Short-course ceftriaxone therapy in spontaneous bacterial peritonitis

Gul Javid, Bashir A Khan, Bilal A Khan, Altaf H Shah, G M Gulzar, Mushtaq A Khan

Summary

Forty patients with spontaneous bacterial peritonitis, three of whom had complicating acute hepatitis syndrome, eight late-onset hepatic failure, and 29 with cirrhosis, were treated with ceftriaxone 2 g intravenously once daily for 5 days. Ascitic fluid culture was positive in 28 patients, with *Escherichia coli* and *Klebsiella* as common isolates. All the bacteria isolated were sensitive to ceftriaxone except *Enterococcus faecalis*, which was isolated in a cirrhotic patient. All culture-positive patients sensitive to ceftriaxone showed bacteriological cure and 26 (65%) patients showed cytological cure after 48 hours of treatment. A total of 95% were cured of their infection after 5 days of treatment. Twelve (30%) patients died during hospitalisation after documented cure of their spontaneous bacterial peritonitis (renal failure, gastrointestinal bleed and cerebral oedema were the primary causes of death). Infection-related mortality due to *Pseudomonas* septicemia was seen in one cirrhotic patient.

Keywords: bacterial peritonitis; ceftriaxone

Spontaneous bacterial peritonitis (SBP) is a bacterial infection of ascitic fluid in the absence of either a contiguous or localised intraperitoneal source of infection and complicates virtually all forms of parenchymal liver diseases. A first-generation cephalosporin (kanamycin) and ampicillin-gentamicin combinations were initially recommended as therapy,¹ however, the use of aminoglycoside in liver disease results in increased renal dysfunction.² A number of non-aminoglycoside options (aztreonam,³ amoxycillin-clavulanic acid,⁴ fluoroquinolones,⁵ and third-generation cephalosporins⁶) have been used in the last two decades with variable efficacy and toxicity. Ceftriaxone, a third-generation cephalosporin, is effective against almost all organisms isolated from SBP patients except *Bacteriodes fragilis* and *Enterococcus faecalis*, which are rarely predisposing organisms.⁷ Ceftriaxone has a half-life of 8 hours, which maintains peritoneal concentrations well above the MIC values of most organisms isolated from SBP patients at a daily dose of 2 g.⁸

Criteria for diagnosis of SBP

Prototype

- ascitic fluid culture positive
- ascitic fluid PMN count >250 cells/mm³

Culture negative neutrocytic ascites

- sterile ascitic fluid culture
- ascitic fluid PMN count >500 cells/mm³

Monomicrobial non-neutrocytic bacteriascites

- ascitic fluid culture positive
- ascitic fluid PMN count <250 cells/mm³

Methods

This prospective study was conducted between October 1995 and April 1997 at Sheri Kashmir Institute of Medical Science in the Department of Gastroenterology with ethical committee approval. Included in the study were patients with SBP and underlying parenchymal liver disease including acute hepatitis, late-onset hepatic failure,⁹ and cirrhosis, irrespective of aetiology, who had ascitic fluid polymorphonucleocyte (PMN) counts >250 cells/mm³ and positive ascitic fluid culture, or culture-negative neutrocytic ascites with ascitic fluid PMN count >500 cells/mm³, or monomicrobial non-neutrocytic ascites with positive ascitic fluid and ascitic fluid PMN count <250 cells/mm³. Patients with tuberculosis, pancreatitis, serositis, peritoneal carcinomatosis, or secondary bacterial peritonitis were excluded. Patients with hypersensitivity to penicillin or cephalosporins or who had received any form of antibiotic therapy within 3 days of consideration of therapy were excluded from the study. All patients with ascites underwent paracentesis on admission to hospital and repeat paracentesis was performed after 48 ± 2 hours of initiation of therapy and after completion of 5 days of therapy. Ascitic fluid was sent to the laboratory for cell count, culture sensitivity and chemical parameters. The American Optical Neubauer Hemacytometer was used for ascitic fluid cell count. The differential was performed manually after Wright staining and therefore the white cell count derived by haemacytometer was corroborated; 10 ml of ascitic fluid was inoculated into each of the two blood culture bottles at the bedside. Isolation and identification of positive culture was performed by

Department of
Gastroenterology,
Sheri Kashmir
Institute of Medical
Science, Gulistan
Manzil, Amira Kadal,
Srinagar - 190 001,
India
G Javid
B A Khan
B A Khan
A H Shah
G M Gulzar
M A Khan

Accepted 23 April 1998

Table 1 Patient characteristics

Age (years)	
Mean ± SD	49.7 ± 12.5
Range	16–58
Sex (male:female)	24:16
Nature of underlying liver disease (%)	
AHS*	3 (7.5)
LOHF**	8 (20)
Cirrhosis	29 (72.5)
Stage of cirrhosis	n (%)
A	0
B	5 (17.2)
C	24 (82.7)

*AHS = acute hepatitis syndrome; **LOHF = late onset hepatic failure

conventional method. Antibiotic susceptibility was studied using the Kirby Bauer method.¹⁰

The diagnosis of acute hepatitis, late-onset hepatic failure, and cirrhosis was established on the basis of clinical and laboratory criteria, with histological confirmation if required. The hepatic reserve in cirrhotics was assessed using Pugh’s modification of Child’s criteria.

