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CLINICAL—LIVER

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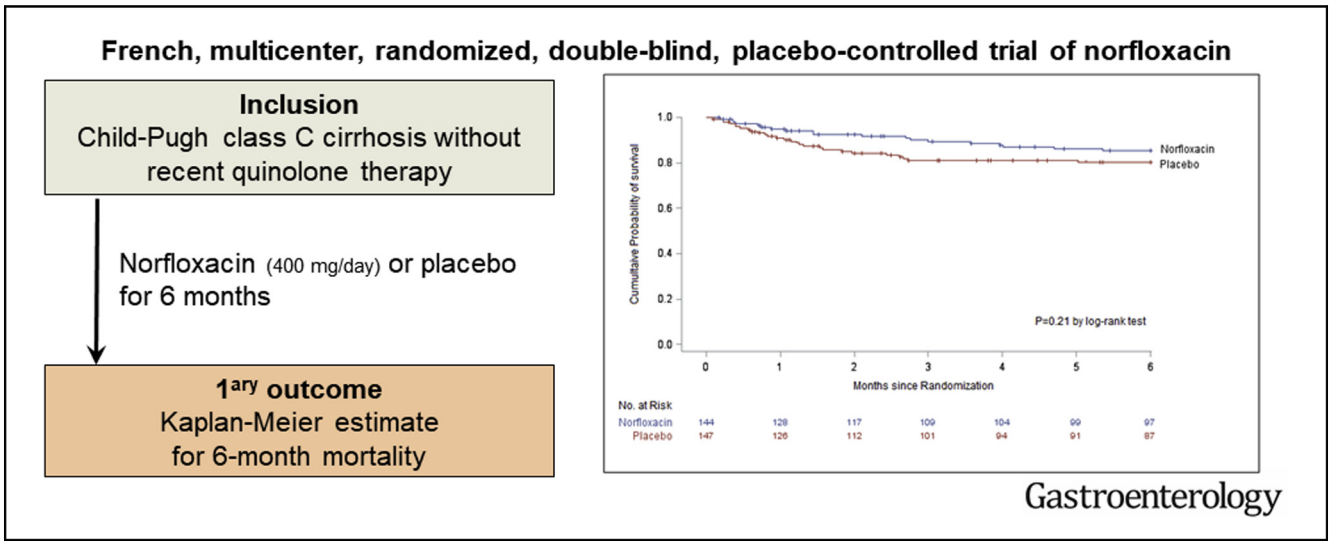

BACKGROUND & AIMS: There is debate over the effects of long-term oral fluoroquinolone therapy in patients with advanced cirrhosis. We performed a randomized controlled trial to evaluate the effects of long-term treatment with the fluoroquinolone norfloxacin on survival of patients with cirrhosis. **METHODS:** We performed a double-blind trial of 291 patients with Child-Pugh class C cirrhosis who had not received recent fluoroquinolone therapy. The study was performed at 18 clinical sites in France from April 2010 through November 2014. Patients were randomly assigned to groups given 400 mg norfloxacin (n = 144) or placebo (n = 147) once daily for 6 months. Patients were evaluated monthly for the first 6 months and at 9 months and 12 months thereafter. The primary outcome was 6-month mortality, estimated by the Kaplan–Meier method, censoring spontaneous bacterial peritonitis, liver transplantation, or loss during follow-up. **RESULTS:** The Kaplan–Meier estimate for 6-month mortality was 14.8% for patients receiving norfloxacin and 19.7% for patients receiving placebo ($P = .21$). In competing risk analysis that took liver transplantation into account, the cumulative incidence of death at 6 months was significantly lower in the norfloxacin group than in the placebo group (subdistribution hazard ratio, 0.59; 95% confidence interval, 0.35–0.99). The subdistribution hazard ratio for death at 6 months with norfloxacin vs placebo was 0.35 (95% confidence interval, 0.13–0.93) in patients with ascites fluid protein concentrations <15 g/L and 1.39 (95% confidence interval, 0.42–4.57) in patients with ascites fluid protein concentrations ≥15 g/L. Norfloxacin significantly decreased the incidence of any and Gram-negative bacterial infections without increasing infections caused by *Clostridium difficile* or multiresistant bacteria. **CONCLUSIONS:** In a randomized controlled trial of patients with advanced cirrhosis without recent fluoroquinolone therapy, norfloxacin did not reduce 6-month mortality, estimated by the Kaplan–Meier method. Norfloxacin, however, appears to increase survival of patients with low ascites fluid protein concentrations. ClinicalTrials.gov ID: NCT01037959.

Keywords: Inflammation; Risk Factor; Liver-Related Complications; NORFLOCIR Trial.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

The effects of long-term oral fluoroquinolone therapy in patients with advanced cirrhosis are unclear.

NEW FINDINGS

In a multicenter double-blind randomized trial conducted in patients with advanced cirrhosis, Norfloxacin decreased 6-month mortality in patients with ascites fluid protein concentrations of less than 15 g/L but not in those with ascites fluid protein concentrations of 15 g/L or more.

LIMITATIONS

291 patients (most with alcoholic cirrhosis) were enrolled rather than the planned 392 patients. Adherence and retention rates were lower than in most trials that assess chronic diseases progression.

IMPACT

Long-term oral norfloxacin may be recommended in patients with advanced cirrhosis and low ascites fluid protein concentrations in order to decrease mortality. Patients with high ascites fluid protein concentrations may not benefit from long-term norfloxacin therapy, if the target is a reduction in mortality.

Bacterial infections, such as spontaneous bacterial peritonitis (SBP), are common and severe in patients with advanced cirrhosis.[1] Bacteria causing infections are often enteric Gram-negative bacteria that have crossed the intestinal barrier and reached the site of infection (eg, ascites) via the systemic circulation.[2] Because fluoroquinolones, norfloxacin or ciprofloxacin, can induce gut decontamination, the ability of their long-term administration to prevent bacterial infections has been evaluated in patients with cirrhosis. Prolonged norfloxacin therapy has been shown to be effective for primary prophylaxis of SBP[3] and any Gram-negative bacterial infection,[4] and for secondary prophylaxis of SBP.[5] However, fluoroquinolone may have beneficial effects on outcomes beyond primary or secondary prophylaxis of bacterial infection. Patients with advanced cirrhosis without ongoing infection have systemic inflammation, which is a result of the recognition by the immune system of bacterial byproducts from the gut.[6,7] Systemic inflammation contributes to the development of end-organ dysfunction, such as acute kidney injury.[8] Intestinal decontamination could improve the outcomes of patients with cirrhosis, not only by preventing bacterial infection but also by reducing the translocation of bacterial byproducts. In addition, a beneficial effect of norfloxacin could be related to a decrease in systemic inflammation through direct "off-label" anti-inflammatory effects of the antibiotic in immune cells.[9] Together, these data suggest that fluoroquinolones could improve survival in patients with cirrhosis. However, prolonged administration of fluoroquinolones can be associated with an increased incidence of infections caused by multidrug-resistant bacteria[10,11]; these might be more severe than infections caused by bacteria sensitive to antibiotics.[12] Therefore, in patients receiving prolonged fluoroquinolone therapy, development of infections by multidrug-resistant bacteria might obscure the beneficial effect of fluoroquinolones on survival.

