

Original Article

Identification of Causative Organisms and Role of Ceftriaxone in Spontaneous Bacterial Peritonitis (SBP) Secondary to Decompensated Liver Disease

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Abstract

Background There is increasing trend of gram positive organism present in ascetic fluid culture as a result of selective gut decontamination of gram negative organisms by prophylactic antibiotics for SBP and due to different invasive procedures. **Objectives** to identify causative organisms in ascetic fluid culture of patients with spontaneous bacterial peritonitis secondary to decompensated liver disease and their sensitivities to ceftriaxone as an empiric therapy. **Methods** A Cross sectional study was conducted at Department of Gastroenterology, Shifa International Hospital, Islamabad. Aseptic technique was adopted to aspirate ascetic fluid. At least 10 ml of ascetic fluid was inoculated in blood culture bottle at bed side before starting ceftriaxone. **Result** Total 97 patients were included in this study. Among them 57 (58.8%) were male and 40 (41.2%) were female. The most common organism was E. coli with a frequency of 42(43.2%) almost half were ESBL strains 20(20.6%) followed by Klebsiella 15(15.4%) among which 5(5.2%) were ESBL strains while Pseudomonas aeruginosa was 12(12.3%). **Conclusion** No increasing trend of gram positive pathogens was observed, however ESBL strains are emerging pathogens. Gram negative organisms are still the common pathogens of SBP.

Keywords

Ceftriaxone, Liver cirrhosis, bacterial, Gram negative, aseptic

Introduction

Spontaneous bacterial peritonitis (SBP) is a fearsome but treatable complication in patients with decompensated liver cirrhosis and its reported mortality is up to 90% without treatment (Gines P et.al, 2010). SBP can be defined as infection of the ascetic fluid in which polymorph nuclear cells (PMN) count is equal or more than 250 cells/ml and produce at least single growth of bacteria and there is no intra or extra abdominal source of infection (Kamani L, et.al, 2008). Culture Negative Neutrocytic Ascites (CNNA) and Bacteriascites (BA) are the two type of SBP (Kamani L, et.al, 2008). Patients with Liver cirrhosis who are

hospitalized have 10-30% incidence of SBP (Riggio O, Angeloni S. 2009). Using blood culture bottle method (BCBM) at bed side the diagnostic yield of culture positive SBP can be achieved up to 80% (Koulaouzidis A, Bhat S, Saeed AA 2009). Most of the culprit organisms which are responsible for SBP are mainly enterobacteriaceae in 60% of cases in which Escherichia coli is (30%) followed by Klebsiella pneumonia (14%) while gram positive organisms in ascetic fluid culture is reported up to 24% (Haider I, et.al 2008). Ceftriaxone is the commonly used empiric antibiotic in SBP which has been found to be effective against Escherichia coli (E coli) in 71.4%,

Klebsiella Pneumonia 66.6% and Gram positive organisms Staphylococcus aureus is found to be 66.6% sensitive to ceftriaxone (Ahmad M, et.al, 2011).

There is increasing trend of gram positive organism present in ascetic fluid culture as a result of selective gut decontamination of gram negative organisms by prophylactic antibiotics for SBP and due to different invasive procedures (Gou YZ, 2010). This is supported by a study conducted in Copenhagen showing an increase in percentage occurrence of gram positive cocci up to 45.9% and the overall antibiotic coverage was 57% with ceftriaxone (Novovic S, et.al, 2011).

Considering the fact as mentioned above that gram positive organism is grown in ascetic fluid culture from patients with SBP and poor response to ceftriaxone as empiric therapy and even significant resistance of gram negative organisms to ceftriaxone in different communities. There is no sufficient evidence of such change in microbial pattern in ascetic fluid from our country. It is essential to look for current trend in causative organisms of SBP and their response to ceftriaxone which is commonly use an empiric therapy in our setup. If there is such change as mentioned above, then a combination of empiric therapy or broad spectrum antibiotic monotherapy would be a suggestion. The basic objective of this study was to identify causative organisms in ascetic fluid culture of patients with spontaneous bacterial peritonitis secondary to decompensated liver disease and their sensitivities to ceftriaxone as an empiric therapy.

