

CLINICAL–LIVER, PANCREAS, AND BILIARY TRACT

Primary Prophylaxis of Spontaneous Bacterial Peritonitis Delays Hepatorenal Syndrome and Improves Survival in Cirrhosis

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Background & Aims: Norfloxacin is highly effective in preventing spontaneous bacterial peritonitis recurrence in cirrhosis, but its role in the primary prevention of this complication is uncertain.

Methods: Patients with cirrhosis and low protein ascitic levels (<15 g/L) with advanced liver failure (Child–Pugh score \geq 9 points with serum bilirubin level \geq 3 mg/dL) or impaired renal function (serum creatinine level \geq 1.2 mg/dL, blood urea nitrogen level \geq 25 mg/dL, or serum sodium level \leq 130 mEq/L) were included in a randomized controlled trial aimed at comparing norfloxacin (35 patients) vs placebo (33 patients) in the primary prophylaxis of spontaneous bacterial peritonitis. The main end points of the trial were 3-month and 1-year probability of survival. Secondary end points were 1-year probability of development of spontaneous bacterial peritonitis and hepatorenal syndrome. **Results:** Norfloxacin administration reduced the 1-year probability of developing spontaneous bacterial peritonitis (7% vs 61%, $P < .001$) and hepatorenal syndrome (28% vs 41%, $P = .02$), and improved the 3-month (94% vs 62%, $P = .003$) and the 1-year (60% vs 48%, $P = .05$) probability of survival compared with placebo.

Conclusions: Primary prophylaxis with norfloxacin has a great impact in the clinical course of patients with advanced cirrhosis. It reduces the incidence of spontaneous bacterial peritonitis, delays the development of hepatorenal syndrome, and improves survival.

Spontaneous bacterial peritonitis (SBP), an infection of ascites caused by translocation of bacteria from the intestinal lumen into the systemic circulation, is a frequent event and a common cause of death in patients with cirrhosis.^{1,2} In some patients the mechanism of death

is an uncontrolled infection and septic shock. More commonly, however, the infection is cured with antibiotics but patients develop hepatorenal syndrome (HRS) and die with severe hepatic and renal insufficiency.^{3–6} Prophylaxis of SBP should, therefore, be associated with an increase in survival.

Most data on prophylaxis of SBP derive from studies assessing long-term intestinal decontamination with oral norfloxacin (or other antibiotics) in patients recovering from an episode of this infection (secondary prophylaxis).^{7–11} The probability of SBP recurrence was reduced drastically in all studies. However, no significant effect on survival was observed. The role of norfloxacin in the primary prophylaxis of SBP is unclear. In the only randomized, placebo-controlled study published to date, no significant effect in the probability of developing SBP or survival was found.¹² An important limitation of these studies, however, was that their design and the patient's selection were inadequate to detect differences in survival.

The ideal population to assess the impact of prophylaxis with norfloxacin in the natural history of cirrhosis is one that includes patients at high risk of developing SBP and HRS. Advanced liver failure and low ascitic fluid protein concentration are important predictors of SBP.^{13–16} Impairment of circulatory and renal function is the best predictor of HRS.^{3–6,17,18} This article reports the results of a double-blind, randomized, placebo-controlled trial showing that primary prophylaxis with norfloxacin in patients at high risk of developing SBP and HRS is associated with a significant improvement in the clinical course of the disease and an increase in survival.

Abbreviations used in this paper: HRS, hepatorenal syndrome; SBP, spontaneous bacterial peritonitis.

