Cefotaxime Resistance in Treatment of Spontaneous Bacterial Peritonitis

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Abstract: Background: Antibiotic-resistant microorganisms have been increasingly reported especially to cefotaxime in treating spontaneous bacterial peritonitis (SBP). **Objectives***:* To evaluate the recent changes in the profiles of microorganisms and cefotaxime effectiveness in treating SBP in Egyptian patients and listing of other antibiotics that can be used as its treatment. **Methods:** 254 cirrhotic patients with clinical suspicious of ascitic fluid infection were classified according to polymorphonuclear leukocytic count and culture to the following: 50 patients (19.6%) were diagnosed as SBP (group I), 161 patients (63.3%) were diagnosed as culture negative neutrocytic ascites (group II), 2 patients (0.7%) had monomicrobial non-neutrocytic ascites (group III), and 41 patients (16.1%) had no evidence of ascitic fluid infection (group IV). Treatment with cefotaxime, as 2gm intravenously every 8 hours started for 5 days. Clinical and biochemical response to cefotaxime was assessed with alternative antibiotics according to culture and sensitivity. **Results:** The isolated organisms found in group I were; Escherichia coli [64%], *Staphylococcus aureus* (coagulase negative) [16%], Citrobacter [12%], Klebsiella [2%], Proteus [2%], *Staphylococcus aureus* (coagulase positive) [2%] and Enterococci [2%]. In group III, *Escherichia coli* was found in 2 patients. Amikacin was found to be the most sensitive antibiotic (71.1%) followed by imipenem (44.2%). While in group I the isolated organisms were sensitive to cefotaxime in (34%) and only one isolated *E. coli* was sensitive to cefotaxime in group II. **Conclusion**: Cefotaxime effectiveness in treating SBP in Egyptian patients had been decreased and failure rate reached (66%) and isolated organisms mostly *in vitro* sensitive to amikacin.
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1. Introduction

Spontaneous bacterial peritonitis (SBP) is a serious complication in cirrhotic patients, and the changes in the microbiological characteristics reported in the last years are impacting the choice of antibiotic used in the treatment (Ozmen *et al.*, 2006). Cefotaxime has been the most extensively studied antibiotic for this infection. It is considered to be one of the first choice antibiotics because of low toxicity and excellent efficacy (Ozmen *et al.*, 2006). Treatment of SBP by intravenous cefotaxime should be administered for a minimum 5 days (Garcia-Tsao *et al.*, 2001)**.** Antibiotic-resistant microorganisms have been increasingly reported especially to cefotaxime and its effect on the clinical outcome in treating SBP (Almeida *et al.,* 2007; Park *et al., 2007)*.

Objectives

The aim of the present study was to evaluate the recent changes in the profiles of microorganisms and cefotaxime effectiveness in treating SBP in Egyptian patients and listing of other antibiotics that can be used as a treatment of SBP.

2. Patients and Methods

Patient Selection

Patients with chronic liver disease and ascites, with clinical suspicious of ascitic fluid infection, were admitted to liver unit, Nasser Institute Hospital for research and treatment. Fifty patients with SBP were selected for our study with the following inclusion criteria: Ascitic fluid sample shows polymorphnuclear leucocytes count equal or more than 250 cells/mm^3 and bedside culture of ascitic fluid showing only one isolated organism. Patients were excluded if they received antibiotics ten days prior to the hospital admission or there is evidence of secondary bacterial peritonitis, tuberculous peritonitis, malignant ascites or ascites due to other causes e.g. cardiac or renal diseases.

Study Design

All patients were subjected to the following: Full history taking, thorough clinical examination, laboratory investigations: Eight ml of venous blood were withdrawn from every patient and were divided in three tubes: EDTA tube for complete blood picture using Beckman Coulter Counter (HmX Hematology Analyzer, Coulter Corporation, Miami, FI 33116-9015), two ml were collected in citrate treated tubes for prothrombin time and the third tube was plain tube to be clotted and centrifuged; the yielding serum was collected and stored at -20˚C till the time of use. Serum was used for detection of liver function tests, renal function tests and serum electrolytes (on synchron CX7 autoanalyzer, Beckman Instruments, Brea, California, USA). Abdominal ultrasonography was done for all

