Norfloxacin vs Ceftriaxone in the Prophylaxis of Infections in Patients With Advanced Cirrhosis and Hemorrhage

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Background & Aims: Oral norfloxacin is the standard of therapy in the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage. However, during the last years, the epidemiology of bacterial infections in cirrhosis has changed, with a higher incidence of infections caused by quinolone-resistant bacteria. This randomized controlled trial was aimed to compare oral norfloxacin vs intravenous ceftriaxone in the prophylaxis of bacterial infection in cirrhotic patients with gastrointestinal bleeding. **Methods:** One hundred eleven patients with advanced cirrhosis (at least 2 of the following: ascites, severe malnutrition, encephalopathy, or bilirubin >3 mg/dL) and gastrointestinal hemorrhage were randomly treated with oral norfloxacin (400 mg twice daily; n = 57) or intravenous ceftriaxone (1 g/day; n = 54) for 7 days. The end point of the trial was the prevention of bacterial infections within 10 days after inclusion. **Results:** Clinical data were comparable between groups. The probability of developing proved or possible infections, proved infections, and spontaneous bacteremia or spontaneous bacterial peritonitis was significantly higher in patients receiving norfloxacin (33% vs 11%, $P = .003$; 26% vs 11%, $P = .03$; and 12% vs 2%, $P = .03$, respectively). The type of antibiotic used (norfloxacin), transfusion requirements at inclusion, and failure to control bleeding were independent predictors of infection. Seven gram-negative bacilli were isolated in the norfloxacin group, and 6 were quinolone resistant. Nonenterococcal streptococci were only isolated in the norfloxacin group. No difference in hospital mortality was observed between groups. **Conclusions:** Intravenous ceftriaxone is more effective than oral norfloxacin in the prophylaxis of bacterial infections in patients with advanced cirrhosis and hemorrhage.

Bacterial infection is a major problem in patients with cirrhosis and gastrointestinal hemorrhage. First, it is very frequent. Between 25% and 65% of these patients present infections at admission or develop them during hospitalization.[1–9] The incidence of infections is particularly high in patients with advanced liver failure and/or severe hemorrhage.[7,10] Second, in patients with ascites, infections may induce acute impairment in systemic circulatory function and hepatorenal syndrome.[11–14] Finally, bacterial infection in patients with variceal bleeding is associated with an increased rate of failure to control bleeding,[15,16] rebleeding,[9,17,18] and hospital mortality.[5,16,19] The recent demonstration that renal failure in cirrhotic patients with spontaneous bacterial peritonitis is associated with a marked increase in portal pressure offers a rational explanation for these features.[13]

Since the pioneer study of Rimola et al demonstrating that oral administration of nonabsorbable antibiotics markedly reduces the incidence of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage,[1] antibiotic prophylaxis is considered a standard of care in these patients.[5,20,21] Selective intestinal decontamination with oral norfloxacin, a poorly absorbable quinolone with antibacterial activity against gram-negative bacteria but not against gram-positive cocci or anaerobic bacteria, is the most commonly used approach for the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage.[2,20] Recent studies, however, have presented evidence suggesting that oral quinolone administration may not be the best regime for the prevention of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage. The prevalence of quinolone-resistant bacteria in the fecal flora[22,23] and the incidence of spontaneous bacterial peritonitis[24] and other infections[25,26] caused by these organisms have increased substantially during the last years. However, a significant number of infections in cirrhotic patients with gastrointestinal hemorrhage are caused by gram-positive bacteria related to the invasive procedures used in these patients.[24]

These considerations led us to perform the current study, which consisted of a randomized controlled trial aimed at comparing oral norfloxacin vs intravenous ceftriaxone in the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage and severe liver failure. Intravenous ceftriaxone was selected for 2 reasons. First, we have recently shown that most quinolone-resistant bacteria isolated in cirrhotic patients with spontaneous bacteremia, spontaneous bacterial peritonitis, and other infections are susceptible to third-generation cephalosporins.[24] Second, antibiotics administered by intravenous route are theoretically more appropriate than those administered orally in the prophylaxis of infection in patients with active upper gastrointestinal bleeding. The end point of the study was to assess whether intravenous ceftriaxone is more effective than oral norfloxacin in reducing the rate of bacterial infections within the first 10 days after the hemorrhage because this is the period within which most infections occur.