Four double-blind, randomized, placebo-controlled clinical trials of fluoroquinolone therapy assessed mortality in patients with cirrhosis and baseline ascitic fluid protein levels <15 g/L (Supplementary Table 1).[3,4,13,14] However, of

Abbreviations used in this paper: **CI, confidence interval; SBP, spontaneous bacterial peritonitis.**

Most current article

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these studies, only 1 had mortality (at 3 months and 1 year) as a primary outcome.[3] In the other studies, the primary outcome was either primary prophylaxis of SBP,[14] prophylaxis (indifferently, primary, and secondary) of SBP,[13] or primary prophylaxis of Gram-negative bacterial infections.[4] Moreover, the trials were performed in small series of patients and the severity of cirrhosis of the enrolled patients differed from one study to the other. The results of the trials were heterogeneous. One trial showed that norfloxacin therapy significantly reduced both the 3-month mortality and incidence of a first episode of SBP.[3] Another trial showed that ciprofloxacin reduced mortality, but had no significant effect on the risk of developing a first episode of SBP.[14] Two trials showing that norfloxacin decreased the risk of developing SBP did not find an effect on mortality.[4,13] Finally, it remains unknown whether there are any benefits of fluoroquinolone prophylaxis in patients with ascitic fluid protein concentrations $\geq$15 g/L.

Based on gaps in knowledge, we performed a double-blind, placebo-controlled trial (called NORFLOCIR [Norfloxacin Therapy for Patients With Cirrhosis and Severe Liver Failure]) to evaluate whether prolonged norfloxacin administration results in reduced mortality at 6 months (primary outcome) and prevention of infections (secondary outcome) in a large series of patients with advanced (ie, Child-Pugh class C) cirrhosis without a recent fluoroquinolone administration. Patients were enrolled without using a prespecified ascitic protein concentration threshold.

Methods

Trial Oversight

The study was an institutionally sponsored, prospective, multicenter, double-blind, randomized, parallel-group, placebo-controlled, phase 3 trial, conducted in 18 clinical sites in France (Supplementary Table 2). The protocol was approved on November 10, 2009, by the appropriate French legal authority (Comité de Protection des Personnes d'Ile de France I) and is available with the full text of this article. Written informed consent was obtained from all patients. All centers had extensive experience in the management of decompensated cirrhosis.

The trial is an investigator-initiated multicenter study led by RM and was funded by the French Ministry of Health. The Direction de la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris, French Ministry of Health, supervised the use of study funding. Although norfloxacin and placebo were purchased from Arrow Génériques SAS (Lyon, France) this company did not participate in any part of the study, including study design, data analysis, or manuscript preparation. The steering committee designed the study, made the decision to submit the manuscript for publication, and vouches for the fidelity of the study to the protocol. Research assistants regularly monitored all centers on site to check adherence to the protocol and the accuracy of recorded data. An investigator was responsible for enrolling patients in the study at each center, ensuring adherence to the protocol, and completing the electronic case-report form. All analyses were performed by the study statistician (BP) and reviewed with the senior epidemiologist (NG) in accordance with the International Conference on Harmonization and Good Clinical Practice guidelines. An independent data and safety monitoring board met regularly (after every 50 included patients) to monitor blinded trial data and safety events. All authors had access to the study data and reviewed and approved the final manuscript. The results of this clinical trial are reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines.[4]

Patients

Patients who were older than 18 years, had Child-Pugh class C cirrhosis (indicating advanced liver disease),[15] and had not received fluoroquinolones within the past month were eligible to be included in the study. The diagnosis of cirrhosis was either biopsy-proven or clinically suspected, based on the usual clinical, laboratory, and radiologic criteria. This trial did not take into account the value of ascitic fluid protein levels when including the patients. Exclusion criteria included pregnancy, treatment with immunosuppressive drugs, human immunodeficiency virus infection, known hypersensitivity or intolerance to norfloxacin, previous seizure, prior transjugular intrahepatic portosystemic shunting, prior solid organ transplantation, or associated illnesses with a life expectancy of 1 month or who could not be regularly followed up. The first patient was enrolled in April 2010 and the last patient completed the double-blind phase in November 2014. In the first version of the protocol, patients with severe alcoholic hepatitis, and those with hepatocellular carcinoma were excluded. However, because of slow recruitment, we decided to change exclusion criteria in order to include patients with severe alcoholic hepatitis (change approved by the Ethics Committee on July 22, 2010). In addition, we decided to be less strict regarding exclusion of patients with hepatocellular carcinoma and to exclude only those with hepatocellular carcinoma to those that did not meet the Milan criteria for transplantation (these criteria included a single lesion $<$5 cm or multiple lesions [maximum of 3], the largest of which measures $\leq$3 cm)[16] (change approved by the Ethics Committee on September 30, 2011).

Trial Design

The trial included blinded treatment and post-treatment periods (Supplementary Figure 1). This article describes the 2 periods. The randomization list was centrally and computer-generated then stratified according to center. Patients were randomly assigned in a 1:1 ratio to receive either norfloxacin (1 tablet of 400 mg daily) or placebo. Study-group assignments were concealed using a centralized, secure, interactive, Web-based response system, CleanWeb, Telemedicine Technologies S.A.S (Boulogne-Billancourt, France) and a randomization list that was balanced by blocks of variable and undisclosed sizes.

Patients received the study treatment for the first 6 months after enrollment. During this period, patients were seen monthly. Treatment adherence was assessed at each visit by interviewing the patient. A new box of the study medication was then provided to the patient. The protocol prespecified that the study treatment be discontinued in patients who received a liver transplant and in nontransplanted patients who recovered from an episode of SBP and received open-label fluoroquinolone therapy for secondary prophylaxis of this infection. Because patients with SBP are at high risk of recurrent infection[17] and fluoroquinolones can prevent this event,[5] we assumed that some patients who developed an episode of

SBP during the double-blind treatment period and recovered would receive long-term open-label fluoroquinolone therapy for secondary prophylaxis of infection. The protocol prespecified that the study treatment would not be stopped in case of short-term (fewer than 8 days), open-label use of a fluoroquinolone due to acute variceal hemorrhage[18] or any bacterial infection other than SBP requiring this antibiotic.