patients by using (ALOCA) device, abdominal probe (3.5 MHz) and all patients were classified according to Modified Child-Turcotte-Pugh classification for cirrhosis (Pugh *et al.,* 1973). Ascitic fluid samples were aspirated under complete aseptic conditions. The needle was introduced in the midline between the umbilicus and the symphysis pubis in the area of maximum dullness to percussion. This site is of fewer collaterals and carries less risk of abdominal wall haematoma. All areas of scarring were avoided since they are often the site of collateral vessels formation or adherent bowel (Runyon, 1986). The aspirated samples were checked for total cell count and polymorphonuclear leucocyte count (PMN) using hemocytometer and microscopic method. In patients with hemorrhagic ascites or in those with traumatic paracentesis, an adjustment of the cell count should be made to account for the presence of blood in the ascitic fluid. This is done by subtracting one polymorphonuclear cell for every 250 red blood cells in the ascitic fluid (Rimola *et al.,* 2000; Angeloni *et al.,* 2003; Parsi *et al.,* 2004). Biochemical assay of total proteins, glucose, lactate dehydrogenase (LDH) levels, ascitic fluid albumin (on synchron CX7 autoanalyzer, Beckman Instruments, Brea, California, USA) and serum-ascites albumin gradient were calculated. Bacteriological culture using aerobic and anaerobic standard blood culture bottles which were inoculated with 10 ml of ascitic fluid at the bedside (Runyon *et al.,* 1990) and then placed in the BacT/ALERT instrument, each bottle contains a sensor which responds to the concentration of CO_2 produced by the metabolism of microorganisms or the consumption of oxygen needed for the growth of microorganisms. The sensor is monitored by the instrument every ten minutes for an increase in its fluorescence, which is proportional to the increasing amount of CO_2 or the decreasing amount of O_2 present in the bottle: A positive reading indicates the presumptive presence of viable microorganisms in the vial. Isolated organisms were identified by microscan (automated biochemical reactions). Discard all negative bottles after 5 days incubation and issue a negative report. Treatment with cefotaxime, as empirical treatment with maximum dose 2gm intravenously (IV) every 8 hours started just after taking ascitic fluid sample for 5 days. Ascitic fluid total cell count and polymorphonuclear leucocyte count after 5 days were repeated to assess the response to cefotaxime (Rimola *et al.,* 2000) or usage of alternative antibiotic according to culture and sensitivity.

Statistical Methods

The data were processed and analyzed using the program Statistical Package for Special Sciences (SPSS) version 16. Description of quantitative variables was expressed in the form of Mean ± Standard deviation (mean ± SD). Description of qualitative variables was expressed by frequency and percentage. Comparison of quantitative variables was carried out by using student t-test for parametric data and one way ANOVA for comparison of more than two groups. Comparison of qualitative variables was carried out by using Chi-square test. $P < 0.05$ was taken as significant.

Ethical Considerations

The study was approved by ethics committee of Ain Shams University and patients gave their written informed consent to participate.

3. Results

Two hundred fifty four (254) patients with liver cirrhosis and ascites and clinical findings suspicious of ascitic fluid infection were admitted to the liver unit, Nasser Institute for research and treatment and underwent abdominal diagnostic paracentesis. They were classified according to polymorphonuclear leukocytic (PMN) count cells/mm³ and culture to the following: 50 patients (19.6%) were diagnosed as SBP (group I), 161 patients (63.3%) were diagnosed as Culture negative neutrocytic ascites (CNNA) (group II), 2 patients (0.7%) had monomicrobial non-neutrocytic ascites (MNBA) (group III), and 41 patients (16.1%) had no evidence of ascitic fluid infection (group IV).

Age and gender of studied groups were comparable in Table 1. There were no statistical significant difference between the studied groups as regards age and sex. Also clinically, table 1 shows no statistically significant difference between the studied groups regarding fever, hepatic encephalopathy without any identified precipitating factor except ascitic fluid infection, modified Child-Turcotte-Pugh classification and history of gastrointestinal bleeding (P >0.05). But on abdominal examination, there was statistically significant abdominal tenderness in all groups in comparison to group IV (P <0.05).

Regarding laboratory parameters, table 2 shows that total leukocyte count (TLC), total bilirubin, serum albumin and ascitic fluid glucose were statistically significant different in groups I, II, III in comparison to group IV (P <0.05).

Table 3 shows isolated organisms with their antibiotic sensitivity in groups I and III. By using gram stain 40 patients (80%) in group I were gram negative and 10 patients (20%) were gram positive. By using the BacT/ALERT culture system *Escherichia coli* (*E. coli*) was present in 32 patients (64%), Citrobacter was present in 6 patients (12%), Klebsiella was present in 1 patient (2%) and Proteus was present also in 1 patient (2%). *Staphylococcus aureus* (coagulase negative) was present in 8 patients (16%), *Staphylococcus aureus* (coagulase positive) was present in 1 patient (2%), Enterococci was present in 1 patient (2%) and no

anaerobes were detected. In group III, only 2 patients and their culture reveal Escherichia coli.

