and glycopeptide should be given. For community acquired SBP studies have shown different results. Depending on the local epidemiologic pattern of antibiotic resistance of gut flora empirical antibiotics should be given. Aim of our study was to find factors that predict antibiotic responsiveness in our patients so that we can start higher antibiotics empirically. Previous studies have shown nosocomial sbp, recent broad spectrum antibiotic exposure, high MELD score, elevated S creatinine, hepatic encephalopathy, recent upper GIT bleed, presence of diabetes, low ascitic fluid neutrophil count, high SAAG[1,3] were associated with non responsiveness to 3rd generation cephalosporins. We have found high MELD score, recent broad spectrum antibiotic usage, presence of encephalopathy, were associated with cefotaxim non responsiveness. The explanation for this may

be high MELD score and presence of hepatic encephalopathy indicate more advanced liver disease and these patients may have more frequent hospitalization with inadequate and inappropriate antibiotic usage in periphery will have more chance of infection with multidrug resistant bacteria. Culture positivity (blood and ascitic fluid) was only 36 (21.4%). Culture positivity between 10%-40% been reported in various studies (12). Our low culture positivity may be due to earlier diagnosis of SBP, low bacterial population (1-2 bacteria/ml) in this population. We have found more culture positivity in cefotaxim non responders but it was statistically not significant. More enterococci in non responders may be due to recent procedures in this group. There were no significant difference in cefotaxim response pattern in between patients who were taking norflox prophylaxis and patients not on norflox prophylaxis indicating norflox usage was not associated with change in bacterial flora in gut. As patients with culture positivity were less in number we didn't do comparative analysis in culture positive cefotaxim responders and non responders. In hospital mortality was higher in cefotaxim non responders compared to cefotaxim responders, although the number is significantly low. We recommend patients with decompensated chronic liver disease and SBP with MELD>19, presence of encephalopathy, recent broad spectrum antibiotic use should be empirically treated with higher antibiotics.

CONCLUSIONS

High MELD score, presence of encephalopathy and recent broad spectrum antibiotic usage emerged as significant risk factor for resistance to 3rd generation cephalosporins. These group of patients with SBP should receive initial empirical treatment with higher antibiotics during admission. Piperacillin–tazobactam could be a favourable choice.

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