Nontransplanted patients who were alive when the study treatment was stopped were followed up in a double-blind fashion until death, liver transplantation, or completion of a 12-month follow-up, corresponding to the post-treatment period of the trial.

Trial Measurements

Patients were seen monthly for the first 6 months and at 9 months and 12 months thereafter. Demographic data were collected at baseline. Clinical and laboratory data were obtained at baseline and at each follow-up visit. The value of ascitic fluid protein levels was collected at baseline. Clinical data included heart rate, mean arterial pressure, temperature, respiratory rate, body weight, the presence of ascites, the presence of encephalopathy and ongoing therapies. At each follow-up visit the investigator collected information on prespecified liver-related complications that may have occurred since the previous visit (eg, infections, including the site of infection, presence of Gram-negative or Gram-positive bacteria, and the presence of septic shock; kidney dysfunction; hepatic encephalopathy; or gastrointestinal hemorrhage; details on the definitions of liver-related complications are provided in Supplementary Table 4). Patients' adherence was assessed as follows: At each visit of the study protocol, the patient was asked to bring back their remaining study treatment. In each center, a clinical research assistant mandated by the sponsor (Assistance Publique-Hôpitaux de Paris) was in charge of counting the number of remaining pills. In addition, treatment adherence was assessed by the investigators at each visit by interviewing the patient. A new box of the study study treatment then was provided to the patient. In each center, the research assistant was also in charge of scheduling visits and calling back patients who did not present for a scheduled visit. Finally, research assistants regularly monitored all centers on site to check the following: existence of the patient, written signed consent, inclusion criteria, occurrence of adverse events and severe adverse events, primary end point, and data quality.

Serious Adverse Events

Serious adverse events, defined as events that were fatal or life-threatening, that resulted in clinically significant or persistent disability that required or prolonged a hospitalization were reported in real time. The protocol stated that every prespecified liver-related complication should be considered as a serious adverse event. The nature and date of occurrence of each serious adverse event were declared by the investigator using a document that was faxed to the Département de la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris. The Medical Dictionary for Regulatory Activities (www.meddra.org) was used to classify the safety events. Coding was performed at the coordinating center, and up to 5 codes were assigned to each safety event. Further classification into different categories was made by 2 members of the steering committee. The accountability of serious adverse events to norfloxacin was reviewed by the sponsor.

Statistical Analysis

Analyses were performed on an intention-to-treat basis. The primary outcome was mortality at 6 months. Data on time to events were estimated with the Kaplan–Meier method[19] and were compared between groups by the log-rank test, with hazard ratios and 95% confidence limits estimated by the Cox model.[20] Proportional hazards assumptions were checked graphically. Similar to a previous study,[3] patients were censored when they developed SBP because patients are expected to receive open-label fluoroquinolones to prevent recurrent infection. Patients were also censored at transplantation (if there was no SBP before) or at 6 months (if they were alive and did not have SBP or transplantation at 6 months). Patients lost to follow-up were censored on the day of their last study visit.

Secondary outcomes of the trial included the mortality rate at 12 months, the incidence of liver-related complications at 6 and 12 months, and safety at 6 and 12 months. For analysis of the outcomes of liver-related complications, death and transplantation were censored, provided that there was no event of interest before death.

In addition, post hoc, we performed competing risk analyses of the primary outcome. First, because transplantation and death can represent competing events, depending on the outcome being assessed,[21] competing risk analyses were performed estimating the cumulative incidence of death at 6 months, while liver transplantation were treated as competing events. In brief, for estimating the cumulative incidence of death, liver transplantation was taken into account as a competing risk, with the use of the cumulative incidence curves, and was then compared between groups by means of the Gray test,[22] whereas the Fine and Gray model was used to estimate the subdistribution hazard ratio.[23] Second, a stratified analysis for ascitic protein concentrations was performed. Patients were divided into 2 subgroups—those with ascitic fluid protein levels <15 g/L and those with protein levels ≥ 15 g/L. Cumulative incidence of death was compared between the 2 subgroups. Finally, the cumulative incidence of death at 6 months was estimated in the per-protocol population and in patients who had had a prior episode of infection unrelated to SBP.

With regard to statistical power, we calculated a sample size of 392 patients. This would be sufficient to detect a decrease in 6-month mortality from 40% in the placebo group to 25% in the norfloxacin group,[3] with 90% power, a 2-sided type I error rate of 0.05 and 5% lost to follow-up. A P value $\leq .05$ was considered to be statistically significant. Data handling and analysis were performed with SAS statistical software, version 9.4 (SAS Institute, Cary, NC).

Results

Trial Population

A total of 626 patients with Child-Pugh class C cirrhosis were admitted to participating hospitals; 355 of these patients were ineligible for the study and the remaining 291 were randomly assigned to either the norfloxacin group (144 patients) or the placebo group (147 patients)