Amikacin was found to be the most sensitive antibiotic with sensitivity (71.1%) in 37 cases and imipenem was sensitive in 23 cases (44.2%). It was found that in group I the isolated organisms were sensitive to cefotaxime in 17 cases (34%), while isolated organisms from 33 cases (66%) were resistant. In group II only one of the isolated *E.coli* from both patients was sensitive to cefotaxime. Those 18 patients were clinical and biochemically improved after five days of cefotaxime treatment. A follow up ascitic fluid sample was taken and analyzed from patients of group I which showed PMN cell count<250 cells/mm³.Chloramphenicol was sensitive in 16 cases (30.7%), ciprofloxacin was sensitive in 12 cases (23%) and both vancomycin and cefoperazone were sensitive in 10 cases (19.2%).

According to culture and sensitivity in group I when the organism was *E. coli* the most sensitive antibiotic was amikacin (75%) while cefotaxime sensitivity was (31%). When the organism was Citrobactar the most sensitive antibiotics was amikacin (66.6%) and cefotaxime sensitivity was (16.6%).When the organism was Klebsiella the most sensitive antibiotic were amikacin and cefotaxime (100%). When the organism was Proteous the most sensitive antibiotic were amikacin, ciprofloxacin and cefotaxime (100%). When the organism was *Staphylococcus aureus* (coagulase negative) the most sensitive antibiotics were amikacin, vancomycin and cefoperazone (62.5%) and cefotaxime sensitivity was (37.5%). When the organism was *Staphylococcus aureus* (coagulase positive) the most sensitive antibiotics were vancomycin (100%) and Cefotaxome sensitivity was (0%). When the organism was Enterococci the most sensitive antibiotics were vancomycin, cefoperazone and cefotaxime (100%). In group III, only 2 patients and their culture reveal *Escherichia coli* and the most sensitive antibiotics was amikacin, imipenem and ciprofloxacin (100%) while cefotaxime sensitivity was (50%).

Table 1: Demographic and clinical features of all patients

Variable	Group I (N=50)	Group II (N=161)	Group III (N=2)	Group IV (N=41)	*P* value
Age	54.46 ± 8.77	56.43 ± 8.355	48 ± 8.485	53.46 ± 7.44	
Male	35 (70)	99 (61.5)	1 (50)	25 (61)	
Female	15 (30)	62 (38.5)	1 (50)	16 (39)	NS
Fever	25 (50)	76 (47.2)	1 (50)	22 (53.7)	
Hepatic Encephalopathy	29 (58)	64 (39.8)	1 (50)	19 (46.3)	
Gastrointestinal bleeding	7 (14)	28 (17.3)	0 (0)	9 (21.9)	
Child B	4 (8)	11 (6.8)	0 (0)	4 (9.7)	
Child C	46 (92)	150 (93.2)	2 (100)	37 (91.3)	
Abdominal tenderness	45(90)	96 (59.6)	2 (100)	13 (31.7)	<0.05

Data are Mean ± Standard Deviation N (%)

Table 2: Laboratory investigations of studied patients

Variable	Group I (N=50)	Group II (N=161)	Group III (N=2)	Group IV (N=41)	*P* value
TLC (x10³/mm³)	9.9±4.9	8.7±0.08	10.5±0.7	6.2±1.7	<0.05
Hemoglobin (gm/L)	10.3±1.8	9.9 ± 2.02	12 ± 1.4	12.8±17.7	
Platelet count (x10³ / mm³)	94.4±65.8	101.05±95.7	121±1.4	100.2±40.7	NS
Total bilirubin (mg/dl)	3.6±2.4	4.5±3.1	6.7± 0.3	2.3±3.2	<0.05
Albumin (gm/dl)	2.1±0.4	2.004±0.3	2.1±0.2	2.3±0.5	<0.05
ALT (IU/L)	31.7±10.9	36.4±22.5	53.3±18.1	33.1±21.6	
AST (IU/L)	34.3±10.7	37.4±21.8	37±4.2	35.2±19.5	
INR	1.9±0.5	3.1±7.1	1.6±0.4	1.9±0.6	
BUN (mg/dl)	37.5±25.2	38.2±24.9	49.5±7.7	33.2±21.2	
Creatinine (mg/dl)	1.2±0.5	1.2±0.4	1.1±0.1	1.2± 0.4	
Sodium (mmol/l)	131.4±5.6	128.2±17.2	130±9.8	132.7± 9.3	
Potassium (mmol/l)	4.1±0.7	3.9±0.8	3.5±0.7	4.1±0.8	
Ascitic fluid: Total proteins (gm/dl)	1.6±0.4	1.9±1.8	0.9±0.07	1.6±0.3	
LDH (IU/L)	135.1±91.7	135.6±67.5	128±0.07	129.8±82.8	
SAAG	1.2±0.1	1.2±0.09	1.1±0.07	1.2±0.08	NS
Glucose (mg/dl)	106±43.8	104.9±38.9	110.5±0.7	135.6 ±3.4	<0.01

