

# The Efficacy of Trimethoprim-sulfamethoxazole Compared to Ciprofloxacin in The Treatment of Spontaneous Bacterial Peritonitis in Cirrhotic Patients with Ascites

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## ABSTRACT

### Background

*The incidence of spontaneous bacterial peritonitis (SBP) is 7 to 23%, and the associated mortality rate is 25 to 40% (Rimola 1992). The aim of this study was to evaluate the efficacy of trimethoprim-sulfamethoxazole compared to ciprofloxacin in the treatment of SBP in cirrhotic patients with ascites.*

### Materials and Method

*This prospective randomized double blind study included 43 cirrhotic patients with ascites (25 males, 18 females, ages 23-75 years, one female patient died prior to laboratory evaluation) enrolled between May 1999 and June 2000, at the Department of Internal Medicine of Mohammad Hoesin General Hospital /the Medical Faculty of Sriwijaya University of Palembang, South Sumatera.*

*Twenty-three patients (53.4%) with SBP were eligible for the study, all were randomized. Patients were divided into 2 groups (13 in group I, and 10 in group II), those receiving trimethoprim-sulfamethoxazole 960 mg once daily for 10 days and those receiving ciprofloxacin 1000 mg once daily for 10 days. Statistically, there was no significant difference in the characteristics of the 2 groups.*

### Results

*The incidence of SBP in our study was 53.4% (23 patients out of 43 cirrhotic patients with ascites).*

*The results of the study demonstrate that trimethoprim-sulfamethoxazole and ciprofloxacin are both effective (91.6% and 90%) in the treatment of SBP. There was a significant decrease in ascitic fluid PMN count after 10 days treatment with both of the drugs ( $p=0.001$  and  $p=0.000$ ). There was no statistically significant difference ( $t$ -test) between the two groups in decreasing the ascitic fluid PMN count after the treatment ( $p=0.664$ ).*

### Conclusion

*Trimethoprim-sulfamethoxazole and ciprofloxacin has similar efficacy in the treatment of spontaneous bacterial peritonitis in cirrhotic patients with ascites.*

**Key word:** *Trimethoprim-sulfamethoxazole, ciprofloxacin, spontaneous bacterial peritonitis.*

## INTRODUCTION

The incidence of spontaneous bacterial peritonitis (SBP) in patients with ascites was 7 to 23%, and the mortality rate was high (25 to 40%, Rimola 1992).<sup>1</sup>

Empirical antibiotic therapy must be initiated immediately after the diagnosis of the infection is

established, without prior knowledge of the causative organisms and their in vitro susceptibility.<sup>2</sup> Recent studies confirmed the effectiveness of cefotaxime and other third generation cephalosporins, amoxicillin and clavulanic acid as the initial treatment for patients with SBP.

<sup>1,2,3,4,5,6,7</sup> However, in recent years cost-effectiveness has become an increasingly important additional factor in the selection of drug therapy.

Several studies have recently reported the value of antibiotic prophylaxis such ciprofloxacin and trimethoprim-sulfamethoxazole as effective in the prevention of SBP in cirrhotic patients.<sup>8,9,10</sup>

Ciprofloxacin is an antibiotic of the fluoroquinolone group. It is active against the majority of enterobacteria, and above all of aerobic gram-negative bacilli, which account for more than two thirds of all cases of SBP. In addition, ciprofloxacin shares the advantage of the majority of fluoroquinolone of being tolerated, even during long-term treatment, and of having very low liver toxicity.<sup>9</sup>

Trimethoprim-sulfamethoxazole is a systemically absorbed antibiotic with in vitro activity against enteric gram-negative bacteria and streptococci, including pneumococci. It has been used extensively as a prophylactic agent in diverse patient populations (for example, patients with granulocytopenia, transplant recipients, patients with human immunodeficiency virus infection, and patients with spontaneous bacterial peritonitis in cirrhosis).<sup>10</sup>

The aim of this study was to evaluate the efficacy of trimethoprim-sulfamethoxazole compared with that of ciprofloxacin in the treatment of SBP in cirrhotic patients with ascites.

## MATERIALS AND METHODS

This prospective randomized double blind study included 43 cirrhotic patients with ascites (25 males, 18

females, age 23-75 years, one female patients was died before laboratorium examined was performane) enrolled between May 1999 and June 2000, at the Department of Internal Medicine Mohammad Hoesin General Hospital/Medical Faculty of Sriwijaya University of Palembang of South-Sumatera.