Table 1. Characteristics of the Patients at Baseline

Characteristics	Norfloxacin (n = 144)	Placebo (n = 147)
Age, *y*, mean ± SD	55.2 ± 8.5	56.0 ± 9.5
Male sex, n (%)	94 (65.3)	108 (73.5)
Etiology of cirrhosis, n (%)		
Alcohol	115 (79.9)	108 (73.5)
Hepatitis C virus	11 (7.6)	9 (6.1)
Hepatitis B virus	1 (0.7)	3 (2.0)
Other cause	17 (11.8)	27 (18.3)
Active alcohol use, n (%)	55 (38.2)	64 (43.5)
Waiting list for liver transplantation, n (%)	17 (11.8)	13 (8.8)
Prior gastrointestinal hemorrhage, n (%)	28 (19.4)	35 (23.8)
History of at least 1 episode of ascites, n (%)	126 (87.5)	131 (89.1)
Large-volume paracentesis during the last 6 mo, n/N (%)	90/143 (62.9)	78/144 (54.2)
Prior episode of SBP, n (%)	6 (4.2)	5 (3.4)
Prior episode of infection unrelated to SBP, n (%)	32 (22.2)	42 (29.6)
History of hepatocellular carcinoma, n (%)	6 (4.2)	3 (2.0)
History of alcoholic hepatitis, n (%)	26 (18.7)	32 (23.0)
Current histologically proven alcoholic hepatitis, n (%)	56 (39.2)	63 (42.9)
Esophageal and/or gastric varices, n (%)		
Unknown	19 (13.2)	28 (19.0)
Grade 0	32 (46.1)	27 (18.4)
Grade 1	31 (21.5)	33 (22.5)
Grade 2	62 (43.1)	59 (40.1)
Ascites, n (%)[a]	116 (80.5)	116 (79.0)
Mild to moderate, n/N (%)	60/116 (51.7)	66/116 (56.9)
Large or refractory, n/N (%)	56/116 (48.3)	50/116 (43.1)
Patients with ascites and available protein ascitic fluid concentration, n/N (%)	77/116 (66.4)	78/116 (67.2)
Protein concentration in ascites, *g/L,* mean ± SD	13.0 ± 6.6	12.3 ± 6.8
Patients with ascitic fluid protein <15 g/L, n/N (%)	46/77 (59.7)	56/78 (71.8)
Encephalopathy, n (%)[a]	26 (18.1)	30 (20.6)
Child-Pugh score,[b,c] mean ± SD	11.4 ± 1.1	11.2 ± 1.0
MELD score,[d,e] mean ± SD	21.4 ± 5.0	21.0 ± 5.3
Prothrombin time, %, mean ± SD	40.4 ± 10.1	41.3 ± 11.0
International normalized ratio,[e] mean ± SD	2.1 ± 0.7	2.0 ± 0.5
Total bilirubin, *mg/dL*, mean ± SD	7.7 ± 6.7	8.0 ± 7.1
Serum albumin, *g/dL,*[c] mean ± SD	2.5 ± 0.5	2.5 ± 0.5
Serum creatinine, *mg/dL.*[f] mean ± SD	0.88 ± 0.44	0.81 ± 0.40
Serum sodium, *mmol/L*, mean ± SD	133.3 ± 4.6	133.7 ± 4.7
Serum potassium, *mmol/L*, mean ± SD	4.0 ± 0.5	4.2 ± 3.2
Aspartate aminotransferase, *U/L*, mean ± SD	130.7 ± 546.4	97.7 ± 62.4
Alanine aminotransferase, *U/L*, mean ± SD	52.7 ± 78.6	45.1 ± 28.2
Hemoglobin, *g/dL*, mean ± SD	10.4 ± 1.8	10.6 ± 1.9
White blood cell count, $\times 10^{-3}/mm^3$, mean ± SD	8.4 ± 4.8	8.1 ± 4.5
Platelets, $\times 10^{-3}/mm^3$, mean ± SD	107.0 ± 57.4	111.3 ± 59.8
C-reactive protein, *mg/dL*, mean ± SD	2.0 ± 2.2	2.4 ± 2.5
Ongoing treatment at enrollment, n (%)		
Diuretics	92 (63.9)	94 (63.9)
β-blockers	60 (41.7)	67 (45.6)
Corticosteroids	30 (20.8)	32 (21.8)
Non-quinolone antibiotics, n/N (%)		
For secondary prophylaxis	1/6 (16.7)	2/5 (40.0)
For other reasons	41/134 (30.6)	40/136 (29.4)

NOTE. To convert values for bilirubin from mg/dL to μmol/L, multiply by 17.1. To convert values for creatinine from mg/dL to μmol/L, multiply by 88.4.
MELD, Model for End-Stage Liver Disease.
[a]Data were missing for 1 patient in the placebo group.
[b]The Child-Pugh score can range from 5 to 15, with scores of 10 or more indicating Child-Pugh class C, which denotes severe liver disease.
[c]Data were missing for 1 patient in the norfloxacin group and for 1 patient in the placebo group.
[d]The MELD score ranges from 6 to 40, with higher scores indicating more severe disease.
[e]Data were missing in 21 patients in the norfloxacin group and 21 patients in the placebo group (missing values for internatinional normalized ratio and MELD score were found in the same patients).
[f]Data were missing for 1 patient in the norfloxacin group.

Table 2. Primary and Secondary Outcomes at 6 Months, According to Study Group

Outcomes	Norfloxacin (n = 144)	Placebo (n = 147)	*P* value	Hazard ratio (95% CI)
Death (primary outcome)[a]				
Patients, n	19	27	—	—
Estimated rate, % (95% CI)	14.8 (9.3–21.6)	19.7 (13.5–26.8)	.21	0.69 (0.38–1.23)
Liver transplantation[b]				
Patients, n	17	15	—	—
Cumulative incidence, % (95% CI)	13.2 (8.0–19.7)	12.8 (7.5–19.7)	.81	1.09 (0.54–2.18)
Liver-related complications[c]				
Infection				
SBP				
Patients, n	10	17	—	—
Cumulative incidence, % (95% CI)	7.9 (4.0–13.5)	14.3 (8.7–21.4)	.15	0.57 (0.26–1.23)
Any infection				
Patients, n	31	46	—	—
Cumulative incidence, % (95% CI)	23.9 (16.9–31.6)	35.0 (26.8–43.3)	.04	0.62 (0.39–0.98)
Any bacterial infection				
Patients, n	30	43	—	—
Cumulative incidence, % (95% CI)	23.0 (16.2–30.6)	33.0 (24.9–41.3)	.06	0.64 (0.40–1.03)
Gram-negative bacterial infection				
Patients, n	4	16	—	—
Cumulative incidence, % (95% CI)	3.2 (1.0–7.4)	13.0 (7.7–19.7)	.005	0.24 (0.08–0.70)
Gram positive bacterial infection				
Patients, n	4	10	—	—
Cumulative incidence, % (95% CI)	3.4 (1.1–7.9)	8.1 (4.1–13.9)	.08	0.37 (0.12–1.18)
Multidrug-resistant bacteria				
Patients, n	2	1	—	—
Cumulative incidence, % (95% CI)	1.5 (0.3–4.9)	0.7 (0.1–3.7)	.56	2.01 (0.18–22.20)
Septic shock				
No. of patients	8	7	—	—
Cumulative incidence, % (95% CI)	6.2 (2.9–11.3)	5.2 (2.3–9.9)	.79	1.15 (0.42–3.17)
Kidney dysfunction				
Patients, n	19	14	—	—
Cumulative incidence, % (95% CI)	15.0 (9.4–21.9)	10.9 (6.2–17.1)	.37	1.37 (0.69–2.74)
Hepatic encephalopathy				
Patients, n	27	35	—	—
Cumulative incidence, % (95% CI)	21.1 (14.5–28.7)	27.5 (20.0–35.6)	.22	0.73 (0.44–1.21)
Gastrointestinal hemorrhage				
Patients, n	7	13	—	—
Cumulative incidence, % (95% CI)	5.5 (2.4–10.5)	11.0 (6.1–17.4)	.16	0.52 (0.21–1.31)

NOTE: *P* values were derived from log-rank tests. The hazard ratios and 95% confidence limits were derived from Cox regression models.

