

# Effect of Cefepime in Patients with Cirrhosis and Spontaneous Acid Infection



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Eur J Gen Med 2010;7(1):63-68

## ABSTRACT

**Aims :** In this study in cirrhosis patients having spontaneous ascites infection (SAI) the investigation of the activity of cefepime being a fourth generation cephalosporin was aimed.

**Method:** 19 patients diagnosed as cirrhosis and having acid infection were taken into the study. Cefepime doses were given to all patients having SAI by adjusting according to the clearance of creatinine, in intervals of 12 hours, in 2 gram as parenterally. Cell counting was made in acid liquid on the 1st, 3rd and 5th days. In the patients who had reproduction in acid liquid culture, antibiogram was made with cefepime and other antibiotics.

**Result:** Age average of patients was 55 years (between 42-73 years). Cirrhosis was secondary to hepatitis B virus infection in 10 patients, to hepatitis C virus infection in 7 patients and to autoimmune hepatitis in 2 patients. On the first day the average cell number in the ascites was 5077/mm<sup>3</sup> (between 530-12400/mm<sup>3</sup>), PMNL number was 3861/mm<sup>3</sup> (between 320-9600/mm<sup>3</sup>). On the third day the average cell number in the ascites was 1847/mm<sup>3</sup> (between 300-7680/mm<sup>3</sup>) and PMNL number was 1025/mm<sup>3</sup> (between 120-3840/mm<sup>3</sup>) ( $p<0.001$ ). Fifth day ascites liquid the average cell number was 548/mm<sup>3</sup> (between 160-1600/mm<sup>3</sup>) and PMNL number was 267/mm<sup>3</sup> (between 80-620/mm<sup>3</sup>) ( $p<0.001$ ). The cefepime resistance in antibiogram was observed only on one patient against E.coli strain.

**Conclusions:** Cefepime, which is a fourth generation cephalosporin, was found out effective in SAI developing on cirrhotic ground.

**Key Words:** Spontaneous ascites infection, cefepime, cirrhosis

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## INTRODUCTION

Ascites is defined as pathological liquid accumulation in peritoneum cavity (1). Ascites infection in that it is not surgically determined a treatable abdominal infection focal is called spontaneous ascites infection (SAI) (2). It is also called primary peritonitis (3). Within one year two of every three cirrhosis patient having SAI is caught again by the infection and their mortality increases (2-40%) (4,5). When suitable treatment is made, mortality speed significantly decreases (6,7). In hospitalized patients with ascites the SAI prevalence is between 10-30% (8,9). SAI composes of 7-23% of all infections seen in patients with cirrhosis (10). Today SAI pathogenesis is explained with translocation theory (11). During and after gastrointestinal bleeding, hypovolemia occurring due to the increase in bacterial translocation from intestinal lumen to mesenteric lymph veins and due to bleedings leads to disorder in phagocytic activity of RES and so make the development of bacterial infections easy. As a result of this, complement in acid liquid and other antimicrobial factors decrease dilutionally and this makes SAI development easy (12). The successful use of diagnostic and prophylactic antibiotherapeutic methods has recently reduced mortality ratio to 20's %. In a patient living a SAI attack yearly recurrence ratio in 70%. Since in cirrhotic patients the ascites culture positivity has quite decreased in consequence of long term use of antibiotic prophylaxes and irregular antibiotic use, that polymorphonuclear leukocyte (PMNL) number is above 250/mm<sup>3</sup> is adequate for diagnosing SAI (9). The specificity of PMNL number is 96%, sensitivity 83% and diagnosis value 92% (9). In the studies made, in approximately 60% of patients with SAI, micro-organism can not be isolated in the culture (13). In the culture positive patients, 89% a single micro-organism is produced. *Escherichia coli* (*E.coli*) and *Klebsiella pneumoniae*. Anaerobe factor was determined only in 1% of all patients with SAI (13). In SAI treatment especially the third generation cephalosporins are the first preferred antibiotics. The application of cephalexin for at least 5 days 4-8 gr per day is the treatment method most often applied in the last years (14). It is seen that in the world in patients being bacteraemia the *Enterobacter* and *Klebsiella* group bacteria among enteric bacteria dominate *E.coli* increasingly and the resistance in increasing ratios is detected (15,16). In various studies made in our country, while there were lower resistance ratios in *E.coli*, in *Enterobacter-Klebsiella* group bacteria it was declared higher resistance ratios between ceftazidim 26-59% and cephalexin 83-91% (17-19). Other studies also