The diagnosis of cirrhosis was made using standard clinical, laboratory, ultrasound and endoscopic evaluation of the upper GI tract. The severity of the liver disease was assessed by the Child-Pugh classification. Confirmation of the diagnosis of SBP required analysis of ascitic fluid, obtained by abdominal paracenteses on admission to the hospital. A diagnosis of SBP requires a positive monomicrobial ascitic fluid culture and an elevated ascitic fluid polymorphonuclear (PMN) leucocytes count ( $=250$  cells/mm<sup>3</sup>) and no evident source of infection.

Patients with SBP are divided into two groups: group A received trimethoprim-sulfamethoxazole 960 mg once daily for 10 days (one double-strength tablet) and group B received ciprofloxacin 1000 mg once daily for 10 days. Abdominal parecenteses were repeated on day 11 to determine the ascitic fluid PMN cell count and culture for evaluate the efficacy of both drugs.

The data were evaluated using t-test and SPSS statistic programe for windows version 7.5.

## RESULTS

The characteristics of the forty-three consecutive patients with cirrhosis and ascites were evaluated (see in table 1).

**Table 1. Clinical Characteristics of 43 Cirrhotic Patients with Ascites**

No	Parameter	Mean $\pm$ SD (n = 43)
1.	Age (year)	55.79 $\pm$ 12.30
2.	Sex : Male	25 (59.6%)
	Female	17 (40.4%)
3.	Serum albumin (g/dl)	2.69 $\pm$ 0.57
4.	Serum globulin (g/dl)	4.38 $\pm$ 1.06
5.	Total billirubin (mg/dl)	3.58 $\pm$ 3.54
6.	WBC (cells/mm <sup>3</sup> )	9.517 $\pm$ 4.452
7.	Platelets (mm <sup>3</sup> )	155.047 $\pm$ 89.722
8.	Serum ALT ( $\mu$ /l)	49.69 $\pm$ 50.58
9.	Serum AST ( $\mu$ /l)	37.59 $\pm$ 52.20
10.	Serum ureum (mg/dl)	35.76 $\pm$ 16.86
11.	Serum creatinine (mg/dl)	1.11 $\pm$ 0.58
12.	Protein level in ascitic fluid (g/dl)	1.39 $\pm$ 1.16
13.	PMN count in ascitic fluid (cells/mm <sup>3</sup> )	277.35 $\pm$ 273.47

Distribution of patients cirrhotic with ascites according to the Child Pugh classification was A (n=0), B (n=14) and C (n=29) (table 2).

**Table 2. Child-Pugh Classification of Cirrhotic Patients with Ascites**

Child-Pugh Classification	SBP (-)	SBP (+)	Total
A	-	-	-
B	11 (55%)	3 (13.4%)	14 (33.3%)
C	9 (45%)	20 (86.4%)	29 (66.7%)
Total	20	23	43

The ascitic fluid PMN cell count and protein level of ascitic fluid, as well as white blood cell count in the SBP group were significantly higher than that of the non-SBP group (see table 3).

**Table 3. Clinical Characteristics of Non-SBP Patients and SBP Patients**

No	Parameter	SBP (-) n = 20 Mean ± SD	SBP (+) n = 23 Mean ± SD	p Value
1.	Age (year)	55.95 ± 13.96	55.65 ± 10.97	NS
2.	Sex : Male	15/20 (75%)	10/22 (43%)	-
	Female	5/20 (25%)	12/22 (57%)	-
3.	WBC (cells/mm <sup>3</sup> )	7.795 ± 2.636	11.082 ± 1.097	p < 0,05
4.	Platelets (mm <sup>3</sup> )	160.700 ± 77.117	149.909 ± 101.381	NS
5.	Total bilirubin (mg/dL)	3.28 ± 3.25	3.86 ± 3.84	NS
6.	ALT (μ/L)	53.90 ± 63.88	45.86 ± 35.64	NS
7.	AST (μ/L)	45.30 ± 72.72	30.59 ± 20.72	NS
8.	Serum albumin (g/dL)	2.99 ± 0.51	2.41 ± 0.47	NS
9.	Serum globulin (g/dL)	3.95 ± 0.95	4.77 ± 1.01	NS
10.	Serum urea (mg/dL)	34.65 ± 16.88	36.77 ± 17.18	NS
11.	Serum creatinine (mg/dL)	1.09 ± 0.59	1.12 ± 0.57	NS
12.	Protein level of ascitic fluid (g/dL)	1.86 ± 1.57	0.98 ± 0.27	p < 0,05
13.	Glucose level of ascitic fluid (g/dl)	1.50 ± 0.9	1.20 ± 0.34	NS
14.	PMN count in ascitic fluid (mm <sup>3</sup> )	34.30 ± 58.01	471.30 ± 235.17	p < 0,05

We have matched the characteristics of patients from group A and B. No significant difference characteristic was found (see table 4).

