

## EFFECT OF INTRAVENOUS ALBUMIN ON RENAL IMPAIRMENT AND MORTALITY IN PATIENTS WITH CIRRHOSIS AND SPONTANEOUS BACTERIAL PERITONITIS

PAU SORT, M.D., MIQUEL NAVASA, M.D., VICENTE ARROYO, M.D., XAVIER ALDEGUER, M.D., RAMON PLANAS, M.D.,  
 LUIS RUIZ-DEL-ARBOL, M.D., LLUIS CASTELLS, M.D., VICTOR VARGAS, M.D., GERMÁN SORIANO, M.D.,  
 MÓNICA GUEVARA, M.D., PERE GINÈS, M.D., AND JOAN RODÉS, M.D.

## ABSTRACT

**Background** In patients with cirrhosis and spontaneous bacterial peritonitis, renal function frequently becomes impaired. This impairment is probably related to a reduction in effective arterial blood volume and is associated with a high mortality rate. We conducted a study to determine whether plasma volume expansion with intravenous albumin prevents renal impairment and reduces mortality in these patients.

**Methods** We randomly assigned 126 patients with cirrhosis and spontaneous bacterial peritonitis to treatment with intravenous cefotaxime (63 patients) or cefotaxime and intravenous albumin (63 patients). Cefotaxime was given daily in doses that varied according to the serum creatinine level, and albumin was given at a dose of 1.5 g per kilogram of body weight at the time of diagnosis, followed by 1 g per kilogram on day 3. Renal impairment was defined as nonreversible deterioration of renal function during hospitalization.

**Results** The infection resolved in 59 patients in the cefotaxime group (94 percent) and 62 in the cefotaxime-plus-albumin group (98 percent) ( $P=0.36$ ). Renal impairment developed in 21 patients in the cefotaxime group (33 percent) and 6 in the cefotaxime-plus-albumin group (10 percent) ( $P=0.002$ ). Eighteen patients (29 percent) in the cefotaxime group died in the hospital, as compared with 6 (10 percent) in the cefotaxime-plus-albumin group ( $P=0.01$ ); at three months, the mortality rates were 41 percent (a total of 26 deaths) and 22 percent (a total of 14 deaths), respectively ( $P=0.03$ ). Patients treated with cefotaxime had higher levels of plasma renin activity than those treated with cefotaxime and albumin; patients with renal impairment had the highest values.

**Conclusions** In patients with cirrhosis and spontaneous bacterial peritonitis, treatment with intravenous albumin in addition to an antibiotic reduces the incidence of renal impairment and death in comparison with treatment with an antibiotic alone. (N Engl J Med 1999;341:403-9.)

©1999, Massachusetts Medical Society.

**S**PONTANEOUS bacterial peritonitis is a common and severe complication in patients with cirrhosis and ascites.<sup>1-7</sup> It probably originates with the passage of bacteria from the intestinal lumen to the systemic circulation and then to the ascitic fluid.<sup>8,9</sup> Although the concentration of bacteria in ascitic fluid is low, the inflammatory response, as estimated by the concentration of polymorphonuclear leukocytes and cytokines (tumor necrosis factor  $\alpha$

and interleukin-6) in ascitic fluid and blood, is very intense.<sup>10,11</sup>

In one third of patients with spontaneous bacterial peritonitis, renal impairment develops despite treatment of their infection with non-nephrotoxic antibiotics.<sup>12</sup> This deterioration of renal function is the most sensitive predictor of in-hospital mortality.<sup>12</sup> Renal impairment occurs in patients with the highest concentrations of cytokines in plasma and ascitic fluid<sup>10</sup> and is associated with marked activation of the renin-angiotensin system.<sup>10</sup> It is considered to be caused by a decrease in effective arterial blood volume as a result of the infection.<sup>10,12</sup>

We conducted a study to determine whether plasma volume expansion with albumin could prevent the impairment of renal function and reduce mortality in patients with spontaneous bacterial peritonitis.

## METHODS

## Patients

A total of 199 consecutive patients with cirrhosis who had spontaneous bacterial peritonitis and who were admitted between November 1995 and September 1997 to seven university hospitals were evaluated for inclusion in the study. The study was approved by the investigational review board at each hospital, and patients gave written informed consent to participate. Inclusion criteria were a polymorphonuclear-cell count in the ascitic fluid of more than 250 per cubic millimeter, in the absence of findings suggestive of secondary peritonitis<sup>13</sup> (10 ml of blood and ascitic fluid was inoculated in blood-culture bottles at the patient's bedside<sup>14</sup>); an age between 18 and 80 years; no antibiotic treatment within one week before the diagnosis of spontaneous bacterial peritonitis (except for prophylactic treatment with norfloxacin); the absence of other infections, shock, gastrointestinal bleeding, ileus, grade 3 or 4 hepatic encephalopathy on the Conn and Lieberthal scale,<sup>15</sup> cardiac failure, findings suggestive of organic nephropathy (proteinuria, hematuria, or abnormal findings on renal ultrasonography), human immunodeficiency virus infection, and any disease (e.g., advanced neoplasia) that could affect the short-term prognosis; a serum creatinine level of no more than 3 mg per deciliter (265  $\mu\text{mol}$  per liter); and the absence of potential causes of dehydration (such as diarrhea or an intense response to diuretic treatment) within one week before the diagnosis of peri-