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Materials and Methods

Patients

The study was performed in patients with cirrhosis admitted to 4 Spanish hospitals for the treatment of an upper gastrointestinal hemorrhage between February 2000 and April 2004. Diagnosis of cirrhosis was based on clinical, laboratory, and ultrasonographic data or on histology. Inclusion criteria were as follows: age 18–80 years, hematemesis and/or melena within 24 hours prior to inclusion, and advanced cirrhosis as defined by the presence of 2 or more of the following signs of liver failure: severe malnutrition (as defined by the presence of clear signs of muscle wasting), serum bilirubin >3 mg/dL, ascites (confirmed by paracentesis), and hepatic encephalopathy (grade 1 or more). Diagnosis of ascites, severe malnutrition, and encephalopathy was made clinically. Exclusion criteria were as follows: allergy to cephalosporins or quinolones, presence of any of the following signs of infection (fever >37.5°C, white blood cell count >15,000 mm^3, immature neutrophils >500 mm^3, polymorphonuclear cell count in ascitic fluid >250/mm^3, more than 15 leukocytes/field in the fresh urine sediment, or data compatible with pneumonia on the chest x-ray), treatment with antibiotics within 2 weeks before the hemorrhage (excluding oral norfloxacin for prophylaxis of spontaneous bacterial peritonitis), previously diagnosed advanced hepatocellular carcinoma (1 nodule greater than 5 cm, 3 nodules with 1 greater than 3 cm, or more than 3 nodules), and human immunodeficiency virus (HIV) infection.

The study was approved by the ethics committee of each hospital participating in the study. Written informed consent was obtained from the patients and, in those with encephalopathy, from their families. The protocol conformed to the Helsinki Declaration and Guidelines for Good Clinical Practice in Clinical Trials.

Treatment of the Hemorrhage

Following admission, a history and physical examination were obtained, and 2 short intravenous cannulas and a nasogastric tube were placed. A central line was also placed in most patients. Urinary catheter was inserted only if indicated. Laboratory measurements including standard liver and renal function tests, blood and ascitic fluid cell count and cultures (samples were inoculated into aerobic and anaerobic blood culture bottles at patient's bedside), and fresh urine sediment and culture were then performed as well as a chest x-ray. Emergency endoscopy and endoscopic treatment (if indicated, sclerotherapy or banding) were done within the first 24 hours after onset of the hemorrhage in all cases. Patients with severe hepatic encephalopathy (grade 3 or 4) were intubated prior to endoscopy. Patients with bleeding from esophageal or gastric varices or from portal hypertensive gastropathy received somatostatin or terlipressin. In cases with uncontrolled variceal bleeding, ballon tamponade was applied after prophylactic orotracheal intubation. Endoscopic treatment was repeated during the hospital admission until eradication of varices if indicated. A transjugular intrahepatic portosystemic shunt (TIPS) or surgical portacaval shunt were performed in patients in whom other treatments failed to control the bleeding. Patients with peptic ulcer or esophagitis received proton-pump inhibitors. Blood transfusions were given to maintain hematocrit levels between 25% and 30%.

Definitions regarding the course of the hemorrhage (failure to control the bleeding and early rebleeding) were based on those proposed by the Baveno III Consensus Workshop.[27] Failure to control the bleeding within the first 6 hours after inclusion was considered when transfusion requirements were equal to or greater than 4 units of blood together with an inability to achieve an increase in systolic arterial blood pressure by 20 mm Hg or to 70 mm Hg or higher. Failure to control the bleeding within the period from 6 to 24 hours after inclusion was considered if there was a new hematemesis together with a decrease in systolic arterial blood pressure equal to or greater than 20 mm Hg and/or transfusions requirements equal to or greater than 2 units to increase hemoglobin levels to 9 g/dL. Whenever balloon tamponade had to be used within these 2 periods, failure to control the bleeding was also considered. Early rebleeding and study rebleeding were defined as new hematemesis or melena from 24 hours to 5 days after inclusion and within the study period (10 days), respectively, with transfusion requirements equal to or greater than 2 units of blood in any of the 24-hour periods and at least 1 of the following: systolic arterial blood pressure lower than 100 mm Hg, decrease in arterial pressure after postural change greater than 20 mm Hg, or heart rate greater than 100 beats/min.

Randomization and Infection Diagnosis

Patients who fulfilled the inclusion criteria were randomly allocated into 2 groups. Patients in the first group received oral norfloxacin 400 mg every 12 hours during 7 days. Patients in the second group received intravenous ceftriaxone 1 g per day during 7 days. Antibiotics were initiated following the emergency endoscopy and always within the first 12 hours after admission into the hospital. Randomization was done using consecutively numbered computer-generated envelopes containing treatment assignment. Randomization was independent at each hospital.

Patients were followed up closely, with special emphasis on the detection of bacterial infections. Physical examination and blood cell count were performed daily, urinary sediment every 48 hours, and chest x-ray every 3 days for 10 days. Blood, ascitic fluid, and urine cultures were taken whenever a patient developed signs of infection.