**Table 4. Clinical Characteristics of the Two Groups of SBP Patients at Admission**

No	Parameter	Trimethoprim- sulfamethoxazole N = 13 (Mean ± SD)	Ciprofloxacin n = 10 (Mean ± SD)	p Value
1.	Age (year)	56.00 ± 12.17	55.20 ± 9.82	NS
2.	Sex : Male	6/12 (50%)	4/10 (40%)	-
	Female	6/12 (50%)	6/10 (60%)	-
3.	Total bilirubin	3.22 ± 1.98	4.61 ± 3.32	NS
4.	Serum ALT	48.66 ± 38.58	42.50 ± 33.50	NS
5.	Serum AST	30.58 ± 16.06	30.60 ± 26.20	NS
6.	Serum albumin	2.31 ± 0.54	2.54 ± 0.37	NS
7.	Serum globulin	4.85 ± 1.10	4.67 ± 0.94	NS
8.	WBC	11.175 ± 6.105	10.970 ± 4.180	NS
9.	Platelets	122.333 ± 40.820	183.000 ± 140.410	NS
10.	Serum urea	35.92 ± 20.54	37.80 ± 13.08	NS
11.	Serum creatinine	1.18 ± 0.68	1.07 ± 0.41	NS
12.	Protein level of ascitic fluid	2.13 ± 1.17	2.86 ± 2.17	NS
13.	Glucose level of ascitic fluid	1.14 ± 0.34	1.05 ± 0.36	NS
14.	PMN count of ascitic fluid	491.66 ± 285.62	459.00 ± 181.99	NS
15.	Child B	2	1	NS
	Child C	11	9	

The bacteria responsible for the infections are listed in table 5.

**Table 5. Bacteria Responsible for Infections in SBP\* Patients**

No	Bacteriae	Frequency	%
1.	Escherichia coli	4/23	17.5 %
2.	Klebsiella pneumoniae	1/23	4.5 %
	Total	5/23	22 %

\* SBP: Spontaneous bacterial peritonitis

Abdominal paracenteses were repeated on day-11 (after therapy) to determine the ascitic fluid PMN cell count and culture to evaluate the efficacy of trimethoprim-sulfamethoxazole and ciprofloxacin in the treatment of SBP. There was a significant reduction in ascitic fluid PMN count and negative monomicrobial culture of the ascitic fluid after 10 days of treatment with either drug ( $p=0.001$  and  $p=0.000$ ), see tables 6 and 7.

**Table 6. The Efficacy of Trimethoprim-Sulfamethoxazole in The Treatment of SBP\***

No	Parameter	Before Treatment Mean $\pm$ SD	After Treatment Mean $\pm$ SD	p < 0.05
1.	PMN count of ascitic fluid	491.66 $\pm$ 285.62	111.75 $\pm$ 166.35	p < 0.05
2.	Culture (+)	3	0	p < 0.05

\* SBP: Spontaneous bacterial peritonitis

**Table 7. The Efficacy of Ciprofloxacin in the Treatment of SBP\***

No	Parameter	Before Treatment Mean $\pm$ SD	After Treatment Mean $\pm$ SD	p < 0.05
1.	PMN count of ascitic fluid	459.00 $\pm$ 181.99	131.50 $\pm$ 105.41	p < 0.05
2.	Culture (+)	1	0	p < 0.05

\* SBP: Spontaneous bacterial peritonitis

The efficacy of trimethoprim-sulfamethoxazole and ciprofloxacin was similar after 10 days treatment (see table 8).

**Table 8. Comparative Clinical Efficacy of Co-trimoxazole and Ciprofloxacin in the Treatment of SBP**

No	Parameter	Trimethoprim-sulfamethoxazole Mean $\pm$ SD	Ciprofloxacin Mean $\pm$ SD	p < 0.05
1.	PMN count of ascitic fluid after treatment	111.75 $\pm$ 166.35	131.50 $\pm$ 105.41	NS

## DISCUSSION

The liver cirrhosis patients included in this study belonged to the B or C Child-Pugh classification (decompensated phase). None belonged to Child A (compensated phase), and most cases belonged to the Child C classification (66.7%) or cases with advance liver damage. This result was not different with other studies where more liver cirrhosis from Child C classification was found, as reported by Lesmana LA. 66.6%,<sup>11</sup> Amiruddin R. 52%,<sup>12</sup> and Djauzi S. 81.3%.<sup>13</sup>

SBP (according to differential ascitic fluid PMN count = 250 cells/mm<sup>3</sup>) was found in 23 patients (53.4%). This result differed from what was found by Runyon B.A.