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Materials and Methods

Patients

We studied patients with cirrhosis and ascites admitted between September 2000 and June 2004. Diagnosis was based on clinical, laboratory, and ultrasonographic data or on histology. Criteria for inclusion were as follows: (1) age 18–80 years, (2) protein levels in ascitic fluid of less than 15 g/L, (3) impaired renal function (serum creatinine level \geq 1.2 mg/dL, BUN \geq 25 mg/dL, or serum sodium level \leq 130 mEq/L) or severe liver failure (Child–Pugh score \geq 9 points with serum bilirubin level \geq 3 mg/dL). The protein concentration in ascitic fluid was selected because it is an important predictor of SBP.^{13–16} Serum bilirubin,^{14–16} serum albumin,¹⁵ and prothrombin time¹⁵ also have been identified as independent predictors of SBP, and for this reason the Child–Pugh score also was chosen. However, because serum bilirubin has been reported as a very powerful predictor of SBP in several studies,^{15,16} the Child–Pugh score was combined with serum bilirubin. A cut-off level of 3 mg/dL of serum bilirubin was selected on the basis of 2 studies that showed that levels greater than 2.5 or 3.2 mg/dL were associated with a high incidence of SBP.^{15,16} Hyponatremia and increased serum creatinine or blood urea nitrogen concentrations were chosen because they are powerful predictors of type-1 HRS.^{3,4,18–20} Exclusion criteria were as follows: (1) previous SBP or norfloxacin prophylaxis, (2) allergy to quinolones, (3) hepatocellular carcinoma, (4) data of organic renal failure (ultrasonographic evidence of obstructive uropathy or parenchymal renal disease or hematuria and/or proteinuria), and (5) human immunodeficiency virus infection. The protocol was approved by the ethics committee of each hospital. Written informed consent was obtained from the patients.

Protocol

Baseline evaluation included history and physical examination, liver and renal tests, ascitic fluid analysis and culture, fresh urine sediment, and abdominal ultrasonography. Patients who fulfilled the inclusion criteria were allocated into 2 groups: patients in the study group received norfloxacin 400 mg/day (1 tablet); patients in the control group received placebo (1 tablet per day). Identical norfloxacin and placebo tablets were prepared by Madaus S.A. (Barcelona, Spain). Randomization was performed using consecutively numbered, computer-generated envelopes containing treatment assignment. Treatment was started immediately after randomization, which was independent at each hospital. Follow-up visits were performed every 2 months. Treatment compliance was assessed by interviewing the patient and by tablet count at each visit. A new box with the study medication then was given. A patient was considered noncompliant when the study medication was not taken for 7 days or more

every 2 months. Norfloxacin or placebo were interrupted when patients developed an episode of SBP, received a liver transplant, or completed a follow-up period of 1 year. They were considered censored at that time. The selection of a maximal period of follow-up evaluation of 1 year was based on 3 points. First, a previous study showed that the greatest difference in the incidence of SBP recurrence between patients treated with norfloxacin or placebo occurred at the 11th month of follow-up evaluation.⁷ Although patients included in the current study did not have a previous history of SBP, we expected a similar difference in the probability of SBP development between groups because of the extremely high risk of infection estimated in patients receiving placebo. Second, we hypothesized that mortality during the study period would be related closely to complications triggered by SBP. Therefore, we decided to assess survival at the time of the greatest difference in the probability of SBP development. Finally, considering that our patients had severely impaired liver and/or renal function, a high mortality rate was expected to occur within the first year after inclusion.

Diagnostic paracentesis was performed only when clinically indicated. Diagnosis of spontaneous bacteremia, SBP, urinary infection, and other infections was made as described previously.²¹ Type-1 and type-2 HRS were diagnosed according to the criteria of the International Ascites Club.²² Transient renal failure was defined as a nonsustained increase in serum creatinine (by $>50\%$) to levels higher than 1.5 mg/dL. Spontaneous bacteremia and SBP were treated with ceftriaxone. Treatment was modified, if required, according to clinical course and microbiologic results. Patients with SBP received intravenous albumin to prevent HRS (1.5 g/kg/bw at infection diagnosis and 1 g/kg/bw on day 3).⁶ Norfloxacin, 400 mg/12 h for 7 days, was given to patients from both groups who developed upper gastrointestinal hemorrhage to prevent bacterial infections.²³ HRS was not treated with vasoconstrictors because at the time of protocol approval (1999) there were very few data on the efficacy of this treatment.