Diagnosis of proved infection was performed as follows: (1) spontaneous bacteremia: positive blood cultures in the absence of any potential source of infection; (2) spontaneous bacterial peritonitis: ascitic fluid polymorphonuclear count equal to or greater than 250/mm^3 (Rimola et al[20]); (3) urinary tract infection: urinary leukocyte count greater than 15 cells per high-power field and positive urine culture[28]; (4) other infections were diagnosed according to clinical, radiologic, and bacteriologic data. Possible infection was diagnosed in patients with fever (>37.5°C during more than 6 hours), leukocytosis (>15,000 mm^3) or increased concentration of immature neutrophils in blood (>500/mm^3), negative cultures, and no other signs of infection. Analysis was performed classifying the patients into 3 groups: (1) patients not developing infections; (2) patients developing proved infections; and (3) patients developing proved or possible infections.

Statistical Analysis

The sample size was calculated on the basis of an expected incidence of bacterial infections (proved plus possible)

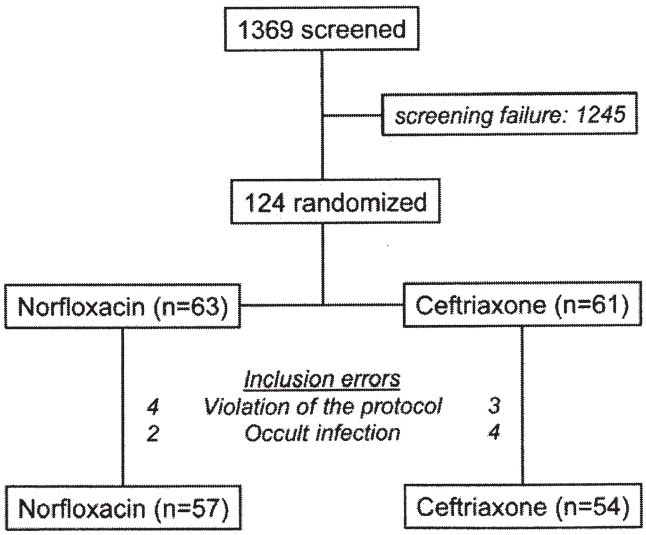

Figure 1. Flow diagram of patient allocation. More detailed information is shown in the text.

of 30% in the norfloxacin group and of 10% in the ceftriaxone group. Sixty-one patients had to be included in each group to obtain a P value $< .05$ with an α error of 5% and a β error of 20%.

Continuous variables were compared by the Student t test. Discontinuous variables were compared by the χ^2 test with the Yates correction when indicated. Probability curves were obtained by the Kaplan–Meier method and compared by the log-rank test. Univariate analysis using the Student t test and the Kaplan–Meier curves was performed to identify possible predictors of infection. Variables showing significant differences were subsequently introduced in a Cox proportional hazards regression model to identify independent predictors of infection. Results are given as relative hazard plus 95% confident interval (CI). The median values of the independent predictors of infection were considered as cut-off levels to identify groups of patients with different risks of infection. Calculations were performed with the SPSS Statistical Package (SPSS Inc. Version 11.0, 2000, Chicago, IL). Differences were considered significant at the level .05. Results are expressed as mean ± SD.

Results

A total of 1369 cirrhotic patients with gastrointestinal hemorrhage were screened. Of these, 1245 patients were not included because of absence of 2 signs of advanced liver failure (884 patients), presence of infection at admission (253 patients), presence of advanced hepatocellular carcinoma or other neoplasia (106 patients), antibiotic treatment other than oral norfloxacin at admission (54 patients), age over 80 years (21 patients), HIV infection (19 patients), and other causes including refusal to participate in the trial (32 patients). Of the 124 patients randomized, 63 in the norfloxacin group and 61 in the ceftriaxone group, 7 patients (4 in the norfloxacin group and 3 in the cefriaxone group) were excluded because of violation of the protocol (presence of only 1 sign of advanced liver failure) and 6 (2 in the norfloxacin group and 4 in the ceftriaxone group) because of occult infection (positive blood cultures obtained prior to randomization). Thus, 111 patients (57 in the norfloxacin group and 54 in the ceftriaxone group) were considered in the final analysis of the results (Figure 1).

Clinical Characteristics of Patients

The median age of the patients was 58 ± 12 years, 77% were male, and the most frequent etiology was alcoholism (68%). Patients had advanced liver insufficiency with high serum bilirubin (4.4 ± 4.0 mg/dL), low serum albumin (26 ± 5 g/L), high INR (1.56 ± 0.39), and high Child–Pugh score (9.8 ± 1.5 points) and Model for End Stage Liver Disease (MELD) score (17.1 ± 4.8 points). Forty-seven percent of the patients were grade B and 53% grade C of the Child–Pugh classification. Seventy-nine percent of patients had ascites, 72% signs of severe malnutrition, 58% a serum bilirubin >3 mg/dL, and 37% hepatic encephalopathy. Forty-one percent of the patients had more than 2 signs of liver failure, and 12% had renal failure at inclusion. Hepatocellular carcinoma was present in 18% of patients and diabetes mellitus in 20%. Only 9% of the patients were receiving oral norfloxacin for prophylaxis of spontaneous bacterial peritonitis at inclusion.