show that cefepime is quite effective on these bacteria (17,20). Cefepime, which is the fourth generation cephalosporin and has wide spectrum, due to its high affinity to proteins bonding penicillin, can quickly penetrate into the bacterium from porin channels in outside membranes of Gram-negative bacteria (21). Since  $\beta$ -lactamases synthesized under the control of plasmid and chromosome show lower affinity to cefepime, cefepime is resistant against these enzymes (22). As a result, cefepime being the first member of the fourth generation cephalosporins has an effective use on other peritonitis types like secondary peritonitis (23-25). However in the literature there isn't too many data concerning the use and effectiveness of cefepime on SAI. In this study it was aimed to determine the effect of cefepime, which has gram-positive effect but especially gram-negative effect and is a fourth generation cephalosporin, and contribute to the literature.

## MATERIAL AND METHODS

Before the study, for this clinical study, the research confirmation numbered KA03/27 was taken from the Baskent University Medical Faculty Research and Ethics Board. Cirrhotic patients being supervised in Gastroenterology Clinic were taken into the study and SAI was researched in cirrhotic patients with ascites. In ascites liquid the cell numbers above 250 PMNL/mm<sup>3</sup> were accepted SAI. 10 cc acid sample from these patients was synchronously poured into standard blood culture bottle at the bedside. Cefepime doses were adjusted according to the clearance of creatinine and then given to SAI patients once in every 12 hours as 2 gr intravenously for short time (5 days). For evaluating the response to the treatment, on the 1st, 3rd and 5th days in ascites liquid the total leukocyte and PMNL were counted. Child-Pugh phasing of patients was made. 19 patients in that there was liver disease diagnosis and acid infection developed were taken into the study. 11 of them were male and 8 were female. In the patients whose acid liquid culture has reproduction, antibiogram was made with cefepime and other antibiotics (ceftazidim, erythromycin, ampicillin, sulbactam-ampicillin, ceftiofur, cefturoxime, ceftazidim, ceftazidim, aztreonam, gentamicin, tobramycin, ciprofloxacin, imipenem, meropenem and amikacin). Antibiotic sensitivities were evaluated with disc-diffusion method according to criteria of National Committee for Clinical Laboratory Standards (NCCLS) in Muller-Hinton culture.

Ascites Analysis: To prevent the contamination of skin

flora, liquid was transferred into the culture tube after the injection end was changed with new one. The culture was taken at the bedside and the pouring was made into standard hemoculture bottles. In the studies it was shown that the factor isolating ratio reached from 50-57% to 77-80% as proportional to conventional methods (3,26). When we send ascites liquid to the laboratory with injector, reproduction ratio of active micro-organism significantly decreases (3,27). When we put 10 ml acid instead of 1 ml into hemoculture bottle of 10 ml, the culture positivity ratio rises from 53% to 93% (6). So we, in our study, poured 10 ml acid liquid into hemoculture bottles. If bleeding occurs in paracentesis, PMNL number in acid becomes higher than its normal. So since it is necessary to calculate adjusted PMNL number by 1 PMNL number abating for every 250/mm<sup>3</sup> erythrocyte, in our study we paid attention this matter in acid cells counting. In ascites infections, cell counting in an ascites is a quick and reliable examination in ascites infection diagnosis. That PMNL number of ascites is more than 500/mm<sup>3</sup> has quite much diagnostic sensitivity and specificity for ascites infection but the minimum limit is 250/mm<sup>3</sup> in the evaluation of PMNL number. If PMNL number is less than 250/mm<sup>3</sup>, we should be far away from SAI diagnosis (2,3,28).