Ceftriaxone (Monoceff, Aristo), 2 g intravenously over 15 minutes, was given once daily for 5 days. The drug therapy was considered to be effective when the ascitic fluid PMN count showed a fall of more than 50%; patients were considered cured when there was no clinical evidence of infection, sterile ascitic fluid, and an ascitic fluid PMN count <250 cells/mm³.¹¹ All the patients who were cured of their infection received prophylactic norfloxacin 400 mg once daily.

Statistical analysis was performed on ascitic PMN count using students *t*-test and chi-square test was used to analyse culture positivity.

Results

Forty patients with SBP were included in the study, 24 men and 16 women; they had underlying acute hepatitis (three patients), late-onset hepatic failure (eight), and cirrhosis (29). Among cirrhotics, 83% of patients were of Child Pugh class C. The mean age of presentation was 49.7 ± 12.5 years (table 1).

Prothrombin activity was reduced in most patients, and liver function tests were consistent with underlying liver disease. Bilirubin and alanine transaminase were raised considerably in the patients with acute hepatitis and late-onset hepatic failure, with mild elevation in cirrhotics. Total serum protein and albumin were reduced in all three groups with lower values in cirrhotics. Kidney function tests were deranged in 15 patients on admission; this was

attributed to acute tubular necrosis and functional renal failure, on the basis of urinary sodium. Ascitic fluid albumin was less than 1 g/dl in 80% of patients and ascitic fluid culture positivity did not correlate with ascitic fluid albumin concentration.

The overall mean ascitic fluid PMN count in the acute hepatitis group was 2870 cells/mm³ (range 2210–4510), late onset hepatic failure group 4255 cells/mm³ (range 920–12 150), and in the cirrhotic group 3279 cells/mm³ (range 288–18 240) (table 2).

Ascitic fluid culture was positive in 28 (70%), with *Escherichia coli* in 17 (60%) patients, *Klebsiella* in seven (25%) patients, *Pneumococcus* in two (7%) patients, and *Streptococcus viridans* and *Enterococcus faecalis* in one patient each (table 3). All the organisms isolated except *E faecalis* showed good *in vitro* sensitivity to ceftriaxone.

After 48 hours of treatment with ceftriaxone 2 g intravenously, the mean ascitic PMN count in acute hepatitis group was 931 cells/mm³, in the hepatic failure group 1224 cells/mm³, and in the cirrhotic group 829 cells/mm³, with percentage reductions of 67.6%, 71.2%, and 74.7%, respectively. A total of 65% showed evidence of cytological cure at 48 hours with ascitic fluid PMN count <250 cells/mm³.

Two patients in the cirrhotic group showed an increase in PMN count and were considered non-responders. In one of these patients *E faecalis* was isolated from ascitic fluid, which was ceftriaxone-resistant but sensitive to ciprofloxacin. The patient responded to treatment with ciprofloxacin. In the other patient, ceftriaxone-resistant, ceftazidime-sensitive *Pseudomonas* was isolated from blood, while ascitic fluid culture was sterile. The patient was treated with ceftazidime, but showed no response and he died of *Pseudomonas* septicaemia. A total of 75% of responders were asymptomatic (afebrile, no abdominal pain) at 48 hours of initiation of therapy. After completion of 5 days of therapy, all responders showed evidence of cytological cure with ascitic fluid PMN count <250 cells/mm³ and no clinical evidence of infection.

Out of 40 patients treated for SBP, 13 (32.5%) died during hospitalisation (nine in the cirrhotic group, three in the hepatic failure group and one in the acute hepatitis group). The difference in ascitic fluid PMN count was not statistically significant among survivors and non-survivors, either before (*p*>0.20) or after 48 hours treatment with ceftriaxone (*p*>0.4). Two-thirds of survivors and one-third of

Table 2 Cytological data of SBP patients before and after treatment

	AHS (n=3)	LOHF (n=8)	Cirrhosis (n=29)
Before treatment			
Ascitic fluid PMN (cells/mm ³)	2870±452	4255±1825	3279±1053
After treatment			
Ascitic fluid PMN (cells/mm ³) 48 ± 2 h	931±220	1224±522	829±323
Day 5	89±9	69±15	38±6

Data are presented as mean±SEM; for abbreviations see table 1

Table 3 Bacteriologic data of SBP patients

	AHS (n=3)	LOHF (n=8)	Cirrhosis (n=29)
Ascitic fluid culture positive	2	4	22
<i>E coli</i>	1	3	13
<i>Klebsiella</i>	1	0	6
<i>Pneumococcus</i>	0	1	1
<i>Enterococcus faecalis</i> *	0	0	1
<i>Streptococcus viridans</i>	0	0	1

*Ceftriaxone resistant, sensitive to ciprofloxacin

non-survivors were initially culture-positive ($p > 0.75$); after treatment all patients were culture-negative.