From the Liver Unit, Institut de Malalties Digestives, Hospital Clínic, and Institut d'Investigacions Biomèdiques August Pi-Sunyer, Barcelona (P.S., M.N., V.A., M.G., P.G., J.R.); the Gastroenterology Unit, Hospital Germans Trias i Pujol, Badalona (X.A., R.P.); the Gastroenterology Unit, Hospital Ramón y Cajal, Madrid (L.R.A.); the Liver Unit, Hospital Vall d'Hebron, Barcelona (L.C., V.V.); and the Gastroenterology Unit, Hospital de la Santa Creu i Sant Pau, Barcelona (G.S.) — all in Spain. Address reprint requests to Dr. Arroyo at the Liver Unit, Institut de Malalties Digestives, Hospital Clínic, Villarroel 170, 08036 Barcelona, Catalunya, Spain, or at arroyo@medicina.ub.es.

tonitis. If the clinical information concerning possible dehydration was not considered reliable, the central venous pressure was measured, and the patient was not included if it was lower than 4 mm Hg.

Seventy-three patients were excluded, for the following reasons: treatment with antibiotics at the time of diagnosis (13 patients), gastrointestinal bleeding at the time of diagnosis (12), organic nephropathy (12), a serum creatinine level higher than 3 mg per deciliter (12), cardiac failure (5), age greater than 80 years (5), septic shock (3), refusal to participate in the study (3), dehydration (2), and absence of more than one of the inclusion criteria (6).

A total of 126 patients were randomly assigned to one of two groups: 63 patients were assigned to treatment with cefotaxime, and 63 to treatment with cefotaxime and intravenous albumin. Randomization was performed independently at each hospital with the use of sealed envelopes containing the treatment assignments, which were based on random numbers generated by the SAS statistical package (SAS Institute, Cary, N.C.). All the investigators were unaware of the treatment assignments. The correct order of randomization was verified before the analysis of the results. Three patients were withdrawn from the study during the first 24 hours after randomization because they did not meet the inclusion criteria (one patient in the cefotaxime-plus-albumin group was more than 80 years old, another patient in the same group had received antibiotic treatment before randomization, and one patient in the cefotaxime group had cardiac failure). These exclusions were made by a single investigator, who remained unaware of the treatment assignments. The patient with cardiac failure died during hospitalization. In the other two patients, the peritonitis resolved without complications, and both were alive at the end of follow-up. The final analysis included all 126 enrolled patients.

### Protocol

Physical examination, chest and abdominal radiography, abdominal ultrasonography, and routine laboratory tests (blood-cell counts and liver and renal tests) and measurement of plasma renin activity were performed before the initiation of therapy in all patients. Laboratory measurements were repeated every three days during the first nine days after enrollment and then weekly until discharge. Intravenous cefotaxime (Primafen, Hoechst Marion Roussel, Barcelona, Spain) was administered at doses of 2 g every 6 hours, 1 g every 6 hours, 1 g every 8 hours, and 1 g every 12 hours for respective serum creatinine levels of less than 1.5 mg per deciliter ( $<133 \mu\text{mol}$  per liter), 1.5 to 2.0 mg per deciliter (133 to  $177 \mu\text{mol}$  per liter), greater than 2.0 to 2.5 mg per deciliter ( $>177$  to  $221 \mu\text{mol}$  per liter), and more than 2.5 mg per deciliter. In patients assigned to receive cefotaxime and albumin, albumin (Albúmina 20 percent, Instituto Grífols, Barcelona, Spain) was given at a dose of 1.5 g per kilogram of body weight during the first six hours after enrollment, followed by 1 g per kilogram on day 3 (laboratory measurements before the initiation of therapy and on day 3 were performed before the administration of albumin). The mean ( $\pm$ SE) central venous pressure, measured in 15 patients before therapy was begun, was  $5 \pm 1$  mm Hg. Diuretic treatment or therapeutic paracentesis was not allowed until the infection had resolved. However, in seven patients with tense ascites (three in the cefotaxime group and four in the cefotaxime-plus-albumin group), a partial paracentesis, with aspiration of 3 liters, was performed before the resolution of infection.