Table 1 shows that with the exception of the frequency of alcoholic cirrhosis, higher in the norfloxacin group, and the incidence of renal failure at inclusion, higher in the ceftriaxone group, there were no significant differences between groups in clinical data and laboratory measurements.

Table 1. Baseline Clinical and Analytical Characteristics

	Ceftriaxone (n = 54)	Norfloxacin (n = 57)
Age (*y*)	58 ± 12	57 ± 12
Male (%)	72	82
Alcoholic cirrhosis (%)	57	77[a]
Active alcoholism (%)[b]	30	40
Serum bilirubin (*mg/dL*)	3.8 ± 3.5	4.9 ± 4.4
Serum albumin (*g/L*)	26 ± 5	26 ± 5
Prothrombin time international normalized ratio	1.56 ± 0.41	1.55 ± 0.37
Child-Pugh score (*points*)	9.7 ± 1.6	9.8 ± 1.5
Child-Pugh score (*% B/C*)	46/54	47/53
MELD score (*points*)	17.1 ± 4.9	17.1 ± 4.7
Serum bilirubin > 3 mg/dL (%)	48	66
Ascites (%)	83	75
Hepatic encephalopathy (%)	37	37
Severe malnutrition (%)	78	67
Signs of liver failure (2/3/4) (%)[d]	56/43/1	61/32/7
Serum creatinine (*mg/dL*)	1.2 ± 0.5	1.0 ± 0.4
Serum sodium (*mEq/L*)	134 ± 5	133 ± 16
Ascitic fluid protein (*g/L*)	11 ± 7	11 ± 6
Renal failure (%)[c]	19	5[a]
Hepatocellular carcinoma (%)	21	17
Diabetes mellitus (%)	22	18
Norfloxacin prophylaxis (%)	13	5

NOTE. Values represent mean ± standard deviation.
[a]$P < .05$ norfloxacin vs ceftriaxone group.
[b]Arbitrarily defined as a daily alcohol intake over 20 g in patients with alcoholic cirrhosis.
[c]Serum creatinine >1.5 mg/dL.
[d]Two, 3, or 4 signs of liver failure (severe malnutrition, serum bilirubin >3 mg/dL, ascites, and hepatic encephalopathy).

Table 2. Characteristics of Hemorrhage at Inclusion and Course of the Bleeding

	Ceftriaxone (n = 54)	Norfloxacin (n = 57)
Characteristics of hemorrhage		
Mean arterial pressure (*mm Hg*)	76 ± 14	81 ± 18
Heart rate (*beats/min*)	89 ± 20	93 ± 18
Hematocrit (%)	28 ± 6	28 ± 7
Hypovolemic shock (%)[a]	7	7
Blood units transfused at inclusion	1.6 ± 1.6	1.6 ± 2.0
Time to endoscopy (*h*)[b]	4.8 ± 5.1	4.5 ± 5.3
Time to antibiotic prophylaxis (*h*)[c]	7.1 ± 2.9	6.5 ± 2.9
Source of bleeding (%)		
Esophageal varices	61	67
Gastric varices	4	7
Peptic ulcer	11	9
Portal hypertensive gastropathy	9	7
Mallory Weiss tear	2	2
Other	13	8
Active bleeding at endoscopy (%)	21	33
Vasoactive therapy (%)	74	81
Sclerotherapy or banding (%)	57	65
Patients submitted to (%)		
Urinary catheter insertion	59	65
Central line insertion	86	90
Tracheal intubation	9	11
Course of bleeding		
Failure to control bleeding (%)	11	16
Early rebleeding (1–5 days) (%)	7	11
Study rebleeding (10 days) (%)	9	12
Balloon tamponade (%)	4	9
TIPS insertion (%)	7	7
Surgical shunt (%)	6	5

NOTE. Values represent mean ± standard deviation.
[a]Systolic pressure < 90 mm Hg and heart rate > 100 b/min.
[b]Time from bleeding to gastroscopy.
[c]Time from bleeding to antibiotic prophylaxis. No differences were observed between groups.

Characteristics of the Hemorrhage

In the whole series of patients, the time elapsed between the initiation of bleeding and the emergency endoscopy was 4.6 × 5.1 hours. The site of bleeding was esophageal varices in 64% of patients, gastric varices in 5%, peptic ulcer in 10%, portal hypertensive gastropathy in 8%, and other in 13%. There was active bleeding at the time of endoscopy in 27% of cases. Vasoactive drugs (somatostatin or terlipressin) were the treatment most commonly used. It was applied to patients bleeding from esophageal varices, gastric varices, or portal hypertensive gastropathy (77% of the cases). Emergency sclerotherapy or banding was used in 61% of cases. Only 6% of patients received balloon tamponade. The median amount of blood transfused was 1.6 ± 1.8 units. Hemorrhagic shock, as defined by a systolic blood pressure <90 mm Hg and a heart rate >100 beats/min, was present at admission in only 7% of the patients. Failure to control bleeding, early rebleeding, and study rebleeding occurred in 13%, 9%, and 11% of the patients, respectively. Seven percent of patients required TIPS and 5% a surgical shunt. The time elapsed between the initiation of bleeding and the first dose of antibiotics was 6.8 ± 2.9 hours.