Material and Methods

Study design

Cross sectional study.

Setting

The study will be carried out in Department of Gastroenterology Shifa International Hospital Islamabad.

Duration of study

Six months.

Sample size

Sample size was calculated by WHO sample size calculator which is 96.

Sampling Technique

Non probability consecutive sampling

Inclusion Criteria

- All patients with cirrhotic ascites having spontaneous bacterial peritonitis whose ascetic fluids yield at least one single growth of microorganism will be included in our study.
- All patients regardless of age and gender will be included.
- Patient taking antibiotic for Prophylaxis of SBP will also be included.

Exclusion criteria

All secondary causes of peritonitis have been excluded due to:

- Malignant ascites: A patient with ascites already having known malignancy or having malignant cells on ascetic fluid cytology.
- Tuberculous ascites. Ascetic fluid having predominantly lymphocytes and high protein in exudative range (equal or more than 4mg/dl).

Data Collection Procedure

Participants were selected by both inpatients and out patients fulfilling the inclusion criteria were enrolled. Informed consent was obtained from participants. Procedure was explained to study population and was by performed by senior post graduate trainees. Full aseptic technique was adopted to aspirate ascetic fluid. At least 10 ml of ascetic fluid was inoculated in blood culture bottle at bed side before starting ceftriaxone. Imaging assistance was also obtained.

Data Analysis

Statistical analysis was performed using SPSS (Version 21). Mean \pm standard deviation was calculated for quantitative variables like age of patients. Frequency and percentages were calculated for qualitative variables like gram Positive and gram negative organisms and sensitivity of ceftriaxone. Chi square test was used to compare sensitivity of ceftriaxone against gram positive and gram negative organism. P value less than 0.05 was taken as level of significance.

Results

Total 97 patients were included in this study. Among them 57 (58.8%) were male and 40 (41.2 %) were female. The mean age was 49.26 ± 16.67 . The total number of gram positive organisms were isolated from ascetic fluids in 28(28.9%) and gram negative organisms were present in 69 (71.1%).

The most common organism was *E. coli* with a frequency of 42(43.2%) almost half

were ESBL strains 20(20.6%) followed by *Klebsiella* 15(15.4%) among which 5(5.2%) were ESBL strains while *Pseudomonas aeruginosa* was 12(12.3%).

The least common organism among gram negative was enterobacter 2(2.6 %) The most common gram positive organisms was *staphylococcus aureus* 12.3 % among which MRSA was 5.2% and MSSA was 7.2 %. The second common organism was enterococcus 9(9.3%) followed by *Staphylococcus epidermidis* 3.09 % and streptococcus SPP 2.1%. (Table# 1)

The sensitivity to ceftriaxone was noted in 33 (34%) and resistant was found in 64 (66%). Among gram positive organisms 12(42.9 %) were sensitive and 16(57.1 %) were resistant to ceftriaxone. While the among gram negative microorganism 21(30.4%) were sensitive while 48(69.6%) were resistant to ceftriaxone but this difference was not statistically different as the p-value was 0.242.

Table 1: Micro-organisms that was Isolated

Type of organism	Frequency	Percent
<i>E. Coli</i> (ESBL)	20	20.6
<i>Staph. Epidermidis</i>	2	2.1
streptococcus SPP	2	2.1
Enterobacter SSP	1	1.0
Enterobacter SSP.(ESBL)	1	1.0
Methicillin resistant <i>staphylococcus epidermidis</i> (MRSE)	1	1.0
<i>Klebsiella</i> (ESBL)	5	5.2
<i>Pseudomonas Aeruginosa</i>	12	12.4
Methicillin Resistant <i>Staph. Aureus</i> (MRSA)	5	5.2
Methicillin Sensitive <i>Staph. Aureus</i> (MSSA)	7	7.2
Enterococcus SPP.	9	9.3
<i>E. Coli</i>	22	22.7
<i>Klebsiella</i>	10	10.3
Total	97	100

Table 2: Cross Tabulation for Sensitivity of Organisms Against Ceftriaxone

		Sensitivity to Ceftriaxone		P-value
		Sensitive	Resistant	
Gram Staining	Gram Positive	12	16	0.242
		42.9%	57.1%	
	Gram Negative	21	48	
		30.4%	69.6%	