[a]For the analysis of 6-mo mortality, data for 10 patients in the norfloxacin group and 17 in the placebo group were censored as of the date of first SBP; data for 14 patients in the norfloxacin group and 12 in the placebo group were censored as of the date of liver transplantation (if there was no SBP before transplantation); and data for non-transplanted patients who had no SBP but were lost to follow-up (4 patients in each group) were censored as of the date of last assessment.

[b]For the analysis of incidence of liver transplantation, data for 22 patients in the norfloxacin group and 36 in the placebo group were censored as of the date of death.

[c]Prespecified definitions for liver-related complications are provided in Supplementary Table 3. For the analysis of incidence of each liver-related complications, data for patients who received a liver transplant were censored as of the date of liver transplantation (if there was no occurrence of the event of interest before liver transplantation) and data for patients who died were censored as of the date of death (if there was no occurrence of the event of interest before death).

(Supplementary Figure 2). Baseline characteristics were similar in the 2 study groups (Table 1). Most patients had alcoholic cirrhosis; 79.7% had ascites (which was mild to moderate in half of them), <5% had had a prior episode of SBP (among these, none had received a fluoroquinolone and only 3 patients were receiving a non-quinolone antibiotic for secondary SBP prophylaxis).

The mean ± SD durations of treatment and follow-up during the double-blind treatment period were 82.7 ± 77.3 days and 157.1 ± 4.6 days, respectively, in the norfloxacin group and 71.7 ± 73.4 days and 155.2 ± 4.6 days, respectively, in the placebo group. Overall, 42.6% of the patients completed the trial according to the protocol (full participation), 54.6% of the patients reduced the number of study visits, transiently forgot to take study pills, or both (ie, modified their consent to less than full study participation) and 2.7% were lost to follow-up (Supplementary Figure 2). The study treatment was discontinued in 40.2%

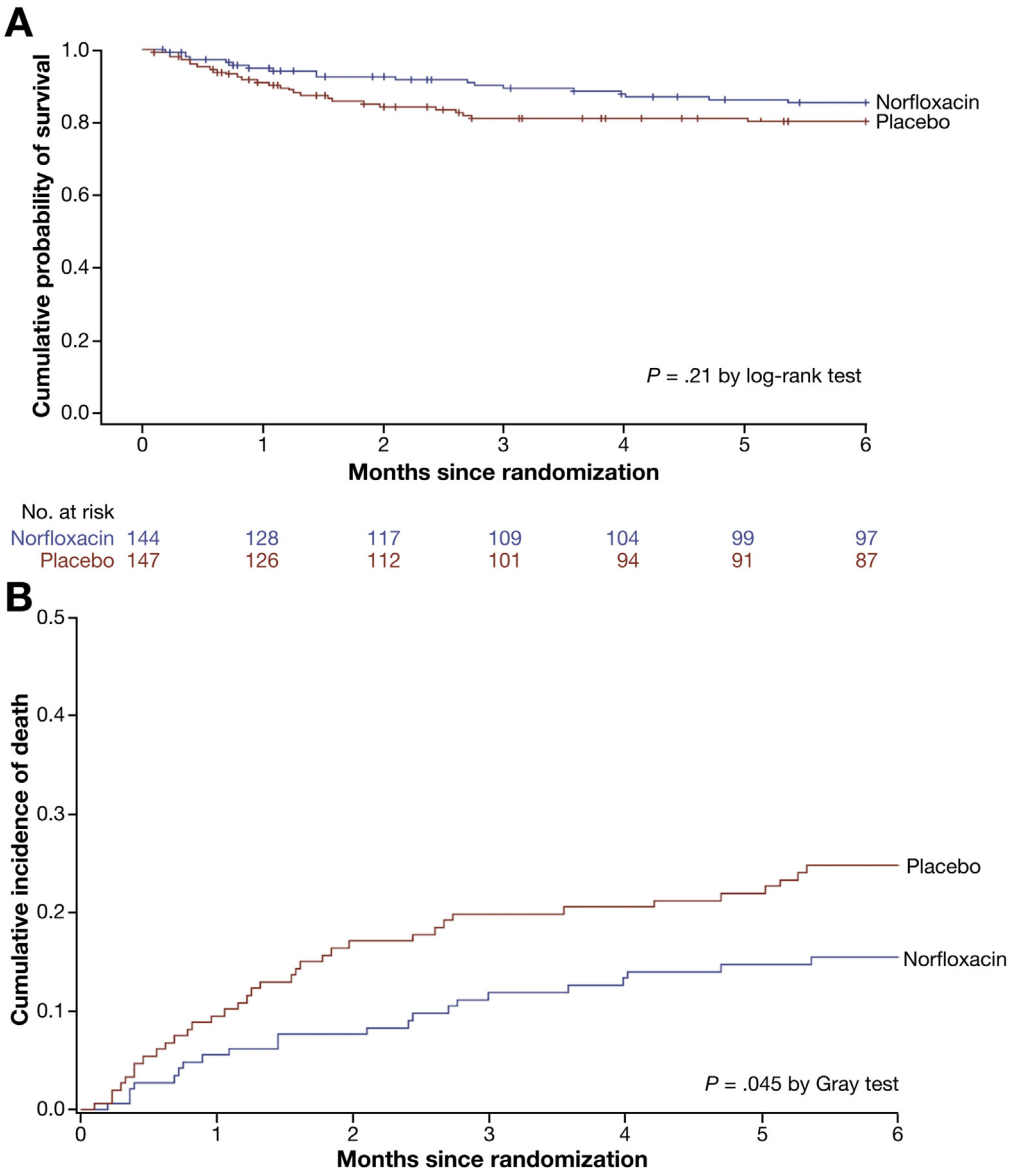

Figure 1. Analyses of the primary outcome of 6-month mortality. (*A*) Cumulative incidence of death at 6 months after randomization, which was estimated using the Kaplan–Meier method, at 14.8% (95% CI, 9.3%–21.6%) in the norfloxacin group and 19.7% (95% CI, 13.5%–26.8%) in the placebo group. Censoring of the data is indicated by the *vertical bars*. Data for patients with SBP were censored as of the date of infection. Data for patients who received a liver transplant were censored as of the date liver transplantation (if there was no SBP before transplantation). Data for patients who were lost to follow-up were censored as of the date of the last assessment. (*B*) Results of a post-hoc analysis of the cumulative incidence of death at 6 months when liver transplantation was taken into account as a competing risk of death and survival data of patients with SBP were not censored. At 6 months, the cumulative incidence of death was estimated at 15.5% (95% CI, 10.1%–21.9%) in the norfloxacin group and 24.8% (95% CI, 18.1%–32.1%) in the placebo group.

of patients because of death in 15.1%, prespecified reasons (ie, occurrence of an episode of SBP or of liver transplantation [if there was no SBP before transplantation]) in 12.7%, consent withdrawal in 11.7%, and other reasons in 0.7% (Supplementary Figure 2). Of note, among the 27 patients who developed SBP during the double-blind treatment period, only 11 received open-label norfloxacin therapy for secondary prophylaxis (5 of the 10 patients who developed SBP in the norfloxacin group and 6 of the 17 patients who developed SBP in the placebo group).