Table 2 shows that there were no significant differences between the study groups in the characteristics of the hemorrhage at inclusion, etiology of the hemorrhage, time elapsed between the initiation of the bleeding and the emergency endoscopy, or prophylactic antibiotic administration and course of the hemorrhage (failure to control the bleeding, early and study rebleeding rates, and need for TIPS or surgical shunt).

Efficacy of Oral Norfloxacin and IV Ceftriaxone in the Prevention of Bacterial Infections

Nineteen patients (33%) in the norfloxacin group and 6 (11%) in the ceftriaxone group developed proved or possible infections within the first 10 days after the initiation of the hemorrhage ($P = .01$) (Table 3). The corresponding figures for proved infections were 15 cases (26%) and 6 cases (11%), respectively ($P = .07$). Seven patients (12%) in the norfloxacin group and only 1 (2%) in the ceftriaxone group developed spontaneous bacteremia or spontaneous bacterial peritonitis ($P = .06$). Urinary tract infection developed in 8 patients in the norfloxacin group and in 3 in the ceftriaxone group. Finally, 1 patient in the norfloxacin group and 2 in the ceftriaxone group developed pneumonia. The isolated organisms were gram-negative bacilli (mainly *Escherichia coli*) in 8 patients and gram-positive cocci in 9 patients. Gram-negative bacilli were cultured in 7 patients receiving norfloxacin and in only 1 receiving ceftriaxone ($P = .03$). Six out of the 7 gram-negative bacilli isolated in the norfloxacin group were resistant to quinolones, whereas that isolated in the ceftriaxone group was susceptible to quinolones. Non-enterococcal streptococci were only isolated in the norfloxacin group. Figures 2 and 3 show the probability curves of infection (proved and possible), proved infection, and spontaneous bacterial peritonitis or spontaneous bacteremia development in the 2 groups. Probabilities were significantly higher in the norfloxacin group. Median time of infection was 3 days (range, 1–9 days) in the norfloxacin group and 6 days (range, 2–7 days) in the ceftriaxone group (P = ns). No adverse effects related to norfloxacin or ceftriaxone administration were observed during the study period.

Predictive Factors of Bacterial Infection Development

Proved and possible infections. Mean arterial blood pressure (71 ± 19 mm Hg in patients with infection vs 81 ± 15 mm Hg in patients without infection, $P = .007$), blood transfusion (2.4 ± 2.3 vs 1.4 ± 1.5 units, $P = .01$) and synthetic plasma expander and/or plasma requirements at inclusion (2.0 ± 2.9 vs 0.7 ± 1.3 units, $P = 05$), failure to control bleeding (28% vs 9%, $P = .001$), and norfloxacin prophylaxis (76% vs 42%, $P = .003$) were found to be predictors of proved or possible bacterial infection development in the univariate analysis. Of these, the Cox regression analysis identified norfloxacin prophylaxis (hazard ratio [HR]: 3.71, 95% CI: 1.47–9.34; $P = .005$), blood transfusion requirements at inclusion (HR: 1.36, 95% CI: 1.14–1.61; $P = .0001$), and failure to control bleeding (HR: 3.18; 95% CI: 1.32–7.68; $P = .01$) as independent predictors for proved or possible infection.

Proved infections. Mean arterial blood pressure (66 ± 16 mm Hg in patients with infections vs 81 ± 15 mm Hg in

Table 3. Proved and Possible Bacterial Infections and Organisms Isolated in the Study

	Ceftriaxone (n = 54)	Norfloxacin (n = 57)	*P* value
Infections, n (%)			
Patients with proved or possible infections	6 (11)	19 (33)	.01
Patients with proved infections	6 (11)	15 (26)	.07
Type of infection:			
Urinary infection	3 (6)	8 (14)	ns
Spontaneous bacteremia	0	4 (7)	ns
Spontaneous bacterial peritonitis	1 (2)	3 (5)	ns
Pneumonia	2 (4)	1 (2)	ns
Organims, n			
Fermentative gram-negative bacilli	0	6	.04
Escherichia coli	0	5	
Klebsiella pneumoniae	0	1	
Non fermentative gram-negative bacilli	1	1	ns
Pseudomonas aeruginosas	1	0	
Alcaligenes faecalis	0	1	
Gram-positive cocci	3	6	ns
Streptococcus pneumoniae	0	1	
Streptococcus viridans	0	2	
Streptococcus agalactiae	0	1	
Enterococcus faecalis	1	2	
Enterococcus faecium	2	0	

