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.)

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Renal Function

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in the cefotaxime-plus-albumin group received the scheduled doses of albumin except for the two patients who were withdrawn from this group because they did not meet the inclusion criteria.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 olofoxacin 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 cefotaxi-
The incidence of renal impairment among patients with cirrhosis and spontaneous bacterial peritonitis 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 = 0.01), serum bilirubin level (P = 0.01), and prothrombin time with a base-line serum bilirubin level of at least 4 mg per deciliter (68 µmol 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 = 0.01), serum bilirubin level (P = 0.01), and prothrombin time with a base-line serum bilirubin level of at least 4 mg per deciliter (68 µmol 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).

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Mean arterial pressure —
Serum sodium — mmol/liter
Serum creatinine — mg/dl

For creatinine to micromoles per liter, multiply by 88.4. For nitrogen to millimoles per liter, multiply by 0.357; to convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357; to convert the values for bilirubin to micromoles per liter, multiply by 17.1.

([P = 0.01]) at base line and treatment assignment ([P = 0.08]; 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 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.²–⁷ 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.¹⁸,²¹ 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 patients treated with cefotaxime and albumin.
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.22-24 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.25,26

Patients with cirrhosis and spontaneous bacterial peritonitis have many of the features of the sepsis syndrome, including blood cultures that are positive for bacteria1,14 and high levels of vasoactive cytokines.10,11 The sepsis syndrome is also associated with arterial vasodilatation, impairment of circulatory function, and activation of neurohumoral vasoconstrictor systems.27-29 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](image_url)

**Figure 1.** Mean (±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.23 The normal mean value in healthy subjects is 1.4±0.4 ng per milliliter per hour.23 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. There is increasing evidence, however, that vasoconstrictors may enhance intrarenal vascular resistance by acting on vascular smooth-muscle cells or stellate cells in the hepatic circulation. 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. In such patients, impaired circulatory function is associated with an increase in portal pressure. 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 Clinic.

We are indebted to the following investigators for their collaboration: Lilian Kolle, M.D. (Hospital de la Santa Creu i Sant Pau, Barcelona, Spain); Gloria Fernandez-Esparrach, M.D., Pere-Juan Ventura, B.S., Waldimiro Jimenez, Ph.D., Antonia Follo, M.D., and Raquel Celis, R.N. (Hospital Clinic, Barcelona); Carme Vilà, M.D., and Ricard Solà, M.D. (Hospital del Mar, Barcelona); Gerardo Clemente, M.D., and Jose Antonio Carnero, M.D. (Hospital Gregorio Marañon, Madrid); and Jesús Maria Urman, M.D., and Mónica González García (Hospital Ramón y Cajal, Madrid).

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