#### Statistical analysis

The results were obtained as mean  $\pm$  SD. Of the results, only the ones with a P value less than 0.05 were found significant. Data were analyzed using the SPSS for Windows (version 9.05; SPSS, Inc., Chicago, Illinois, USA). In addition, Mann-Whitney U test and the relationship between variables were examined with Pearson and Spearman correlation.

#### RESULTS

19 patients in that liver disease diagnosis was available and ascites infection developed were taken into the study. 11 of them were male and 8 were female. The average age of patients was 55 years (interval; 42-73 years). Cirrhosis was secondary to hepatitis B virus infection in 10 patients, to hepatitis C virus infection in 7 patients and to autoimmune hepatitis in 2 patients. Two patients were in Child-Pugh and 17 patients were in Child-Pugh C phase. As a result of pouring ascites liquid into standard hemoculture bottles, reproduction occurred in 11 (57.9%) out of 19 patients. E.coli reproduced in 6 patients having reproduction, streptococcus in 2 of them, enterococcus in 1 of them and S.aureus in 2

of them. On the first day the average cell number in the ascites was 5077/mm<sup>3</sup> (between 530-12400/mm<sup>3</sup>), PMNL number was 3861/mm<sup>3</sup> (between 320-9600/mm<sup>3</sup>). On the third day the average cell number in the ascites was 1847/mm<sup>3</sup> (between 300-7680/mm<sup>3</sup>) and PMNL number was 1025/mm<sup>3</sup> (between 120-3840/mm<sup>3</sup>) ( $p < 0.001$ ). Fifth day ascites liquid the average cell number was 548/mm<sup>3</sup> (between 160-1600/mm<sup>3</sup>) and PMNL number was 267/mm<sup>3</sup> (between 80-620/mm<sup>3</sup>) ( $p < 0.001$ ). The cefepime resistance in antibiogram was observed only on one patient against E.coli strain. In the culture antibiogram in patients having reproduction the antibiotic resistance ratio results were in this way: erythromycin 33.3%, ampicilline 50%, sulbactam-ampicilline 57%, cefoxitin 33%, cephuroxime 25%, ceftriaxone 20%, cephtazidim 20%, aztreonam 25%, gentamicin 28%, tobramycine 16%, ciprofloxacin 33%, imipenem 0%, meropenem 0%, amicasin 0%, cephotaxim 14.3% and sefepime 0.9% resistance ratios were detected in antibiogram.

#### DISCUSSION

Infections are one of the most important mortality reasons in cirrhotic patients. SAI was detected in 10-30% of cirrhotic patients taken into the hospital due to ascites (9). The successful use of diagnostic and prophylactic antibio-therapeutic methods in the last years has reduced mortality ratio from 57% to 20% (29). In a patient living a SAI attack yearly recurrence ratio is 70% (9). In cirrhotic patients since ascites culture positivity has significantly reduced in consequence of long term use of antibiotic prophylaxes and irregular antibiotic use, that polymorphonuclear leukocyte (PMNL) number is above 250/mm<sup>3</sup> is adequate to diagnose SAI (9). In ascites the specificity of PMNL number for SAI is 96% and sensitivity of it is 83% and diagnosis value 92% (9). In the studies made, in approximately 60% of SAI patients, micro-organism can't be isolated in the culture (13). In our study in 43% patients the reproduction in ascites culture did not occur. In contrary to this, the reproduction occurred in 57% patients. In the studies made, in the culture positive patients, 89% a single micro-organism is produced and Escherichia coli and Klebsiella pneumoniae are the most often met factors (13). In the study we made, in the parallelism of this literature information, E.coli reproduced in 6 out of 11 patients being culture positive. In SAI treatment especially the third generation cephalosporins are the first preferred antibiotics. The most often used ones are cephotaxim and ceftriaxone. The application of cephotaxim at least for 5 days 4-8 gr/day is the