Discussion

SPB is a serious complication of liver cirrhosis. Its reported mortality is up 90 % without treatment. Therefore, early recognition, high index of suspicion and prompt treatment is necessary. There are various methods to diagnosed SBP including ascetic fluid routine analysis, strip method and blood culture bottle method at bed side. Even treatment can be initiated on clinical suspicion but before treatment diagnostic ascetic tap is mandatory. Even American society for study of liver disease (ASSLD) has recommended that every hospitalized patient with ascites should have diagnostic ascetic tap as 10 to 30 % of patients with asymptomatic ascites have SBP. For this reason, it should be a standard practice everywhere. Blood culture bottle method at bed side has significantly increased the culture yield up to 80 % as compared to conventional methods. Ascetic fluid culture is necessary before giving antibiotics. A single dose of ceftriaxone is sufficient to decrease cultures yield up to 84 %. As there is evidence of resistant pathogens and more evidence of resistance to third generation cephalosporin it is important to get culture before giving antibiotics. There is also change in the pathogens of SBP and there is a trend toward gram positive bacteria. This is due to invasive procedure like endoscopies and over use of antibiotics. In order to check these two possibilities, we conducted our study to look for any change in pathogens towards gram positive bacteria

and sensitivity pattern of ceftriaxone against various organisms.

In our study the most common organisms responsible for SBP are gram negative organisms which are almost identical to local and international data. The total number of gram positive organisms which were isolated from ascetic fluids was 28(28.9%) and gram negative organisms were 69 (71. 1%).Gram negative organisms are still the commonest pathogens of causing SBP in cirrhotic patients. The incidence of gram positive and gram negative organisms in our study are comparable with local and international data with slight variation in different studies. Haider et al reported gram negative pathogens 60% and gram positive organisms up to 30 %. Mukhtar et al reported gram negative pathogens up to 52.63% and gram positive up to 36.84 %. Which are comparable to our study. In the study (Kamani L et al 2008) in AKU the overall gram positive organism was 391.8% and gram negative 60.7%.

The most common organism’s organism in our study was E. coli 43.2 % (n = 42) almost half were ESBL strains 20.6 %(n = 20) followed by Klebsiella 15.4% (n =15) among which 5.2% were ESBL strains (n =5) while Pseudomonas aeruginosa was 12.3 %(n =12). The least common organism among gram negative was Enterobacter 2.6 % (n= 2). The most common gram positive organisms in our study were staphylococcus species 15.5 % among which MRSA was

5.2% and MSSA was 7.2 %, staphylococcus epidemidis 2.1%, and methicillin resistant staphylococcus epidermidis (MRSE) 1 %. The second common organism was enterococcus 9.3% (n =9) followed by streptococcus SPP 2.1% (n =2). Local data suggest that streptococcus is common pathogen among gram positive organisms. Iqbal S et al reported streptococcus 18.60%, (Kamani L et al, 2008) 11.3 %. This change in our study could be due to contamination of ascetic fluid with skin flora due previous attempts of abdominal paracentesis and also due to unsterile technique.

There is evidence that gram positive organisms are becoming increasing in ascetic fluid infections. This is due to selective gut decontamination by antibiotics such as quinolones as well various invasive procedures. This is supported by study conducted in Copenhagen by Novovic et al in which positive cocci were 45.9% and Enterobacteriaceae were 31.7%.⁷ Similar changes was also observed in study conducted by Gou YZ et al in northern china.⁶ In our study there was no increase in positive organisms this might be due to the fact that most of our population did not undergo invasive procedure and prophylaxis for SBP in our population was not common. It is important to conduct further studies in such population to know about this change in trend towards gram positive bacteria.