patients without infections, $P = .0001$), hematocrit (25% ± 6% vs 29% ± 7%, $P = .03$), blood transfusion (2.7 ± 2.4 vs 1.4 ± 1.5 units, $P = .003$) and synthetic plasma expander and/or plasma requirements at inclusion (2.4 ± 3.1 vs 0.7 ± 1.3 units, $P = .02$), failure to control the bleeding (29% vs 10%, $P = .003$), and norfloxacin prophylaxis (71% vs 47%, $P = .03$) were found to be predictors of bacterial infection development in the univariate analysis. Of these, the Cox regression analysis identified norfloxacin prophylaxis (HR: 3.21, 95% CI: 1.24–8.32; $P = .02$), blood transfusion requirements (HR: 1.22; 95% CI: 1.01–1.47; $P = .04$), and mean arterial pressure at inclusion (HR: 0.96; 95% CI: 0.93–0.99; $P = .005$) as independent predictors for proved infection.

Efficacy of Oral Norfloxacin and IV Ceftriaxone in the Prevention of Bacterial Infections in Patients With High Risk of Infection Development

Thirty-five patients (20 in the norfloxacin group and 15 in the ceftriaxone group) had at least 1 independent predictor of proved or possible infection development and were considered to have a high risk of infection. Twenty-nine patients (16 in the norfloxacin group and 13 in the ceftriaxone group) had transfusion requirement >2 units and 15 (9 and 6, respectively) had failure to control the bleeding within the first 24 hours.

Ten out of 20 high-risk patients in the norfloxacin group (50%) developed proved or possible bacterial infections within the first 10 days following inclusion. In contrast, this only occurred in 2 out of 15 (13%) patients in the ceftriaxone group ($P = .02$). Probability curves of proved plus possible and proved bacterial infections in these 2 groups are shown in Figure 4. Significant differences were observed between groups.

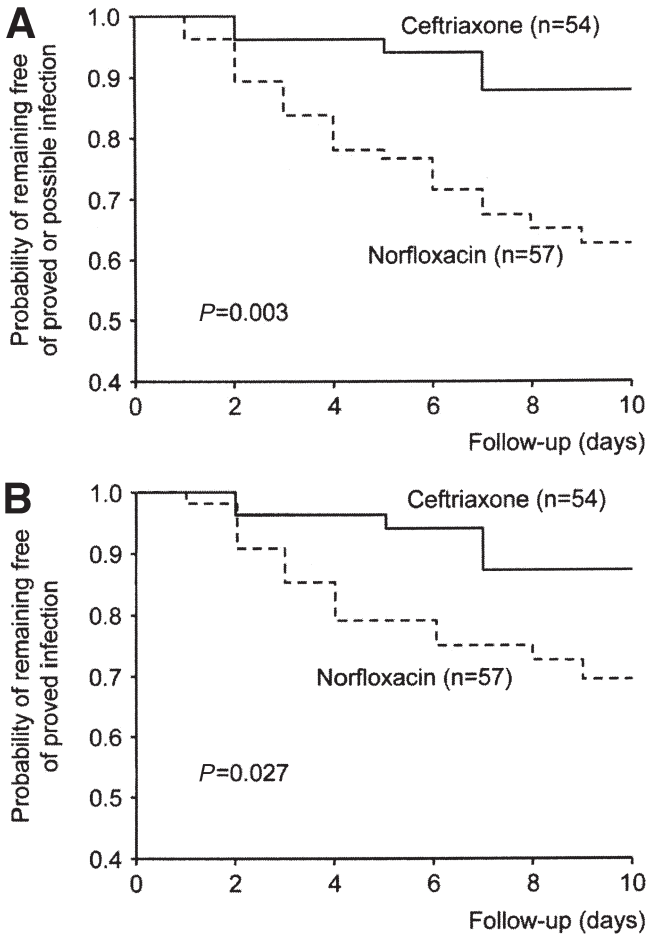

Figure 2. Probability of remaining free of proved and possible infections (*A*) and proved infections (*B*) in patients receiving ceftriaxone (*continuous line*) and norfloxacin (*dotted line*). There were significant differences between groups.

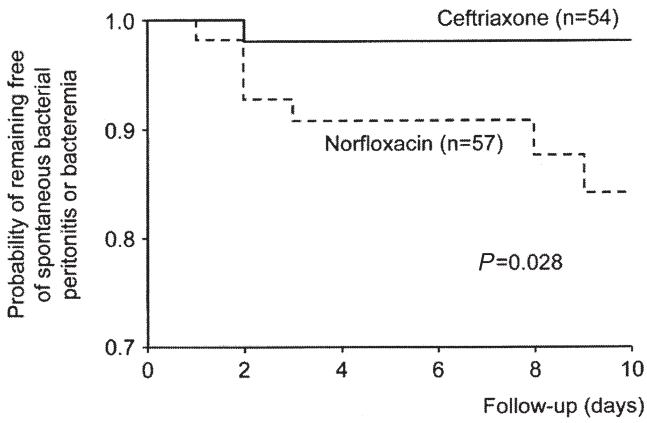

Figure 3. Probability of remaining free of spontaneous bacterial peritonitis or bacteremia in patients receiving ceftriaxone (*continuous line*) and norfloxacin (*dotted line*). There were significant differences between groups.