Statistical Analysis

The main end points of the trial were 3-month and 1-year probability of survival. Although previous investigations assessing SBP prophylaxis did not show significant differences in survival between patients receiving norfloxacin and those receiving placebo,^{7,12} the current trial but not these studies included mainly patients at high risk of developing type-1 HRS associated with SBP and, therefore, with a high probability of dying within a short period of time. We estimated a 1-year probability of survival of 25% in the placebo group based on previous studies showing a 1-year probability of survival of 20%, 26%, and 38% in patients with type-2 HRS,²⁴ dilutional hyponatremia (P. Gines, unpublished observa-

tion^{25,26}), and low protein ascites with high bilirubin level and/or low platelet count,¹⁶ respectively. The 1-year probability of survival of patients in the norfloxacin group was estimated as 55% considering that selective intestinal decontamination would drastically reduce the incidence of SBP, which is the most frequent precipitating event of type-1 HRS¹⁹ and a common cause of death in patients with advanced cirrhosis. Moreover, recent studies have shown that the administration of norfloxacin to patients with cirrhosis and ascites is associated with a significant improvement in systemic hemodynamics, with an increase in mean arterial pressure and a suppression of plasma renin activity.^{27,28} These 2 parameters are the most sensitive predictors of survival in patients with cirrhosis and ascites.^{19,29} Based on these assumptions, 34 patients had to be included in each group to obtain a *P* value of less than .05 with an α error of 5% and a β error of 20% in a 1-tailed test. Secondary end points were 1-year probability of developing SBP and HRS. The trial was evaluated on an intention-to-treat basis.

Variables were compared by the Student *t* test or the χ^2 test with the Yates correction when indicated. Probability curves were constructed with the Kaplan–Meier method and compared by the log-rank test. Results are given as relative hazard plus 95% confident interval or as mean \pm SD. Calculations were performed with the SPSS Statistical Package (version 11.0, 2000; SPSS Inc., Chicago, IL). Differences were considered significant at the *P* value of .05.

Results

Study Population

A total of 157 patients with low protein ascites and advanced liver failure or impaired renal function were screened. Of these, 83 were not studied because of the presence of exclusion criteria (61 patients), death between evaluation and randomization (14 patients), and refusal to participate (8 patients). Of the 74 patients randomized, 6 were excluded from the analysis of the results. Five (3 in the norfloxacin group and 2 in the placebo group) were lost to follow-up evaluation immediately after randomization. The sixth patient (from the placebo group) was excluded because of violation of the protocol (unknown primary prophylaxis with norfloxacin). Thus, the final analysis of the trial included 68 patients: 35 in the norfloxacin group and 33 in the placebo group. Reasons for inclusion in the study were impaired renal function in 20 patients (29%), severe liver failure in 14 (21%), and both criterion in 34 (50%). There were no differences between groups in the inclusion criteria. Sixty-five percent of the patients were included in the study during a hospitalization, 23 of 35 patients in the norfloxacin group (66%) and 21 of 33 in the placebo group (64%). The main cause of admission was ascites, followed by encephalopathy and infections