Spontaneous bacterial peritonitis was considered to have resolved when signs of infection had disappeared and the polymorphonuclear-cell count in ascitic fluid was less than or equal to 250 per cubic millimeter.<sup>3,4,16</sup> In patients who did not have a response to cefotaxime, antibiotic treatment was modified according to the *in vitro* susceptibility of the isolated organism or was modified empirically in patients with negative blood and ascitic-fluid cultures. Prophylactic norfloxacin therapy (400 mg per day, given orally) was initiated after the resolution of infection and was maintained throughout the follow-up period.<sup>17</sup>

Renal failure at the time of enrollment was diagnosed when the

blood urea nitrogen level was more than 30 mg per deciliter (11 mmol per liter) or the serum creatinine level was more than 1.5 mg per deciliter. Renal impairment was defined as a nonreversible deterioration of renal function during hospitalization. In patients without renal failure at enrollment, renal impairment was diagnosed when the blood urea nitrogen or serum creatinine level increased by more than 50 percent of the pretreatment value, to levels higher than 30 mg per deciliter or 1.5 mg per deciliter, respectively. In patients with preexisting renal failure, an increase in the blood urea nitrogen or serum creatinine level by more than 50 percent from base line was required for a diagnosis of renal impairment.

After the resolution of infection, patients with tense ascites were treated with total paracentesis and the administration of albumin,<sup>18</sup> regardless of treatment assignment, followed by sodium restriction and diuretic therapy, and those with moderate ascites were treated only with sodium restriction and diuretics. After discharge from the hospital, patients were followed weekly during the first month and then monthly until 90 days after enrollment.

### Statistical Analysis

The main end points of the study were the development of renal impairment and mortality. The end point chosen to calculate the sample size was the development of renal impairment. Assuming that renal impairment develops in approximately 30 percent of patients with spontaneous bacterial peritonitis that is treated with cefotaxime,<sup>12</sup> a minimum of 50 patients per group was required to allow detection of a difference of 25 percent between the two groups in the proportion of patients with this complication during hospitalization, with a two-sided type I error rate of 5 percent and a type II error rate of 20 percent. The final analysis was conducted on an intention-to-treat basis. Comparisons between groups were performed with use of the chi-square test or Fisher's exact test for categorical data and Student's *t*-test for continuous data. The same univariate analyses were also used to identify factors predicting the development of renal impairment and in-hospital mortality. These factors were identified from a list of 28 variables that included information from the medical history and base-line clinical evaluation and laboratory tests, as well as the treatment assignment. Variables that reached statistical significance in univariate analyses were subsequently included in multivariate analyses (by stepwise logistic regression) in order to identify independent predictors of the two main end points.

The analysis of the results was verified by a central review committee at the Hospital Clínic of Barcelona. Results are presented as means  $\pm$ SE. All reported *P* values are two-tailed. Values of less than 0.05 were considered to indicate statistical significance.

## RESULTS

### Base-Line Characteristics of the Patients

There were no significant differences between the groups in clinical and laboratory data at enrollment (Table 1). All the patients in the cefotaxime-plus-albumin group received the scheduled doses of albumin except for the two patients who were withdrawn from this group because they did not meet the inclusion criteria. There were no adverse effects of the albumin infusion. One patient in the cefotaxime group was treated with intravenous ofloxacin because of a previous allergic reaction to cephalosporins.

### Renal Function

The infection resolved in most of the patients in each group. Despite a similar rate of resolution of infection, the incidence of renal impairment was markedly lower among the patients treated with cefotax-

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE 126 PATIENTS ACCORDING TO THE ASSIGNED TREATMENT.\*

CHARACTERISTIC	CEFOTAXIME (N=63)	CEFOTAXIME PLUS ALBUMIN (N=63)
Age — yr	62±1	60±1
Sex — M/F	38/25	43/20
Alcoholic cirrhosis — no. (%)	19 (30)	18 (29)
Hepatocellular carcinoma — no. (%)	7 (11)	10 (16)
Hepatic encephalopathy — no. (%)	15 (24)	13 (21)
White-cell count — per mm <sup>3</sup>	9221±814	7883±560
Ascitic-fluid polymorphonuclear cells — per mm <sup>3</sup>	4228±750	5223±1541
Serum bilirubin — mg/dl	6±1	4±1
Serum albumin — g/dl	2.5±0.1	2.7±0.1
Prothrombin time — % of control	58±2	55±2
Child–Pugh score†	10±0.2	10±0.2
Renal failure — no. (%)	28 (44)	25 (40)
Diuretic treatment — no. (%)	41 (65)	45 (71)
Spironolactone — mg/day	73±5	81±6
Furosemide — mg/day	19±1	18±2
Previous prophylactic treatment with norfloxacin — no. (%)	5 (8)	6 (10)
Isolated organisms — no. (%)‡	36 (57)	32 (51)
<i>Escherichia coli</i>	22	20
Other gram-negative bacilli	6	7
Other bacteria	8	5

\*Plus-minus values are means ±SE. No significant differences were found between the two groups in any of the characteristics. To convert the values for serum bilirubin to micromoles per liter, multiply by 17.1.

†The Child–Pugh score (range, 5 to 15, where 5 indicates good liver function and 15 indicates poor liver function) was calculated on the basis of the presence and degree of hepatic encephalopathy, the presence and degree of ascites, the serum bilirubin level, the serum albumin level, and the prothrombin time.