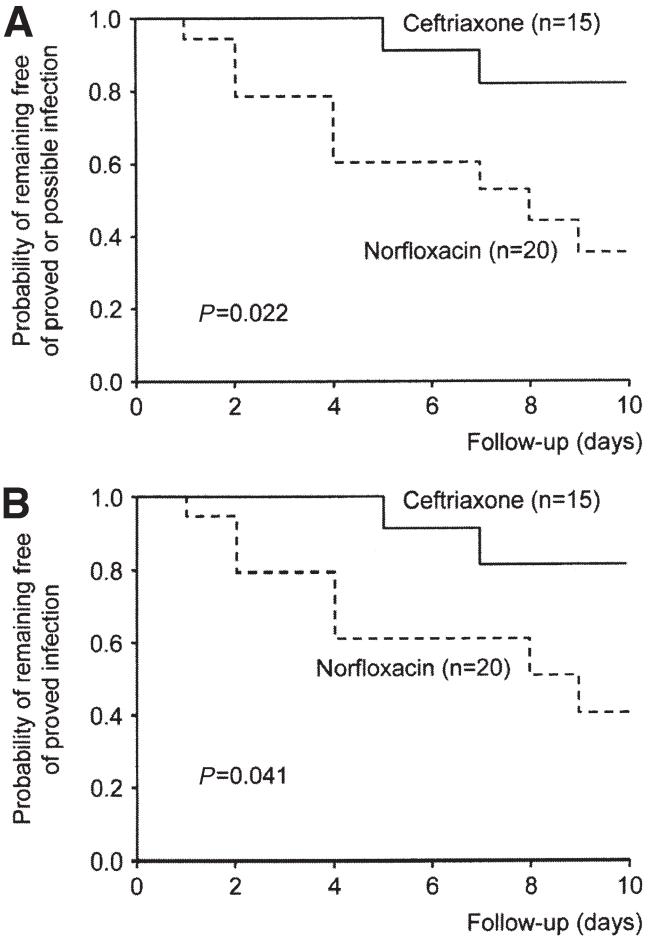

Figure 4. Probability of remaining free of proved and possible infection (*A*) and proved infections (*B*) in patients at high risk for infection (blood transfusion requirements >2 units and/or failure to control bleeding) who received ceftriaxone (*continuous line*) or norfloxacin prophylaxis (*dotted line*). There were significant differences between groups.

Mortality Rate

There was no significant difference in mortality within the 10 days after inclusion between patients treated with norfloxacin and those treated with ceftriaxone (5 and 6 patients, respectively, died). Mortality during hospitalization was also similar in the 2 groups (6 and 8 patients, respectively, died during hospital admission). Causes of death were hepatic failure in 7 patients (4 in the ceftriaxone group and 3 in the norfloxacin group), uncontrolled bleeding in 4 patients (3 and 1 patients, respectively), septic shock in 2 patients (1 in each group), and hepatorenal syndrome in 1 patient from the norfloxacin group.

Discussion

The results of the current study confirm that patients with cirrhosis, gastrointestinal hemorrhage, and advanced liver failure are at great risk of developing bacterial infections. Despite the prophylactic administration of antibiotics, 25 of the 111 patients (23%) included in the study developed bacterial infections within 10 days after inclusion. In 8 patients, the infection was severe (spontaneous bacteremia or spontaneous bacterial peritonitis).

An important finding of the current study is that the efficacy of oral norfloxacin in the prophylaxis of bacterial infection in patients with gastrointestinal hemorrhage and severe liver failure is relatively poor. Nineteen of the 57 patients treated with norfloxacin in this study (33%) developed bacterial infections (either proved or possible), 15 (26%) proved infections and 7 (12%) spontaneous bacteremia or spontaneous bacterial peritonitis. Most organisms isolated in these patients were gram-negative bacilli or non-enterococcal streptococci of probably cutaneous or respiratory origin resistant to quinolones.