The cause of death among non-survivors after SBP resolution were hepatorenal syndrome (creatinine clearance < 5 ml/min) in six patients, major variceal bleed in four patients and cerebral oedema as evidenced by bradycardia, hypertension, and decerebrate rigidity in two patients. Infection-related mortality due to *Pseudomonas* septicaemia was seen in one patient in the cirrhotic group.

Discussion

Until the end of 1980s, few prospective therapeutic trials had been carried out on patients with SBP. Carbera *et al*² showed a high sensitivity to nephrotoxicity caused by aminoglycosides in cirrhotics. Ariza *et al*³ showed an unacceptable superinfection rate with aztreonam. Grange *et al*⁴ analysed the use of amoxycillin-clavulanic acid combination, while Felisart *et al*⁵ showed that cefotaxime has greater efficacy and safety in treatment of severe infections in cirrhotics and listed it as the treatment of choice. Gomez Jimenez *et al*⁷ compared cefonicid (2 g every 12 h) and ceftriaxone (2 g every 24 h) and found ceftriaxone-susceptible strains in 94% patients and cefonicid-susceptible in 91.5% patients. All the patients treated with ceftriaxone and 94% of those treated with cefonicid were cured of their infections.

Ceftriaxone has an excellent spectrum of activity against Gram-negative organisms and good activity against Gram-positive organisms, including *Streptococcus pneumoniae*.⁷ Almost all organisms isolated from SBP patients were sensitive to ceftriaxone except *Bacteroides fragilis* and *E faecalis*, which are rarely predisposing organisms.⁷ Ceftriaxone has a unique half-life of 8 hours and can be given once daily.⁸ The antibiotic concentration in ascitic fluid:MIC ratio for ceftriaxone (2 g) was greater than 100 throughout the dose interval (24 h) against organisms isolated from SBP patients.⁷ Runyon *et al*¹² reported that short-course (5-day) treatment of SBP is as efficacious as long-course (10-day) therapy. It is because of these characteristics that ceftriaxone 2 g once daily for 5 days was used in this study.

In 1982, Thomas and Fromkes¹³ reported two patients with acute hepatitis B who developed SBP. In a series of 82 patients with acute hepatitis decompensated with ascites, 26 (32%) had SBP.¹⁴ Bacteraemia and/or SBP were reported in 12 out of 47 patients with late onset hepatic failure,⁹ while SBP was found in 38% of a series of 148 cases of subacute hepatic failure,¹⁵ and up to 15% of 224 patients with chronic liver disease.¹⁶

Bedside inoculation of ascitic fluid in blood culture bottles has yielded better results than delayed inoculation in the laboratory. In our study, ascitic fluid culture positivity was seen in 28 (70%) patients, of whom 96% were sensitive to ceftriaxone. Toledo *et al*¹⁷ found culture positivity in 57% of SBP patients most of which were Gram negative. Gomez Jimenez *et al*⁷ in 1993 found culture positivity in 78% of 60 patients with SBP, of whom 94% were susceptible to ceftriaxone.

Ascitic fluid opsonic activity is an important protective mechanism against SBP. A prospective study demonstrated that patients with low concentrations of protein in ascitic fluid were susceptible to SBP.¹⁸ Ascitic fluid protein was found to be less than 1 g/dl in 88.5% patients with acute hepatitis.¹⁴ Our study confirmed these results, although there was no statistically significant difference in culture positivity in patients with ascitic fluid albumin > 1 g/dl.

In our study, the 48-hour treatment with ceftriaxone showed cytological evidence of cure in 65% of patients and 100% bacteriological cure in ceftriaxone-susceptible strains. A total of 95% patients were cured of their infection after receiving ceftriaxone for 5 days. Our results were consistent with those of Gomez Jimenez,⁷ who recorded a cytological cure in 59% of patients and 100% bacteriological cure after 72 hours of treatment. Out of 40 patients, 27 (67.5%) left the hospital alive and 13 (32.5%) died during hospitalisation due to underlying liver disease. On admission 15 patients had deranged kidney function tests (creatinine > 2 mg/dl); in nine of these kidney functions improved while in the other six there was progressive deterioration in renal function, leading to death. Four patients died of major variceal bleed and cerebral oedema was the cause of death in two patients on ventilatory support; one patient died of *Pseudomonas* septicaemia.

In our study there was no statistically significant difference in culture positivity among survivors and non-survivors. Runyon *et al*⁹ reported a 50% mortality of culture-negative neutrocytic ascites, which was not statistically different from that of culture-positive ascites (70%). Other studies have reported an 85% cure rate with cefotaxime,⁶ and amoxycillin-clavulanic acid.⁴ In contrast, our study with ceftriaxone 2 g once daily for 5 days showed a 95% cure rate; our results are supported by those of Gomez Jimenez, who achieved 100% cure rate in SBP. The duration of therapy with ceftriaxone is much shorter, and the hospital stay of patients is markedly reduced, which adds to the cost effectiveness of this regimen. Therefore ceftriaxone may be regarded as empiric treatment of choice in patients of SBP with underlying parenchymal liver disease.

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