‡Organisms were isolated from ascitic fluid or blood.

ime and albumin (6 of 63 [10 percent]) than among those treated with cefotaxime alone (21 of 63 [33 percent],  $P=0.002$ ) (Table 2). On days 3, 6, and 9, the blood urea nitrogen and serum creatinine levels were lower and the serum sodium level was higher in the cefotaxime-plus-albumin group than in the cefotaxime group (Table 3). Renal impairment developed in 27 patients, and in 23 of these patients, the worsening of renal function followed a progressive course characterized by oliguria or anuria, marked increases in blood urea nitrogen and serum creatinine levels (the peak values were  $94\pm 8$  mg per deciliter [ $34\pm 3$  mmol per liter] and  $3.4\pm 1$  mg per deciliter [ $301\pm 88$   $\mu$ mol per liter], respectively), and severe hyponatremia ( $124\pm 1$  mmol of sodium per liter). For the series of patients as a whole, independent predictors of the development of renal impairment included base-line serum bilirubin and creatinine levels ( $P<0.001$  and  $P=0.01$ , respectively) and treatment with cefotaxime alone ( $P=0.02$ ; odds ratio, 4.6; 95 percent confidence interval, 1.3 to 16.1). The incidence of renal impairment among patients

**TABLE 2.** CLINICAL OUTCOME ACCORDING TO THE ASSIGNED TREATMENT.\*

OUTCOME VARIABLE	CEFOTAXIME (N=63)	CEFOTAXIME PLUS ALBUMIN (N=63)	P VALUE
Resolution of infection — no. (%)†	59 (94)	62 (98)	0.36
Duration of antibiotic therapy — days	6±1	5±1	0.48
Paracentesis for ascites after resolution of infection — no. (%)‡	16 (25)	14 (22)	0.83
Hospital stay — days	13±1	14±1	0.48
Renal impairment — no. (%)	21 (33)	6 (10)	0.002
Death — no. (%)			
In hospital§	18 (29)	6 (10)	0.01
At three months¶	26 (41)	14 (22)	0.03

\*Plus-minus values are means ±SE.

†The infection resolved with the initial cefotaxime therapy in 53 of the 63 patients (84 percent) in the cefotaxime group and in 57 of the 63 patients (90 percent) in the cefotaxime-plus-albumin group. In the other patients, the infection resolved after modification of the antibiotic therapy.

‡These patients required at least one therapeutic paracentesis for the management of ascites.

§The causes of in-hospital death were combined liver and renal failure (13 patients in the cefotaxime group and 5 in the cefotaxime-plus-albumin group), massive gastrointestinal hemorrhage (2 patients in the cefotaxime group and 1 in the cefotaxime-plus-albumin group), septic shock (2 patients in the cefotaxime group), and liver failure (1 patient in the cefotaxime group).

¶Seven patients (four in the cefotaxime group and three in the cefotaxime-plus-albumin group) were lost to follow-up after discharge from the hospital. The three-month mortality rates were calculated as the number of known deaths at this time divided by the total number of enrolled patients in each group.

with a base-line serum bilirubin level of at least 4 mg per deciliter ( $68$   $\mu$ mol per liter) was 48 percent (14 of 29 patients) in the cefotaxime group, as compared with 12 percent (3 of 25 patients) in the cefotaxime-plus-albumin group, regardless of the serum creatinine level. Corresponding results in patients with a serum bilirubin level of less than 4 mg per deciliter and a serum creatinine level of at least 1 mg per deciliter were 32 percent (6 of 19 patients) and 14 percent (3 of 21 patients), respectively. The incidence of renal impairment among patients with a serum bilirubin level of less than 4 mg per deciliter and a serum creatinine level of less than 1 mg per deciliter was very low in both treatment groups (7 percent and 0 percent in the cefotaxime and cefotaxime-plus-albumin groups, respectively).

**Mortality**

Mortality during hospitalization was significantly lower among patients treated with cefotaxime and albumin than among those treated with cefotaxime alone (10 percent vs. 29 percent,  $P=0.01$ ) (Table 2). Independent predictors of in-hospital mortality were the blood urea nitrogen level ( $P=0.001$ ), serum bilirubin level ( $P=0.01$ ), and prothrombin time

**TABLE 3.** RENAL FUNCTION, SERUM SODIUM LEVELS, AND MEAN ARTERIAL PRESSURE AT ENROLLMENT AND DURING THE FIRST NINE DAYS OF HOSPITALIZATION IN THE 126 PATIENTS.\*