Data are Mean ± Standard Deviation

TLC: Total leukocyte count; ALT: Alanine transaminase; AST: Aspartate transaminase; INR: International normalized ratio; BUN: Blood urea nitrogen; LDH: Lactate dehydrogenase; SAAG: Serum-ascites albumin gradient

Table 3: Organisms detected by the BacT/ALERT culture system and gram staining with their antibiotics sensitivity pattern for each isolated organism

Species	Amikacin	Imipenem	Cefotaxime	Chloramphenicol	Ciprofloxacin	Vancomycin	Cefoperazone
Group I (SPB)							
Gram negative (N=40)							
Escherichia coli (N=32)	24(75)	18(56.2)	10(31)	10(31)	7(21.8)	2(6.25)	2(6.25)
Citrobactar (N=6)	4(66.6)	2(33.3)	1(16.6)	2(33.3)	1(16.6)	1(16.6)	1(16.6)
Klebsiella (N=1)	1(100)	0(0)	1 (100)	0(0)	0(0)	0(0)	0(0)
Proteous (N=1)	1(100)	0(0)	1 (100)	0(0)	1(100)	0(0)	0(0)
Gram positive (N=10)							
Staph-coagulase negative (N=8)	5(62.5)	1 (12.5)	3(37.5)	3(37.5)	1(12.5)	5(62.5)	5(62.5)
Staph-coagulase positive (N=1)	0(0)	0(0)	0(0)	0(0)	0(0)	1(100)	0(0)
Enterococci (N=1)	0(0)	0(0)	1(100)	0(0)	0(0)	1(100)	1(100)
Group III (MNBA) *Escherichia coli* (N=2)	2(100)	2(100)	1(50)	1(50)	2(100)	0(0)	1(50)
Total (N=52)	37(71.1)	23 (44.2)	18 (34)	16 (30.7)	12 (23)	10 (19.2)	10 (19.2)

N (%)

4. Discussion

Starting with 1985, after some clinical studies, cefotaxime has been considered the first choice empiric antibiotic in SBP treatment (Felisart *et al.,* 1985; Runyon *et al.,* 1991; Rimola *et al.,* 2000). It covered 95% of the flora isolated from ascitic fluid and achieves high ascitic fluid concentrations during therapy (Runyon and American Association for the Study of Liver Diseases Practice Guidelines Committee, 2004).

Antibiotic-resistant microorganisms have been increasingly reported especially to cefotaxime and its effects on the clinical outcome in treating SBP (Park *et al.,* 2003; Almeida *et al.,* 2007; Park *et al.,* 2007).

The prevalence of SBP in cirrhotic patients with ascites ranges between 10%and 30% (Rimola and Navasa, 1999). Angeloni *et al.* (2008) reported the prevalence of SBP was 17%, which is similar to our study (19.6%). Differences in frequency of occurrence of SBP are possibly related to differences in etiological factors of chronic liver disease in various geographical areas with different patients' criteria of selection.

In the present study, incidence of SBP was found not related to age and sex, in agreement with other study (Puri *et al.*, 1996).

Regarding clinical examination of studied patients, the most frequently encountered symptoms and signs of SBP were fever (50%) and abdominal tenderness (90%) which coincides with various studies (Webster *et al.,* 1996; Kaymakoglu *et al.*, 1997; Angeloni *et al.*, 2008). As with end stage liver disease, patients may be mildly hypothermic and immunocompromised so absence of fever in these patients, points to the importance of considering SBP even in asymptomatic patients in order not to miss this serious infection (Hoefs and Runyon, 1985).

In current study, no statistical difference was found among studied groups regarding hepatic encephalopathy. Hepatic encephalopathy is a frequently overlooked symptom in SBP patients; this is due to release of different pyrogens which make disturbance of blood brain barrier. But hepatic encephalopathy could be also precipitated by different causes other than SBP (McHutchison and Runyon, 1994; Parsi *et al.,* 2004).

SBP has been related to variceal bleeding in terms of increasing portal pressure (Goulis *et al.*, 1999). Also

SBP can be reduced by prompt antibiotic prophylaxis in cirrhotic patients with gastrointestinal bleeding (Bernard *et al.*, 1999). A possible explanation being that the hemorrhagic shock increases bacterial translocation, and intestinal permeability (Runyon, 1993). However our study results did not confirm this relationship.