Details on the events that occurred during the double-blind post-treatment period are provided in Supplementary Table 4.

Primary Outcome

Primary analysis. There were 19 patients in the norfloxacin group (n = 144) and 27 in the placebo group (n = 147) who died within 6 months, giving rise to Kaplan–Meier estimates for 6-month mortality of 14.8% (95% confidence interval [CI], 9.3–21.6) and 19.7% (95% CI, 13.5–26.8) in the norfloxacin and placebo group ($P = .21$). The hazard ratio for 6-month mortality was 0.69 (95% CI, 0.38–1.23), indicating nonsignificant reduction in mortality in the norfloxacin group compared to that in the placebo group (Table 2 and Figure 1*A*).

Supplementary Table 2 shows that there were 5 large centers that enrolled 222 (76%) patients and 13 small centers that enrolled the remaining 69 patients (Supplementary Table 2). We found no significant interaction between the effect of study treatment on mortality and the size of center ($P = .14$).

Post-hoc analyses. Outcomes in patients censored for SBP included 12 deaths (3 in the norfloxacin group and 9 in the placebo group) and 6 liver transplantations (3 in each group). Twenty-six of the patients who did not develop SBP were censored for liver transplantation (14 and 12 in the norfloxacin and placebo groups, respectively). The cumulative incidence of death at 6 months in the competing risk

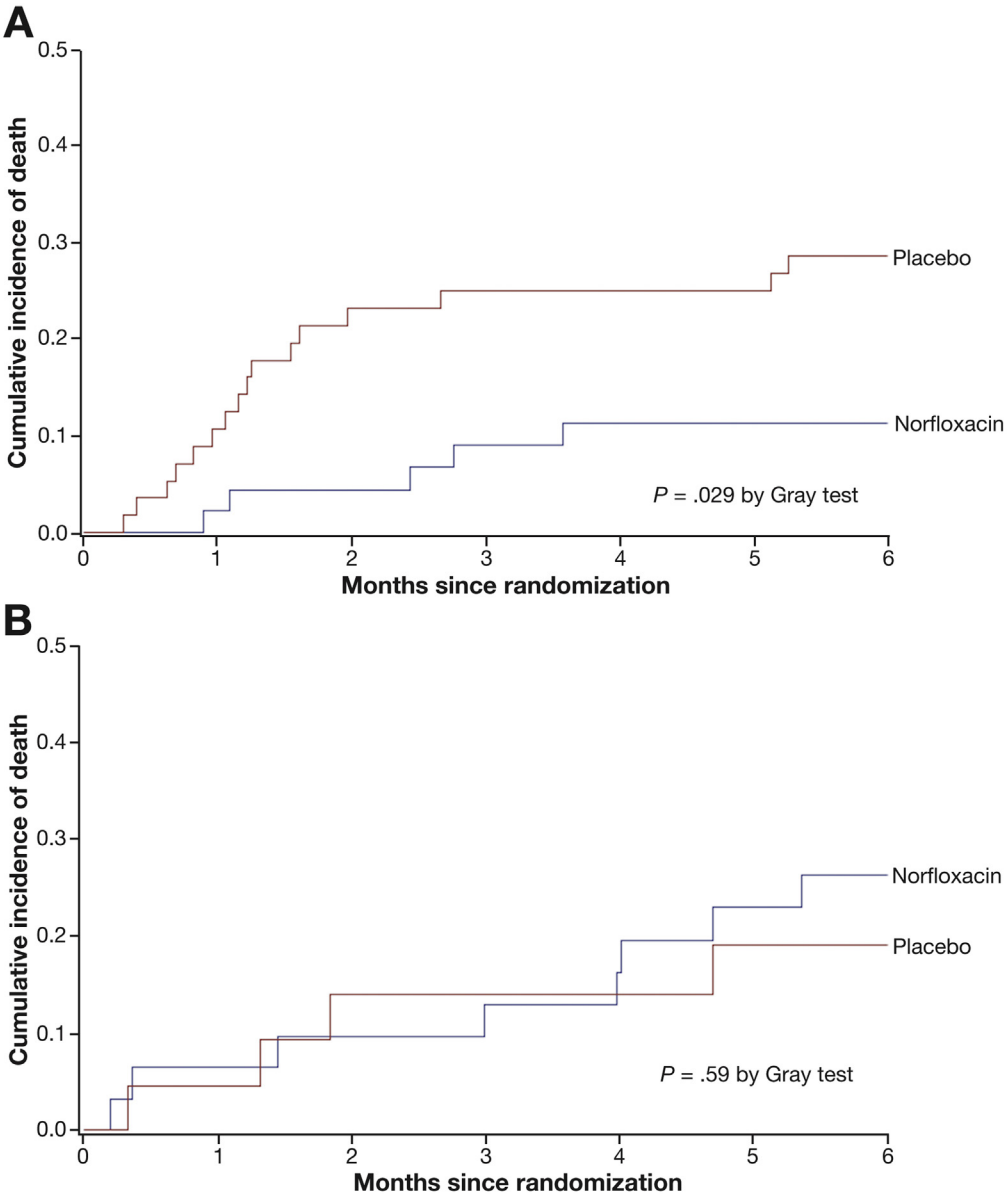

Figure 2. Post-hoc analysis of the cumulative incidence of death at 6 months according to the value of ascitic fluid protein levels obtained at enrollment. (*A*) Cumulative incidence of death in the 102 patients known to have baseline ascitic fluid proteins <15 g/L at enrollment. At 6 months, the estimated cumulative incidence of death was 11.3% (95% CI, 4.1%–22.6%) in the norfloxacin group (46 patients) and 28.6% (95% CI, 17.4%–40.8%) in the placebo group (56 patients). (*B*) Cumulative incidence of death in the 53 patients known to have baseline ascitic fluid proteins ≥15 g/L at enrollment. At 6 months, the estimated cumulative incidence of death was 26.3% (95% CI, 12.2%–42.9%) in the norfloxacin group (31 patients) and 19.2% (95% CI, 5.7%–38.6%) in the placebo group (22 patients). In the 2 analyses, liver transplantation was taken into account as a competing risk of death and survival data of patients with SBP were not censored.

analysis was significantly lower in the norfloxacin group than in the placebo group, with a subdistribution hazard ratio of 0.59 (95% CI, 0.35–0.99) (Figure 1*B*).