VARIABLE	CEFOTAXIME (N=63)	CEFOTAXIME PLUS ALBUMIN (N=63)	P VALUE
Blood urea nitrogen — mg/dl (no. of patients)			
Day 0	31±3 (63)	28±3 (63)	0.48
Day 3	34±3 (59)	25±3 (58)	0.03
Day 6	36±3 (58)	22±3 (57)	0.003
Day 9	36±3 (48)	22±3 (53)	0.01
Serum creatinine — mg/dl (no. of patients)			
Day 0	1.1±0.1 (63)	1.2±0.1 (63)	0.66
Day 3	1.3±0.1 (61)	1±0.1 (60)	0.16
Day 6	1.3±0.1 (59)	1±0.1 (59)	0.03
Day 9	1.4±0.1 (48)	1±0.1 (55)	0.04
Serum sodium — mmol/liter (no. of patients)			
Day 0	133±1 (63)	134±1 (63)	0.24
Day 3	130±1 (59)	134±1 (61)	0.001
Day 6	130±1 (56)	134±1 (57)	<0.001
Day 9	130±1 (51)	134±1 (53)	0.002
Mean arterial pressure — mm Hg (no. of patients)			
Day 0	86±2 (63)	86±2 (63)	0.91
Day 3	81±2 (59)	81±2 (59)	0.91
Day 6	79±2 (55)	80±1 (57)	0.71
Day 9	81±2 (51)	81±2 (55)	0.72

\*Plus-minus values are means ±SE. To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357; to convert the values for creatinine to micromoles per liter, multiply by 88.4.

(P=0.01) at base line and treatment assignment (P=0.05; odds ratio for death associated with treatment with cefotaxime alone, 4.5; 95 percent confidence interval, 1.0 to 20.9). Table 4 shows the in-hospital mortality rate for each treatment group according to variables with predictive value. Mortality was also significantly lower at three months among the patients treated with cefotaxime and albumin (22 percent, vs. 41 percent among the patients treated with cefotaxime alone; P=0.03) (Table 2).

Twenty-one (78 percent) of the 27 patients in whom renal impairment developed died during hospitalization, as compared with 3 (3 percent) of the 99 patients without renal impairment (P<0.001). The mortality rates at three months among the patients with renal impairment and among those without renal impairment were 89 percent (24 deaths) and 16 percent (16 deaths), respectively (P<0.001).

#### Renin-Angiotensin System

At base line, plasma renin activity was similar in the two groups of patients. However, on days 3, 6, and 9, the level of plasma renin activity was significantly higher in the patients treated with cefotaxime alone than in those treated with cefotaxime and albumin (Fig. 1A), indicating that additional stimulation of the already activated renin-angiotensin system

**TABLE 4.** IN-HOSPITAL MORTALITY ACCORDING TO VARIABLES WITH INDEPENDENT PREDICTIVE VALUE.\*

VARIABLE	CEFOTAXIME (N=63)		CEFOTAXIME PLUS ALBUMIN (N=63)	
	BUN <30 mg/dl	BUN ≥30 mg/dl	BUN <30 mg/dl	BUN ≥30 mg/dl
	no. of patients who died/total no. (%)			
Bilirubin <4 mg/dl				
Prothrombin time ≥60% of control	0/13	3/6 (50)	0/10	1/10 (10)
Prothrombin time <60% of control	0/7	2/8 (25)	0/14	2/5 (40)
Bilirubin ≥4 mg/dl				
Prothrombin time ≥60% of control	1/3 (33)	1/5 (20)	0/0	0/1
Prothrombin time <60% of control	4/12 (33)	7/9 (78)	0/16	3/7 (43)
Total	5/35 (14)	13/28 (46)	0/40	6/23 (26)

\*The cutoff points for the predictive variables are the median values in the overall group of patients. To convert the values for blood urea nitrogen (BUN) to millimoles per liter, multiply by 0.357; to convert the values for bilirubin to micromoles per liter, multiply by 17.1.

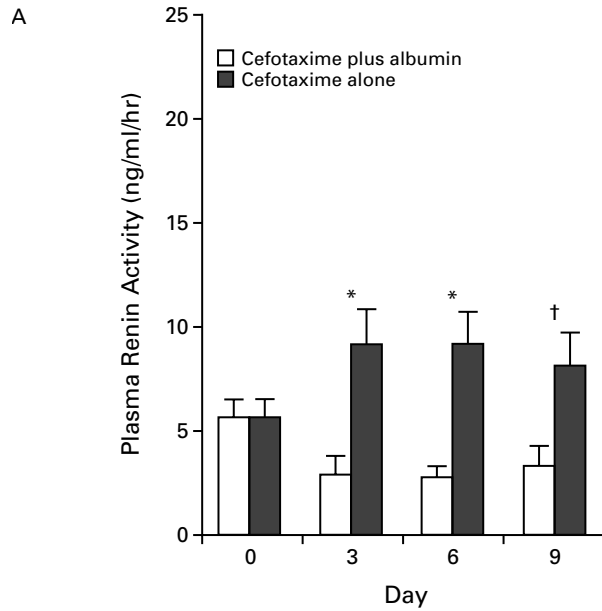
occurred in the patients who did not receive albumin. No significant differences in arterial pressure were found between the two groups of patients at any time during the study (Table 3).

There was a close relation between the development of renal impairment and the increase in plasma renin activity (Fig. 1B). Plasma renin activity increased markedly in the patients in whom renal impairment developed but did not change significantly in the patients without renal impairment.