Table 1. Baseline Clinical and Analytic Data

	Norfloxacin (n = 35)	Placebo (n = 33)
Age, y	62 \pm 11	61 \pm 12
Sex, M/F	22/13	23/10
Alcoholic cirrhosis, n (%)	20 (57)	16 (49)
Active alcoholism, n (%) ^a	10 (29)	7 (21)
Mean arterial pressure, mm Hg	83 \pm 8	84 \pm 9
Hematocrit level, %	31 \pm 5	31 \pm 5
White cell count, per mm ³	6880 \pm 3227	6020 \pm 2843
Platelet count, per mm ³	120,314 \pm 74,952	94,061 \pm 53,571
Serum bilirubin level, mg/dL	3.5 \pm 2.3	4.4 \pm 4.6
Serum albumin level, g/L	28 \pm 6	26 \pm 5
International normalized ratio	1.49 \pm .30	1.56 \pm .36
Child–Pugh score ^b	9.9 \pm 1.5	10.4 \pm 1.5
Model for End-stage Liver Disease score ^c	16.7 \pm 3.0	18.1 \pm 3.7
Previous variceal bleeding, n (%)	6 (17)	5 (15)
Previous hepatic encephalopathy, n (%)	5 (14)	8 (24)
Treatment with β -blockers, n (%)	15 (43)	19 (58)
Refractory ascites, n (%)	13 (37)	9 (27)
Serum creatinine level, mg/dL	1.2 \pm .4	1.2 \pm .4
Blood urea nitrogen level, mg/dL	27 \pm 17	29 \pm 15
Serum sodium level, mEq/L	131 \pm 4	131 \pm 6
Ascitic fluid protein level, g/L	9 \pm 4	9 \pm 3
Inclusion during hospitalization, n (%)	23 (66)	21 (64)
Main cause of initial hospitalization, n		
Ascites	16	15
Hepatic encephalopathy	3	3
Infection other than SBP	2	2
Upper gastrointestinal bleeding	2	1

NOTE. Plus-minus values are means \pm SD. No significant differences were found between groups in any of the data. To convert the values for serum bilirubin to micromoles per liter, multiply by 17.1; to convert the values for creatinine to micromoles per liter, multiply by 88.4; to convert the values for blood urea nitrogen to micromoles per liter, multiply by .357.

^aArbitrarily defined as a daily alcohol intake greater than 20 g in patients with alcoholic cirrhosis.

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

^cThe Model for End-stage Liver Disease score (range, 6–45, where 6 indicates good prognosis and 45 indicates poor prognosis) was calculated on the basis of the prothrombin time (international normalized ratio), the serum bilirubin level, the serum creatinine level, and the need for dialysis in the past week.

other than SBP. No significant differences between patients receiving norfloxacin or placebo were observed at baseline (Table 1). Baseline characteristics also were similar between patients included in the study during a hospital-

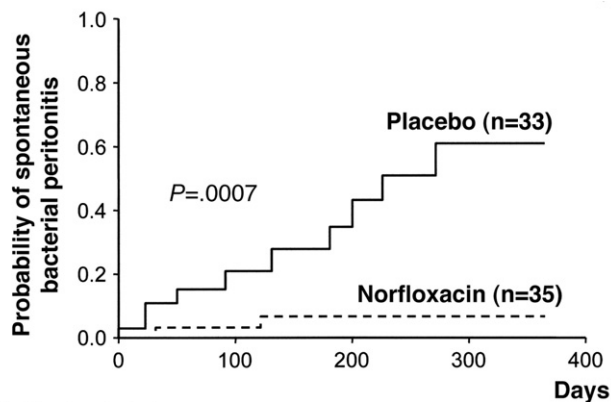
ization and those who were not, except for refractory ascites, which was more frequent in patients included during hospitalization (43% vs 12%, $P = .02$).

Incidence of SBP and Other Bacterial Infections

Two patients in the norfloxacin group and 10 in the placebo group developed SBP ($P = .02$) and 0 and 4 patients, respectively, developed spontaneous bacteremia ($P = .05$). The frequency of other infections was similar in the 2 groups (Table 2). The 1-year probability of developing SBP was significantly lower in the norfloxacin group (Figure 1). Seven of the 44 patients (16%) included in the study during a hospitalization developed SBP during the follow-up evaluation. This incidence was similar to that observed in patients recruited at the outpatient clinic (5 of 24; 21%).