The frequency of Ecoli is quite variable from different studies in our country. Kamani et al reported E. coli 61.3%, Iqbal S et al reported 58.13 % Haider et al reported Ecoli 30% which is low. Soriano et al reported E. coli 50% in his study which comparable to our study.^{2, 63, 5, 64} The study conducted in Copenhagen which was published in Scandinavian journal of gastroenterology in which Novovic et al

reported E. coli 16.55 % which is very low.⁷ In our study almost half of the isolates of E. coli were ESBL strains which are extended spectrum beta lactamase producing strains which is an unusual finding pointing towards the development of highly resistant strain of gram enterobacteriaceae. These unusual findings which might be due to urinary catheterization, previous use of antibiotics, central venous lines, previous hospital admission and invasive procedures. These patients with ESBL strains have high hospital mortality which has observed in study conducted by cheol- in Kang et al.⁶⁵ It is important to conduct a large study to look for various factors responsible for emergence of ESBL strains and their antibiotic sensitivity as these organisms are highly resistant and having high mortality.

The total number of patients with positive ascetic fluid culture were 97. The total number of gram positive organisms which were isolated from ascetic fluids was 28 (28.9%) and gram negative organisms were 69 (71.1%). The total number of sensitive organisms to ceftriaxone was 33 (34%) and resistant organisms were 64 (66%). There is no difference in the sensitivity and resistant pattern of gram positive organisms. When Chi square test was applied to check this difference it was found that there was no difference with P value of 0.24 which was not significant statistically. Among gram positive organisms 42.9 % were sensitive (n =12) and 57.1 % (n = 16) were resistant to ceftriaxone. While the percent sensitivity and resistance among gram positive organism to ceftriaxone was 36.4 % and 25 % respectively. The total number of sensitive and resistant organisms among gram negative organisms were 21 (30.4%) and 48 (69.6%) respectively. The percent sensitivity and resistant of gram negative organisms were 34 % and 66% respectively.

The commonest organism in our study was E. coli. Two types of E. coli were isolated. E coli ESBL was 100% resistant to ceftriaxone while non ESBL strain was 27.3% sensitive and 72.7 % resistant to ceftriaxone. Among gram positive organisms Staphylococcus coccus epidermidis and streptococcus Spp have 100 % sensitivity to ceftriaxone, methicillin sensitive staphylococcus aureus (MSSA) has 85.7% sensitivity, enterococcus Spp have 22.2 % sensitivity while methicillin resistant staphylococcus aureus (MRSA) and Methicillin Resistant Staphylococcus epidermidis are 100% resistant to ceftriaxone in our study. There is high percentage of resistant organisms as compared to local and some international data. In study conducted in AKU Kamani L et al reported that overall resistant to ceftriaxone was 29.5 % and there was 22% resistance to gram negative organisms and 50 % to gram positive organisms. The sensitivity of gram positive organisms is comparable to our study but gram negative organisms in our study are showing very high percentage of resistance which is quite high. This high percentage of resistance is due to high prevalence of ESBL strains in both E coli and Klebsiella. Almost half of the isolates among E. coli were ESBL. The second reason might be due to high incidence of nosocomial or health care associated SBP in our study. The study conducted by Ariza X et al 66 showing high resistance of SBP pathogens to ceftriaxone up to 59.1% in nosocomial acquired SBP.

There is growing evidence of resistance to ceftriaxone against various pathogens of SBP in liver cirrhosis patients across the globe. We need further research work to know the ideal broad spectrum antibiotics in patients with SBP especially in patients with high risk of resistant to cephalosporin's. This will help to reduce the mortality of

patients with SBP which is a serious complication of liver cirrhosis

Limitations of Study

This was a single center study. In our study we did not categorize the high risk population such as patients having community acquired SBP or nosocomial, whether they have central venous lines, catheterizations, previous use of antibiotics, underwent invasive procedures or not. These factors can alter microbial sensitivity and some of the factors are associated with high incidence of gram positive bacteria in SBP.

Conclusion

No increasing trend of gram positive pathogens was observed, however ESBL strains are emerging pathogens. Gram negative organisms are still the common pathogens of SBP. Both gram positive and gram negative organisms have equal sensitivity and resistance pattern to ceftriaxone. There is increasing trend of resistance to ceftriaxone which should be replaced with another broad spectrum antibiotic. Knowledge of ascitic fluid pathogens in particular population is important in selecting appropriate antibiotics.

Conflict of Interest

N/A

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