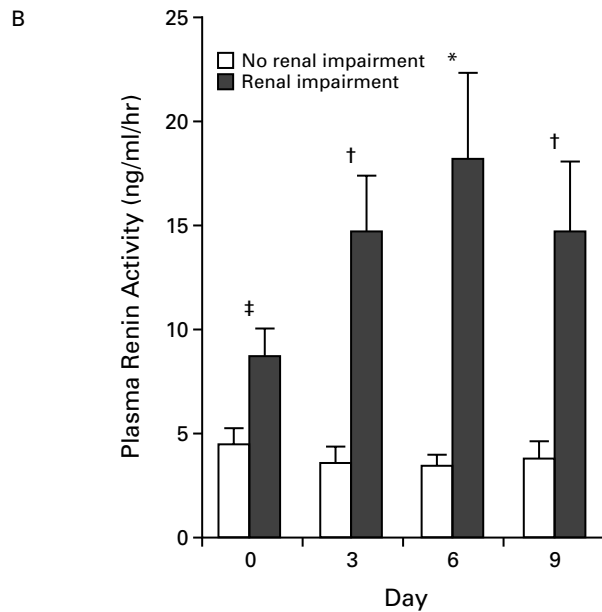
#### DISCUSSION

We found that the administration of albumin prevents renal impairment and reduces mortality in patients with cirrhosis and spontaneous bacterial peritonitis. The incidence of renal impairment was significantly lower among patients treated with cefotaxime and albumin than among patients treated with cefotaxime alone. In-hospital mortality in the group of patients treated with cefotaxime (29 percent) was similar to that reported in most studies.<sup>2-7</sup> By contrast, in-hospital mortality in the group treated with cefotaxime and albumin was only 10 percent. This rate is slightly higher than that reported for patients hospitalized for the treatment of ascites.<sup>18,21</sup> In multivariate analyses, treatment (cefotaxime and albumin or cefotaxime alone) was an independent predictor of renal impairment and in-hospital mortality.

The impairment of renal function is an important clinical event in patients with cirrhosis and spontaneous bacterial peritonitis. In our study, nonreversible renal impairment developed in one third of the patients treated with cefotaxime alone, and in most



NO. OF PATIENTS	0	3	6	9
Cefotaxime plus albumin	63	60	58	57
Cefotaxime alone	63	60	56	51



NO. OF PATIENTS	0	3	6	9
No renal impairment	99	96	96	94
Renal impairment	27	24	18	14

cases it was progressive, despite rapid resolution of the infection.

The pathogenesis of renal impairment associated with spontaneous bacterial peritonitis is probably hemodynamic. Patients with cirrhosis and ascites have a circulatory dysfunction characterized by arteriolar vasodilatation, hypotension, high cardiac output, decreased effective arterial blood volume, homeostatic activation of the renin-angiotensin and sympathetic nervous systems, and increased circulating levels of arginine vasopressin and endothelin.<sup>22-24</sup> Because these systems act as renal vasoconstrictors, renal perfusion and glomerular filtration are maintained in these patients by compensatory activation of renal vasodilators, especially prostaglandins.<sup>25,26</sup>

Patients with cirrhosis and spontaneous bacterial peritonitis have many of the features of the sepsis syndrome, including blood cultures that are positive for bacteria<sup>1,14</sup> and high levels of vasoactive cytokines.<sup>10,11</sup> The sepsis syndrome is also associated with arterial vasodilatation, impairment of circulatory function, and activation of neurohumoral vasoconstrictor systems.<sup>27-29</sup> Therefore, the high frequency and severity of renal impairment after the onset of spontaneous bacterial peritonitis are probably due to the combination of circulatory failure induced by infection and circulatory failure already present as a consequence of cirrhosis. This combined effect probably overcomes the compensatory action of renal vasodilators and thus leads to decreases in renal perfusion and the glomerular filtration rate. Our finding that renal impairment is associated with additional stimulation of the already activated renin-angiotensin system is consistent with this hypothesis. The absence of a change in arterial pressure does not rule out this possibility, because a reduction in arterial pressure might have been offset by the vasoconstrictor activity of the renin-angiotensin system.

The development of circulatory dysfunction, renal impairment, and mortality were found to be strongly related in patients with spontaneous bacterial peritonitis. Whether circulatory dysfunction and subsequent renal impairment contribute to the poor prognosis for these patients is unknown. It could be that both

**Figure 1.** Mean ( $\pm$ SE) Plasma Renin Activity on Days 0, 3, 6, and 9. Panel A shows plasma renin activity in patients treated with cefotaxime plus albumin and in patients treated with cefotaxime alone. Panel B shows plasma renin activity in patients in whom renal impairment did not develop and in those in whom it did. Plasma renin activity was measured by radioimmunoassay.<sup>19</sup> The normal mean value in healthy subjects is  $1.4 \pm 0.4$  ng per milliliter per hour.<sup>20</sup> Asterisks indicate  $P < 0.001$ , daggers indicate  $P = 0.005$ , and the double dagger indicates  $P = 0.02$  for the comparison between patients who received cefotaxime plus albumin and those who received cefotaxime alone (Panel A) or for the comparison between patients without renal failure and those with it (Panel B).