Most bacteria isolated in the norfloxacin group were gram-negative bacilli (Table 2). Gram-positive cocci and gram-negative bacilli were isolated with similar frequency in the placebo group. Eleven of 13 gram-negative bacilli isolated in the norfloxacin group were resistant to quinolones compared with only 1 of 6 isolated in the placebo group ($P = .01$). No cases of SBP caused by quinolone-resistant bacteria were detected in the study. Resistant bacteria were isolated mainly in urinary infections.

Eleven patients in the norfloxacin group and 18 in the placebo group were censored before completion of the



Patients at risk

	0	100	200	300	400
Norfloxacin	35	26 (1)	17 (2)	14 (2)	10 (2)
Placebo	33	13 (5)	7 (8)	2 (10)	1 (10)

Figure 1. Probability of developing SBP in patients receiving norfloxacin (dotted line) or placebo prophylaxis (continuous line). Figures in parentheses indicate the cumulative number of subjects who developed SBP.

1-year follow-up period because of development of SBP (2 and 10 patients, respectively), liver transplantation (6 and 6 patients, respectively), and lost to follow-up evaluation (3 and 2 patients, respectively). Three patients in each group were noncompliant. Causes of noncompliance were treatment abandonment (3 and 1 patients, respectively) and poor adherence to therapy (0 and 2 patients, respectively). These 6 patients were included in the final analysis of the results. No side effects related to norfloxacin or placebo were observed.

Incidence of HRS

Renal failure developed significantly less frequently in patients receiving norfloxacin (7 vs 16 patients; $P = .03$). Causes of renal failure were as follows: type-1 HRS (6 patients) and transient renal failure (1 patient) in the norfloxacin group, and type-1 HRS (9 patients), type-2 HRS (1 patient), acute glomerulonephritis (1 patient), and transient renal failure (5 patients) in the placebo group. HRS was associated with bacterial infection in 4 patients in the norfloxacin group (3 urinary infections and 1 cholangitis) and in 6 patients in the placebo group (3 urinary infections, 1 SBP, 1 spontaneous bacteremia, and 1 pneumonia). HRS developed within the first 3 months of follow-up evaluation in 9 patients in the placebo group and in only 1 patient in the norfloxacin group ($P = .006$). The 1-year probability of developing HRS was significantly lower in the norfloxacin group (Figure 2).

Mortality

Ten patients in the norfloxacin group and 13 in the placebo group died. Causes of death are shown in Table 3. The main cause of death in both groups of patients was HRS (5 and 8 patients, respectively). Mor-

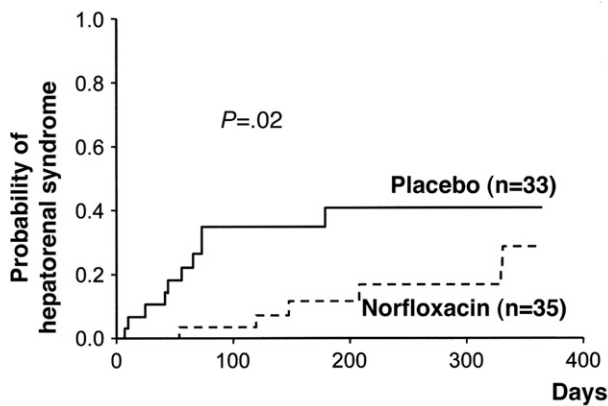
Table 2. Bacterial Infections and Isolated Organisms

	Norfloxacin (n = 35)	Placebo (n = 33)	P
Patients with infection, n (%)	14 (40%)	19 (58%)	NS
SBP	2 (6%)	10 (30%)	.02
Spontaneous bacteremia	0	4 (12%)	.05
Urinary tract infection ^a	6 (17%)	4 (12%)	NS
Pneumonia	1 (3%)	3 (9%)	NS
Other infections ^b	7 (20%)	4 (12%)	NS
Infections, n	24	26	NS
Isolated organisms, n			
Gram-negative bacilli	13	6	NS
<i>Escherichia coli</i>	9	3	
<i>Klebsiella pneumoniae</i>	2	1	
<i>Aeromonas hydrophyla</i>	0	1	
<i>Pseudomonas aeruginosas</i>	1	0	
<i>Enterobacter chloacae</i>	0	1	
<i>Alcaligenes faecalis</i>	1	0	
Gram-positive cocci	2	7	NS
MS <i>Staphylococcus aureus</i>	0	1	
<i>Staphylococcus epidermidis</i>	1	0	
<i>Streptococcus viridans</i>	0	2	
<i>Streptococcus mitis</i>	0	1	
<i>Peptostreptococcus</i>	0	1	
<i>Enterococcus spp</i>	1	2	