SBP occurs due to bacterial translocation, mainly in patients with advanced cirrhosis and severe liver functional damage (Levison and Bush, 2005; Tandon and Garcia-Tsao, 2008; Zhang *et al.*, 2010); this is confirmed in this study as SBP developed more in patients with child class C than class B.

Various studies have shown that, examination of the blood picture, in patients with SBP, usually reveal peripheral leukocytosis (Kaymakoglu *et al.*, 1997; Sherlock and Dooley, 2002) which was confirmed by our study.

In the present study, as regard the mean serum albumin concentration, it was statistically significant lower in ascitic fluid infection groups, in comparison to non ascitic fluid infection group, the same like other studies (Gonzalez and Kannewurf, 1998; Thanopoulou *et al.*, 2002).

As regard serum total bilirubin, it was found higher in groups I, II, III (ascitic fluid infection) than group IV (no ascitic fluid infection). Our study serum total bilirubin results agreed with Cireraet *et al.* (2001) who found that a serum bilirubin level more than 2.5 mg/dl is an independent predictive factor of SBP.

As regard the ascitic fluid chemistry of our studied patients, ascitic fluid glucose concentration was the only statistical significant different variable among studied groups. It was much lower in SBP than in non ascitic infection group in agreement with a study which showed that glucose concentration in the ascitic could be consumed by bacteria and stimulated white blood cells during uncontrolled infection. In gut perforation, the ascitic fluid glucose level can drop to zero mg/dL (Akriviadis and Runyon, 1990).

Insignificant SAAG ratio among studied groups in our study indicates good selection of our patients by exclusion of other cases with ascites due to other causes.

Regarding organisms isolated in our study, gram negative bacteria were the most frequent (42/52; 80.7%) and E. coli was the most predominant; however Gram positive bacteria were isolated in 10 patients. This agree with Abdelkader *et al.* (1995) found that E. coli was present in 39.6 % of SBP patients. Lipka *et al.* (1998) found that E. coli were the most common organisms isolated in his study. Butani *et al.* (2004) stated that E. coli and citrobacter were the most frequent bacteria isolated from the infected ascitic fluid. This can be explained that *E.coli* stains can translocate the intestinal mucosa more often, probably because of a higher capacity to adhere to it and because of a higher virulence that determines a higher resistance to the defense mechanisms of the host (Guarner *et al.,* 1997). Although the bowel flora is predominantly anaerobic, SBP is very seldom produced by anaerobic microorganisms due to their incapacity to translocate the intestinal mucosa and due to the high volume of oxygen in the intestinal wall and in the tissues that surround it (Caruntu and Benea, 2006).

After five days of cefotaxime treatment (2gm IV, every 8 hours) clinical data and ascitic fluid cell count were followed and analyzed. Cefotaxime, as suggested, the first-line empiric antibiotic treatment failed clinical and biochemically in 66% of our cases and organism were not sensitive to cefotaxime in vitro culture and sensitivity. The need for changing antibiotic treatment is higher than that reported by Badawy *et al.* (2013) which was (19%) and Chen *et al.* (2005) was (21.1%) and Angeloni *et al.* (2008) was 40%. The failure of cefotaxime is probably due to the fact that the isolated organisms were primary resistant to cefotaxime or capable of degrading the expanded-spectrum cephalosporins such as (ESBL-producing *E. coli)*. Other explanation came from the fact that cirrhotic patients have frequent need of hospital assistance including outpatient visits, diagnostic invasive examinations and day-hospital admissions which may facilitate contact with nosocomial antibiotic-resistant pathogens.

In our present study and according to culture and sensitivity the most sensitive antibiotics were amikacin and imipenem (71.1% and 44.2% respectively). Amikacine were more sensitive against *E. coli*, Citrobacter, *Staphylococcus aureus* (coagulase negative), while Imipenem were more sensitive against *E. coli* and Citrobacter. This disagrees with a randomized study (Chen *et al.,* 2005) which showed that amikacin was less sensitive than cefotaxime *in vivo*. The explanation for this is probably due to the fact that our study was done only by using of cefotaxime *in vivo* and the isolated organisms were sensitive to amikacin only *in vitro*, or may be due to the geographical difference between the two studies.

Finally, it is important to conclude that cefotaxime effectiveness in treating SBP in our Egyptian patients had been decreased and failure rate reached (66%) and isolated organisms mostly in vitro sensitive to amikacin. Further studies needed to asses amikacin as an empirical treatment for SBP.

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