conditions are only markers of terminal liver failure and do not contribute directly to the poor outcome. Alternatively, the vasoconstrictor mechanisms that are activated as a homeostatic response to circulatory dysfunction may be harmful in patients with cirrhosis: as discussed previously, the overactivity of neurohumoral vasoconstrictors may induce renal hypoperfusion by acting on the renal circulation.<sup>23,30</sup> There is increasing evidence, however, that vasoconstrictors may enhance intrahepatic vascular resistance by acting on vascular smooth-muscle cells or stellate cells in the hepatic circulation.<sup>31-33</sup> This effect would reduce hepatic blood flow and aggravate portal hypertension and liver failure. The deleterious effects of circulatory dysfunction on the kidneys and liver may thus account for the poor outcome in patients with spontaneous bacterial peritonitis.

A close relation between impaired circulatory function and mortality has also been reported in patients with cirrhosis who were treated by large-volume paracentesis.<sup>20</sup> In such patients, impaired circulatory function is associated with an increase in portal pressure.<sup>34</sup> Thus, the most likely explanation for the reduced rate of early mortality in patients who are treated with albumin is that such treatment prevents circulatory dysfunction (i.e., maintaining the effective arterial blood volume) and the subsequent activation of vasoconstrictor systems. However, the possibility that the beneficial effects of albumin involve mechanisms other than those related to plasma expansion cannot be ruled out.

Intravenous albumin is expensive (approximately \$5 per gram in Spain) and has limited availability in some settings. Therefore, studies should be performed to determine whether treatment of spontaneous bacterial peritonitis with lower doses of albumin or with artificial plasma expanders, which are less expensive, would have similar beneficial effects on renal function and survival.

Supported by grants from the Fondo de Investigación Sanitaria (FIS 94/0956 and FIS 96/1723) and the Hospital Clínic.

*We are indebted to the following investigators for their collaboration: Lilyan Kelle, M.D. (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Glòria Fernández-Esparrach, M.D., Pere-Joan Ventura, B.Sc., Wladimiro Jiménez, Ph.D., Antonio Follo, M.D., and Raquel Cela, R.N. (Hospital Clínic, Barcelona); Carme Vila, M.D., and Ricard Solà, M.D. (Hospital del Mar, Barcelona); Gerardo Clemente, M.D., and Jose Antonio Carneros, M.D. (Hospital Gregorio Marañón, Madrid); and Jesús María Urman, M.D., and Mónica González García (Hospital Ramón y Cajal, Madrid).*