MS, methicillin susceptible.

^aThree patients (2 from the norfloxacin group and 1 from the placebo group) developed more than 1 urinary tract infection.

^bOther infections include catheter sepsis, cellulitis, cholangitis, and bronchitis.



Patients at risk						
Norfloxacin	35	26 (1)	17 (3)	14 (4)	10 (6)	
Placebo	33	13 (9)	7 (10)	2 (10)	1 (10)	

Figure 2. Probability of developing HRS in patients receiving norfloxacin (dotted line) or placebo prophylaxis (continuous line). Figures in parentheses indicate the cumulative number of subjects who developed HRS.

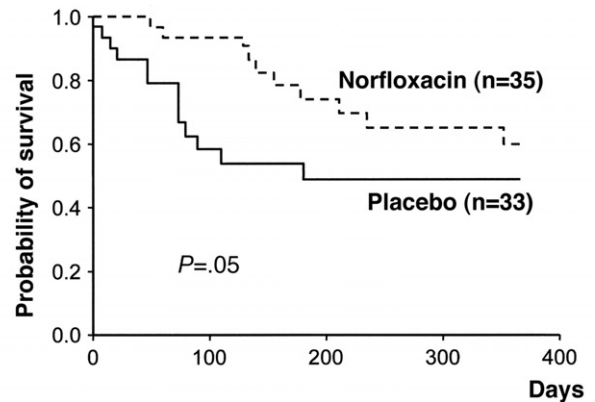
tality within the first 3 months of follow-up evaluation was significantly higher in the placebo group (10 vs 2 patients; $P = .02$). Three-month (94% in patients receiving norfloxacin vs 62% in patients receiving placebo, $P = .003$) and 1-year probability of survival (60% vs 48%, respectively; $P = .05$, Figure 3) were significantly longer in patients receiving norfloxacin.

Discussion

In this study, a population of cirrhotic patients with a high risk of developing SBP and HRS was identified using simple parameters that estimate the antibacterial activity of the ascitic fluid, the degree of hepatic insufficiency, and the severity of renal dysfunction. The 1-year probability of developing SBP and HRS in the placebo group were 61% and 41%, respectively. It is important to remark that patients developing SBP received intravenous albumin to prevent the development of HRS and that this was extremely effective. Only 1 of the 12 patients with SBP (8%) developed HRS associated with

Table 3. Causes of Death

	Norfloxacin (n = 35)	Placebo (n = 33)	P
At 3 months	2	10	.02
HRS, n	1	7	.02
Liver failure, n	1	1	NS
Variceal bleeding, n	0	1	NS
Septic shock	0	1	NS
At 1 year	10	13	NS
HRS, n	5	8	NS
Liver failure, n	4	1	NS
Variceal bleeding, n	1	2	NS
Septic shock	0	1	NS
Stroke	0	1	NS



Patients at risk						
Norfloxacin	35	26 (2)	17 (7)	14 (9)	10 (10)	
Placebo	33	13 (11)	7 (13)	2 (13)	1 (13)	

Figure 3. Probability of 1-year survival in patients receiving norfloxacin (dotted line) or placebo prophylaxis (continuous line). Figures in parentheses indicate the cumulative number of subjects who died.

the infection. This frequency is considerably lower than the 30%–40% incidence that should be expected to occur in the absence of albumin administration.⁶