most often applied treatment method in the last years (14). In the other side, the effective use of cefepime, which is the first member of the fourth generation cephalosporins, on other peritonitis types like secondary peritonitis was declared in the literature (23-25). However there is not a study concerning the use and efficiency of cefepime in SAI. The most often suggested treatment in SAI is cephalexin being the third generation cephalosporin. Naturally it is expected that cefepime being the fourth generation will be more effective. In this study, it was aimed to determine the efficiency of cefepime, which gram-positive effect but especially gram-negative effect and is a fourth generation cephalosporin, and contribute to the literature.

In cirrhosis patients spontaneous bacteraemia and peritonitis (SBP) generally develop with enteric bacteria. It is declared that most of SBP cases compose of intestine flora and that they are related with high ascites liquid partial oxygen pressure, anaerobic bacteria's weak translocation abilities from intestinal mucosa and inadequate culture techniques (30,31). While reproduction ratio in the culture is 42-43% with conventional method, it is about 23-91% with inoculation method into standard culture bottles (32). Antibiotics to be chosen according to the culture results are very important. Because the resistance enteric gram-negative bacteria show against antimicrobial agents exhibit increase in our country as in all the world. Especially for bacteria of Enterobacter and Klebsiella group, it is reported that ampicilline, amoxicilline-clavulanic acid and cephalotin have become far away from being used for empiric purpose (15,19). In various studies made in our country, while there were lower resistance ratios in E.coli, it was declared high resistance ratios in Enterobacter-Klebsiella group bacteria between ceftazidim 26-59% and cephalexin 83-91% (17,19). In a study made, in mixed patient groups having hospital infection, the cefepime resistance of patients having bacteraemia and reproduction in blood culture was determined as 9% and 4% in Enterobacter-Klebsiella group bacteria and E.coli, respectively (20). In addition to this drop in PMNL number in ascites liquid, clinical findings of ascites infection decreased in all patients and on the 5th day of cefepime treatment wasn't any clinical symptom such as gripe, fever and peritoneal sensitivity. As understood from these results, cefepime SAI is seen as very effective agent. Other studies also show that cefepime is quite effective in these bacteria (17,20). Cefepime, which

is classified as the fourth generation cephalosporin and has wide spectrum, due to its high affinity to proteins bonding penicillin, can quickly penetrate into the bacterium from porin channels in outside membranes of Gram-negative bacteria (21). Since  $\beta$ -lactamases synthesized under the control of plasmid and chromosome show lower affinity to cefepime, cefepime is resistant against these enzymes. (22). In contrary, the present application in the treatment of SBP is antibiotics most often preferred instead of the third generation cephalosporins being effective on probable pathogens. In the studies made in this direction it was shown that cephalexin was a suitable option since its effect spectrum, reliability and acidity were good (3,33). In addition, it was declared that ceftriaxone and ceftizoxime were effective in the treatment of SBP (34,35). In a study made it was emphasized that amoxicilline-clavulanic acid and ofloxacin had efficiency as well as the third generation cephalosporins (36-38). Cephalexin, in their first studies, was applied in the dose 2 gr/6 hours but later it was determined that the application in the way 2 gr/12 hours had the effect in the same level (treatment success 77% and 79% respectively) (6,39,40). In 75-90% of SBP patients the response to the third generation cephalosporin is got. Among factors negatively affecting the response to the treatment can be said that the infection develops while staying in the hospital, there is renal failure and the age of the hospital is old (8). Yearly mortality ratio of cirrhosis patients having acid infection is 25-40% and iteration ratio is about 60% yearly. So in a patient having acid infection necessary operations should be started for liver transplantation.

As a result, cefepime, which is a fourth generation cephalosporin, was found out effective in SAI developing on the ground of cirrhosis. However in the future for better understanding cefepime efficiency, it should be compared with other medicines, including cephalexin, being effective in SAI and it is needed prospective studies involving great numbers of patients.

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