Baseline ascitic fluid protein levels were available in 66.8% (155 of 232) of patients with ascites. In the 102 patients with ascitic fluid protein levels <15 g/L, the cumulative incidence of death at 6 months was significantly lower in the norfloxacin group than in the placebo group (Figure 2*A*), with a subdistribution hazard ratio for death at 6 months of 0.35 (95% CI, 0.13–0.93) with norfloxacin vs placebo. In contrast, the cumulative incidence of death at 6 months in the 53 patients with ascitic fluid protein levels ≥15 g/L did not differ between the norfloxacin group and the placebo group (Figure 2*B*), with a subdistribution hazard ratio for death at 6 months of 1.39 (95% CI, 0.42–4.57) with norfloxacin vs placebo.

We performed a per-protocol analysis of the primary outcome in the 124 patients with full participation at last visit (62 patients in each of the 2 study groups). At 6 months, the cumulative incidence of death did not differ significantly between the norfloxacin group and the placebo group (Supplementary Figure 3). The subdistribution hazard ratio for death at 6 months was 0.54 (95% CI, 0.28–1.05) with norfloxacin vs placebo ($P = .069$ by Gray test).

We also performed an analysis of the primary outcome in 74 patients (32 in the norfloxacin group and 42 in the placebo group) who had a prior episode of infection unrelated to SBP before enrollment. At 6 months, the cumulative incidence of death did not differ significantly between the norfloxacin group and the placebo group (Supplementary Figure 4). The subdistribution hazard ratio

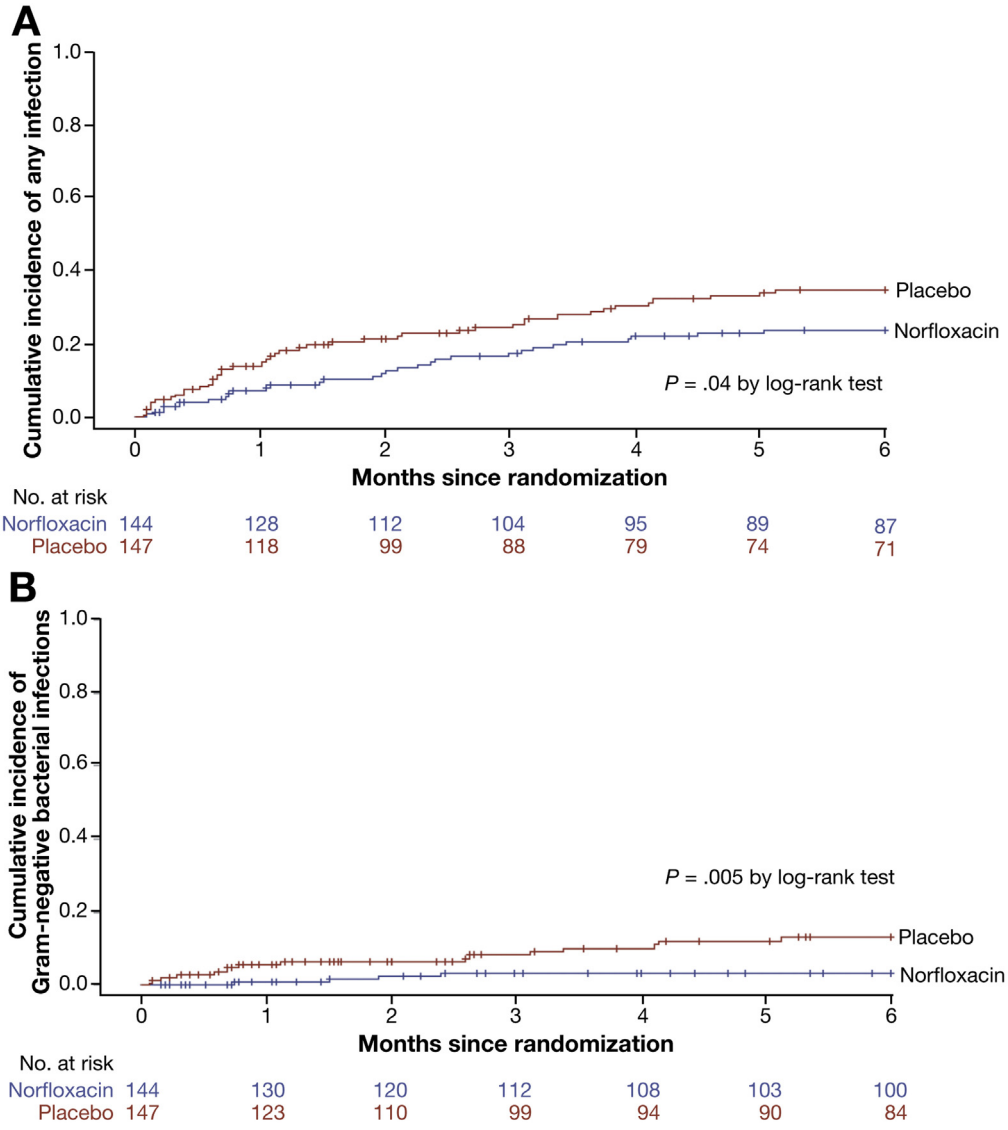

Figure 3. Kaplan–Meier analyses of infectious outcomes during the double-blind treatment period. (*A*) Cumulative incidence of any infection over time; at 6 months the cumulative incidence was estimated at 23.9% (95% CI, 16.9%–31.6%) in the norfloxacin group and 35.0% (95% CI, 26.8%–43.3%). (*B*) Cumulative incidence of Gram-negative bacterial infections over time; at 6 months the cumulative incidence was estimated at 3.2% (95% CI, 1.0%–7.4%) in the norfloxacin group and 13.0% (95% CI, 7.7%–19.7%) in the placebo group.

for death at 6 months was 0.83 (95% CI, 0.27–2.50) with norfloxacin vs placebo ($P = .74$ by Gray test).