The study aimed to assess if long-term norfloxacin administration has a significant effect on the natural history of patients with advanced cirrhosis. For this reason, end points of the trial were the 1-year probability of SBP, HRS, and survival. Although our population consisted of a restricted group of patients with decompensated cirrhosis, it probably represents a significant number of patients listed for liver transplantation in most hospitals (32% of the 459 patients listed in our center within the past 5 years). The inclusion of the 3-month probability of survival as a primary end point was related to this feature. We wanted to know if patients waiting for liver transplantation may benefit from primary prophylaxis with norfloxacin.

Our study indicates that norfloxacin administration has a great impact on the clinical course of patients with advanced cirrhosis. It was associated with a significant decrease in the 1-year probability of developing SBP and HRS. Moreover, the 3-month and 1-year probability of survival was increased significantly in patients receiving norfloxacin. It is important to remark, however, that this difference in the probability of survival between groups was particularly important at the third month and decreased at 1-year of follow-up evaluation. Because we underestimated the 1-year probability of survival of patients receiving placebo in the calculation of the sample size, our study was underpowered to draw strong conclusions regarding this specific end point.

Recent studies have suggested that prophylaxis of SBP with norfloxacin may not be as effective as in the past because of an increased frequency of quinolone-resistant bacteria in the fecal flora of cirrhotic patients secondary to the widespread use of these agents.^{21,30–33} Our study

does not support this concept. Only 2 of 35 patients in the norfloxacin group developed SBP during the study period and in no case was the infection caused by quinolone-resistant bacteria. These bacteria were isolated mainly in urinary infections. On the other hand, the 1-year probability of SBP development in the norfloxacin and placebo groups of the current study were comparable with those observed by Gines et al⁷ in 1990 in their pioneer study assessing norfloxacin in the prophylaxis of SBP recurrence.

The mechanism by which norfloxacin reduced the probability of developing HRS was independent of its effect on the prevention of SBP because only 1 patient in the placebo group developed HRS triggered by this infection. It also was unrelated to the prevention of other infections because they were equally frequent in the 2 groups. Recent studies have indicated that selective intestinal decontamination with norfloxacin in patients with cirrhosis without bacterial infection induces a significant improvement in circulatory function as indicated by an increase in arterial pressure and systemic vascular resistance and a suppression of plasma renin activity.^{27,28} This was related to a significant decrease in the circulating levels of lipopolysaccharide binding protein (a marker of endotoxemia), cytokines, and nitric oxide metabolites, and was attributed to a reduction in the translocation of bacterial products from the intestine into the systemic circulation.²⁷ Improvement in systemic hemodynamics promoted by norfloxacin is an attractive hypothesis to explain our results because the degree of impairment in circulatory and renal function is the most important predictor of HRS development in patients with cirrhosis and ascites.^{17,18} Fifteen of the 16 patients developing HRS died and this was the most frequent cause of death in our study. Although there were no significant differences in the frequency of HRS between groups, this complication occurred significantly later in patients treated with norfloxacin. Differences in the probability of survival between groups, therefore, likely were related to differences in the timing of HRS development.

An outstanding observation of the current study was that the beneficial effect of norfloxacin on HRS development and mortality was restricted mainly to the first 3 months of follow-up evaluation. We have no clear explanation for this finding because the effect of norfloxacin on SBP development occurred during the entire follow-up period. We also have no explanation for the higher probability of survival observed in patients in the placebo group, as compared with that reported in previous studies in patients with severe liver failure or impaired renal function.

In conclusion, primary prophylaxis with norfloxacin in patients with advanced cirrhosis and low protein ascites is associated with a significant decrease in the 1-year probability of SBP and HRS development and a significant increase in the 3-month and 1-year probability of

survival. Long-term norfloxacin administration is, therefore, clearly indicated in these patients, particularly if they are awaiting liver transplantation, because it may increase the applicability of this procedure.

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