This low efficacy of norfloxacin is consistent with the changes in the epidemiology of bacterial infections in cirrhosis detected during the last few years. Traditionally, bacterial infections in cirrhosis were mainly caused by gram-negative bacilli susceptible to quinolones.[29–36] Only in patients receiving prophylaxis with norfloxacin was the incidence of infections caused by gram-positive bacteria higher than that caused by gram-negative bacilli.[37] In contrast, at present, bacterial infections in cirrhosis are caused by both gram-negative bacilli and gram-positive cocci in a similar proportion. In patients receiving long-term norfloxacin prophylaxis, the most commonly isolated bacteria are gram-negative organisms resistant to quinolones and not gram-positive cocci. Finally, in patients not receiving norfloxacin, the incidence of infections caused by quinolone-resistant gram-negative bacilli is also relatively high.[24] The frequent use of invasive procedures in patients with cirrhosis, which predispose to infections by gram-positive cocci, and the high prevalence of quinolone-resistant gram-negative bacilli in the fecal flora in the general population and in cirrhotic patients owing to the widespread use of these antibiotics are the most likely mechanisms of this change in epidemiology.

Other features that could explain the low efficacy of oral norfloxacin observed in the study may be related to some specific characteristics of this treatment. Selective intestinal decontamination with oral norfloxacin is probably not achieved until several days after the initiation of treatment; thus, there is an initial period in which patients may be less protected against infections. Moreover, the oral route is probably not adequate to treat patients with active gastrointestinal hemorrhage, vomiting, submitted to periodic aspiration through a nasogastric tube, and with an extremely rapid intestinal transit. The observation that bacterial infections in our patients treated by norfloxacin tended to occur earlier than those in patients treated with IV ceftriaxone supports this contention.

The most important result of our trial is that IV ceftriaxone was significantly more effective than oral norfloxacin in the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal hemorrhage and severe liver failure. Only 6 of 57 patients (11%) treated with IV ceftriaxone developed infections, only 1 developed spontaneous bacterial peritonitis, and none developed spontaneous bacteremia. The higher efficacy of ceftriaxone over norfloxacin was due to the fact that both non-enterococcal streptococci and quinolone-resistant gram-negative bacteria, the most common organisms causing infection in patients treated with norfloxacin, are highly susceptible to third-generation cefalosporins. The incidence of infections caused by enterococci, a bacteria resistant to both quinolones and third-generation cephalosporins, was comparable in the 2 groups.

In the current series of patients with severe liver failure, only the type of the prophylactic antibiotic used and 2 parameters related to the severity of the hemorrhage (transfusion requirements at inclusion and failure to control bleeding) were found to be independent predictors of infection development. Using these 2 predictive factors, a subset of patients with high risk of bacterial infections was identified. Intravenous ceftriaxone was also much more effective than oral norfloxacin in the prophylaxis of bacterial infections in these patients, further indicating that it is an excellent antibiotic for the prevention of bacterial infections in cirrhotic patients with advanced liver failure and severe hemorrhage.

Allergy to β-lactamic antibiotics is relatively common in the general population. In these cases, two possible alternatives to third-generation cephalosporins exist. The first is the intravenous administration of quinolones or trimethoprim sulfamethoxazole, which are effective in the prophylaxis of spontaneous bacterial peritonitis by oral route. However, they do not prevent infections caused by quinolone-resistant bacteria, which are also frequently resistant to trimethoprim sulfamethoxazole.[24] The second alternative is aztreonam, an antibiotic active against gram-negative bacilli, plus a glycopeptide (vancomycin or teicoplanin), active against gram-positive cocci. The nephrotoxic potential of glycopeptides may be a problem of this combination. Further studies assessing possible alternatives to β-lactamic antibiotics in the prophylaxis of bacterial infections in cirrhotic patients with gastrointestinal bleeding are clearly needed.

We could not confirm recent studies suggesting that bacterial infections in patients with cirrhosis are associated with a higher rate of failure to control bleeding,[15,16] higher rate of rebleeding,[9,17,18] and higher hospital mortality.[5,16,19] Differences in the designs of the studies probably account for this discrepancy. Whereas, in these studies, both patients admitted to hospital with infections and patients developing infections during hospitalization were considered, in our trial, only patients without infection at inclusion were included into the study. This is a fundamental difference because, in our series, all patients developed infections when the endoscopic and/or the pharmacologic treatment of the hemorrhage had already been applied. There was also no difference in hospital survival between groups, but the study was not designed to assess differences in mortality.

In summary, the current study indicates that IV ceftriaxone is more effective than oral norfloxacin in the prophylaxis of bacterial infections in patients with cirrhosis, gastrointestinal hemorrhage, and severe liver failure. This is related to 2 features. First, patients treated with norfloxacin are predisposed to develop infections because of gram-negative bacilli and non-enteroccocal streptococci resistant to quinolones. By contrast, these bacteria are highly susceptible to third-generation cephalosporins. Second, intravenous administration of prophylactic antibiotics is better than oral administration in patients with severe hepatic failure, encephalopathy, and active gastrointestinal bleeding. Intravenous ceftriaxone should, therefore, be used instead of oral norfloxacin in the prophylaxis of bacterial infections in cirrhotic patients with advanced cirrhosis and upper gastrointestinal bleeding. Because the epidemiology of bacterial infections differs greatly between geographic areas, further studies in other countries are needed to support this contention.

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