21%,<sup>4</sup> Amiruddin R. 23.1%,<sup>12</sup> Djauzi S. 25.61%,<sup>13</sup> and Wang SS. 21%.<sup>14</sup> The difference was due to differences in patient characteristic and laboratory equipments.

The causative microorganism of 60-70% of SBPs is gram-negative bacteria from the bowel, gram-positive bacteria in about 30% cases, and very rarely, SBP may be caused by anaerob bacteria. The most-commonly isolated gram-negative bacteria were Escherichia coli and Klebsiella pneumoniae, while the most-commonly isolated gram-positive bacteria was Streptococci.<sup>4,15</sup> In this study, we found only 5 (20%) patients with positive ascitic fluid culture. This result was not different from a

study reported by Lesmana LA. 27%,<sup>11</sup> but was very different from other studies reported by Amiruddin R. 56.21%<sup>12</sup> and Djauzi S. 80.9%.<sup>13</sup> The low proportion of positive ascitic fluid culture was probably due to a relatively low concentration of bacteria in ascitic fluid compared to infections in other organic fluid (e.g. urine), or it might have been due to the use of different culture methods.<sup>2</sup> We found 2 kinds of bacteria, *Escherichia coli* in 4 patients (17.5%) and *Klebsiella pneumoniae* in 1 patient (4.5%). This result was similar to previous studies, which found *Escherichia coli* and *Klebsiella pneumoniae* in the culture of ascitic fluid.<sup>11,13,14</sup>

Treatment with trimethoprim-sulfamethoxazole was performed in 13 patients, but only 12 patients could be evaluated till the end of the study, since 1 patient died after 2 days of treatment due to encephalopathy. Evaluation of these 12 patients demonstrated 11 patients (91.6%) with an ascitic fluid PMN cell count of  $< 250/\text{mm}^3$  and all cultures were negative following treatment, while 1 patient remained with an ascitic fluid PMN cell count of  $> 250/\text{mm}^3$  (from  $650/\text{mm}^3$  before the treatment to  $625/\text{mm}^3$ ). If the average ascitic fluid PMN cell count before treatment ( $491.66 \pm 285.62/\text{mm}^3$ ) was compared with that after treatment ( $111.75 \pm 166.35/\text{mm}^3$ ) using *t*-test, we statistically found the difference to be very significant ( $p = 0.001$ ).

Ten SBP patients were treated with ciprofloxacin. After treatment with 1000 mg ciprofloxacin 10 days, we found 9 patients (90%) with an ascitic fluid PMN cell count of  $< 250/\text{mm}^3$ , 1 patient with an ascitic fluid PMN cell count of  $> 250/\text{mm}^3$  (from  $500/\text{mm}^3$  before treatment to  $350/\text{mm}^3$  after treatment). The microorganism culture from the ascitic fluid of all patients became negative. The average ascitic fluid PMN cell count before treatment was ( $459 \pm 181.99/\text{mm}^3$ ) compared to after treatment ( $131.50 \pm 105.41/\text{mm}^3$ ). Using *t*-test, the differences were found to be statistically very significant ( $p = 0.000$ ).

After analyzing the effect of the reduction in ascitic fluid PMN cell count before and after treatment, we found that very significant results with trimethoprim-sulfamethoxazole treatment (91.6%) as well as with ciprofloxacin (90%). The effect of the two drugs compared before and after treatment using *t*-test were found not to be significantly different ( $p = 0.664$ ). The results of this study was similar to the study by Fong et al<sup>3</sup>, which compared the effect of ampicillin and gentamycin with cefotaxim, where the result were not different in reducing the ascitic fluid PMN cell count nor microorganism culture.

Based on this study, trimethoprim-sulfamethoxazole and ciprofloxacin appears to be excellent single-agent drugs for empiric as well as definitive treatment of spontaneous ascitic fluid infection, even in patients with bacteremia.

## CONCLUSION

1. Trimethoprim-sulfamethoxazole and ciprofloxacin are an effective agents in the treatment of spontaneous bacterial peritonitis in cirrhotic patients with ascites.
2. The efficacy of trimethoprim-sulfamethoxazole and ciprofloxacin are not significantly different in the treatment of spontaneous bacterial peritonitis in the cirrhotic patients with ascites.

## SUGGESTIONS

The administration of trimethoprim-sulfamethoxazole or ciprofloxacin seems as an adequate therapeutic alternative in spontaneous bacterial peritonitis in cirrhotic patients with ascites.

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