## REFERENCES

- Navasa M. Treatment and prophylaxis of spontaneous bacterial peritonitis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, eds. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis, and treatment. Malden, Mass.: Blackwell Science, 1999:538-49.
- Toledo C, Salmeron JM, Rimola A, et al. Spontaneous bacterial peritonitis in cirrhosis: predictive factors of infection resolution and survival in patients treated with cefotaxime. *Hepatology* 1993;17:251-7.
- Runyon BA, McHutchison JG, Antillon MR, Akriviadis EA, Montano AA. Short-course versus long-course antibiotic treatment of spontaneous bacterial peritonitis: a randomized controlled study of 100 patients. *Gastroenterology* 1991;100:1737-42.
- Rimola A, Salmerón JM, Clemente G, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. *Hepatology* 1995;21:674-9.
- Felisart J, Rimola A, Arroyo V, et al. Cefotaxime is more effective than is ampicillin-tobramycin in cirrhotics with severe infections. *Hepatology* 1985;5:457-61.
- Navasa M, Follo A, Llovet JM, et al. Randomized, comparative study of oral ofloxacin versus intravenous cefotaxime in spontaneous bacterial peritonitis. *Gastroenterology* 1996;111:1011-7.
- Grange JD, Amiot X, Grange V, et al. Amoxicillin-clavulanic acid therapy of spontaneous bacterial peritonitis: a prospective study of twenty-seven cases in cirrhotic patients. *Hepatology* 1990;11:360-4.
- García-Tsao G, Albillos A, Barden GE, West AB. Bacterial translocation in acute and chronic portal hypertension. *Hepatology* 1993;17:1081-5.
- Llovet JM, Bartolí R, March F, et al. Translocated intestinal bacteria cause spontaneous bacterial peritonitis in cirrhotic rats: molecular epidemiologic evidence. *J Hepatol* 1998;28:307-13.
- Navasa M, Follo A, Filella X, et al. Tumor necrosis factor and interleukin-6 in spontaneous bacterial peritonitis in cirrhosis: relationship with the development of renal impairment and mortality. *Hepatology* 1998;27:1227-32.
- Le Moine O, Devière J, Devaster JM, et al. Interleukin-6: an early marker of bacterial infection in decompensated cirrhosis. *J Hepatol* 1994;20:819-24.
- Follo A, Llovet JM, Navasa M, et al. Renal impairment after spontaneous bacterial peritonitis in cirrhosis: incidence, clinical course, predictive factors and prognosis. *Hepatology* 1994;20:1495-501.
- Such J, Guarner C, Runyon BA. Spontaneous bacterial peritonitis. In: Arroyo V, Ginès P, Rodés J, Schrier RW, eds. Ascites and renal dysfunction in liver disease: pathogenesis, diagnosis, and treatment. Malden, Mass.: Blackwell Science, 1999:99-115.
- Runyon BA, Canawati HN, Akriviadis EA. Optimization of ascitic fluid culture technique. *Gastroenterology* 1988;95:1351-5.
- Conn HO, Lieberthal MM. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins, 1979.
- Pelletier G, Salmon D, Ink O, et al. Culture-negative neutrocytic ascites: a less severe variant of spontaneous bacterial peritonitis. *J Hepatol* 1990;10:327-31.
- Ginès P, Rimola A, Planas R, et al. Norfloxacin prevents spontaneous bacterial peritonitis recurrence in cirrhosis: results of a double blind, placebo-controlled trial. *Hepatology* 1990;12:716-24.
- Ginès P, Arroyo V, Quintero E, et al. Comparison of paracentesis and diuretics in the treatment of cirrhotics with tense ascites: results of a randomized study. *Gastroenterology* 1987;93:234-41.
- Asbert M, Jiménez W, Gaya J, et al. Assessment of the renin-angiotensin system in cirrhotic patients: comparison between plasma renin activity and direct measurement of immunoreactive renin. *J Hepatol* 1992;15:179-83.
- Ginès A, Fernández-Esparrach G, Monescillo A, et al. Randomized trial comparing albumin, dextran-70, and polygeline in cirrhotic patients with ascites treated by paracentesis. *Gastroenterology* 1996;111:1002-10.
- Ginès P, Arroyo V, Vargas V, et al. Paracentesis with intravenous infusion of albumin as compared with peritoneovenous shunting in cirrhosis with refractory ascites. *N Engl J Med* 1991;325:829-35.
- Schrier RW, Arroyo V, Bernardi M, Epstein M, Henriksen JH, Rodés J. Peripheral arterial vasodilation hypothesis: a proposal for the initiation of renal sodium and water retention in cirrhosis. *Hepatology* 1988;8:1151-7.
- Arroyo V, Ginès P, Jiménez W, et al. Renal dysfunction in cirrhosis. In: Bircher J, Benhamou J, McIntyre N, Rizzetto M, Rodés J, eds. Oxford textbook of clinical hepatology. 2nd ed. Vol. 1. Oxford, England: Oxford University Press, 1999:733-61.
- Moore K, Wendon J, Frazer M, Karani J, Williams R, Badr K. Plasma endothelin immunoreactivity in liver disease and the hepatorenal syndrome. *N Engl J Med* 1992;327:1774-8.
- Arroyo V, Planas R, Gaya J, et al. Sympathetic nervous activity, renin-angiotensin system and renal excretion of prostaglandin E2 in cirrhosis: relationship to functional renal failure and sodium and water excretion. *Eur J Clin Invest* 1983;13:271-8.
- Bataller R, Ginès P, Guevara M, Arroyo V. Hepatorenal syndrome. *Semin Liver Dis* 1997;17:233-47.
- Parker MM, Parrillo J. Septic shock: hemodynamics and pathogenesis. *JAMA* 1983;250:3324-7.
- Suffredini AF, Fromm RE, Parker MM, et al. The cardiovascular response of normal humans to the administration of endotoxin. *N Engl J Med* 1989;321:280-7.

- 29.** Voerman HJ, Stehouwer CD, van Kamp GJ, Strack van Schijndel RJ, Groeneveld AB, Thijs LG. Plasma endothelin levels are increased during septic shock. *Crit Care Med* 1992;20:1097-101.
- 30.** Arroyo V, Ginès P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. *Hepatology* 1996;23:164-76.
- 31.** Bhathal PS, Grossman HJ. Reduction of the increased portal vascular resistance of the isolated perfused cirrhotic rat liver by vasodilators. *J Hepatol* 1985;1:325-37.
- 32.** Pinzani M, Failli P, Ruocco C, et al. Fat-storing cells as liver-specific pericytes: spatial dynamics of agonist-stimulated intracellular calcium transients. *J Clin Invest* 1992;90:642-6.
- 33.** Zhang JX, Pegoli W Jr, Clemens MG. Endothelin-1 induces direct constriction of hepatic sinusoids. *Am J Physiol* 1994;266:G624-G632.
- 34.** Ruiz-del-Arbol L, Monescillo A, Jiménez W, García-Plaza A, Arroyo V, Rodés J. Paracentesis-induced circulatory dysfunction: mechanism and effect on hepatic hemodynamics in cirrhosis. *Gastroenterology* 1997;113:579-86.