Causes of Death

The number of liver-related deaths was 16 of 19 (84.2%) in the norfloxacin group and 23 of 27 (85.2%) in the placebo group. Among liver-related deaths, 12 were related to infection (5 in the norfloxacin group, 7 in the placebo group). Only 2 pathogens were identified as a cause of infection related to death (*Pneumocystis jiroveci* in the norfloxacin group and *Serratia marcescens* in the placebo group).

Secondary Outcomes

Efficacy outcomes at 6 months. *Infection.* In a time-to-event analysis, the cumulative incidence of any infection was significantly lower in the norfloxacin group than in the placebo group (Table 2 and Figure 3*A*). The incidence of Gram-negative bacterial infections was also significantly lower in the norfloxacin group than in the placebo group (Table 2 and Figure 3*B*). The incidence of other infectious outcomes (in particular, SBP and infection caused by multidrug-resistant bacteria) was similar between the 2 study groups (Table 2).

Of the 291 patients, 77 (26.5%) had at least 1 infectious episode (31 in the norfloxacin group and 46 in the placebo group) (Supplementary Table 5). Of note, among patients with a first infectious episode, the proportion of those who had Gram-negative bacterial infections was significantly lower in the norfloxacin group than in the placebo group. Very few patients in each group had more than 1 infectious episode; only 7 patients in the norfloxacin group and 6 in the placebo group had a second infection. One patient in the norfloxacin group had 4 infectious episodes and one in the placebo group had 3 episodes (Supplementary Table 5). The total number of infectious episodes was 41 in the norfloxacin group and 53 in the placebo group, with a

mean number of infectious episodes per patient that did not differ between the 2 groups (Supplementary Table 5). There were no significant between-group differences in the total number of episodes of either SBP, pneumonia, urinary tract infection, bacteremia, or soft-tissue infections (Supplementary Table 5). The total number of infections caused by Gram-negative bacteria was significantly lower in the norfloxacin group than in the placebo group (4 and 17, respectively; $P = .01$) (Supplementary Table 5). There were no significant differences in the total number of infections caused by either Gram-positive bacteria, mixed bacteria (Gram-negative and Gram-positive), or other pathogens. Of note, the total number of infections caused by multidrug-resistant bacteria was 2 in the norfloxacin group and 1 in the placebo group ($P = .58$) (Supplementary Table 5). No infection caused by *Clostridium difficile* occurred, in particular in the norfloxacin group.

Other outcomes. In a time-to-event analysis, the cumulative incidence of liver transplantation, kidney dysfunction, hepatic encephalopathy, and gastrointestinal hemorrhage were similar between the 2 study groups (Table 2).

Efficacy outcomes at 12 months. Outcomes are shown in Supplementary Figure 5 and Supplementary Table 6. Overall, infectious complications were less frequent in the norfloxacin group, except septic shock. The incidence of noninfectious outcomes did not differ between the 2 groups.

Safety. None of the serious adverse events were attributed to the study treatment. There was no between-group difference in the incidence of nonfatal serious adverse events, other than liver-related complications that had occurred at 6 months and 12 months (Supplementary Tables 7 and 8, respectively).

Discussion

This trial included patients with advanced cirrhosis who had not received recent fluoroquinolone therapy. Unlike previous trials, in our trial, the value of ascitic fluid protein levels was not used to include or exclude patients. The trial was divided into 2 successive double-blind periods; patients received the study treatment during the first period (double-blind treatment period), the planned duration of which was 6 months. During this period, norfloxacin administration did not reduce the 6-month mortality (primary outcome) estimated by the Kaplan–Meier method. At 6 months, norfloxacin significantly decreased the cumulative incidences of any infection and Gram-negative bacterial infections, but not the incidence of SBP. Norfloxacin therapy was not associated with an increased incidence of infections caused by multidrug-resistant bacteria. Norfloxacin did not change the cumulative incidence of liver transplantation at 6 months or the risk of developing liver-related complications, such as kidney dysfunction, hepatic encephalopathy, and gastrointestinal hemorrhage. Of note, the beneficial effect of norfloxacin on the risk of any infection and Gram-negative bacterial infections was maintained and even extended to Gram-positive bacterial infections during the double-blind post-treatment period. Because 77% of the enrolled patients had alcoholic cirrhosis, our results apply mainly to patients with alcoholic cirrhosis.

Previous double-blind, randomized, placebo-controlled trials of a fluoroquinolone were performed in the context of primary prophylaxis of SBP because they exclusively enrolled patients without a prior SBP episode.[3,4,14] Our trial was conducted in a similar context because we enrolled very few patients with a prior SBP episode (<5%) and we excluded patients with recent fluoroquinolone therapy.

Of the 11 patients with a prior SBP episode, only 3 were receiving a non-fluoroquinolone antibiotic at the time of enrollment. During the trial, 50% of the patients who developed SBP during follow-up were not given open-label prophylaxis with norfloxacin, contrary to what was recommended by the study protocol. The reasons why every patient who developed SBP did not receive systematically long-term antibiotic prophylaxis are unclear. A fear of selecting multiresistant strains or patients' reluctance for additional drug intake may be considered as a plausible explanation.

It has been suggested that prolonged norfloxacin administration was associated with increased risk of infections caused by multi-drug resistance bacteria.[10–12] This contention was not confirmed by our results, as the incidence of infections caused by multidrug-resistant bacteria was low in the overall study population and did not differ between the norfloxacin group and the placebo group. Our results are in agreement with findings of a large prospective, observational study conducted worldwide showing that in patients with cirrhosis, the incidence of infections caused by multiresistant bacteria was not higher among patients who received norfloxacin than among those who did not receive this antibiotic.[24]

The strengths of our study include the multicenter design and double-blind randomization to assigned treatment, a well-defined study protocol that included prespecified criteria for liver-related complications, and an intention-to-treat analysis. We also conducted a number of secondary analyses that provided important insights that may reconcile inconsistencies existing in the literature on this topic.

In our primary analysis of 6-month mortality, patients with SBP and liver transplantation were censored. While the reason for the prespecified decision to censor SBP was the expectation that secondary prophylaxis would be used routinely, the open-label use of fluoroquinolones after an episode of SBP was found in <50% of our patients. Given the inter-relations among infection, including SBP, death, and transplantation, competing risk analyses have been advocated in this setting.[21] In our analysis incorporating liver transplantation as a competing risk, reduced mortality at 6 months was detected in patients receiving norfloxacin. This lower mortality may have been a result of the combined effects of the lower incidence of SBP in the norfloxacin group (Table 2) and fewer deaths after SBP in patients who were assigned to receive norfloxacin than in those who received placebo (3 deaths vs 9 deaths, respectively).

Previous trials have been selectively performed in patients with low baseline ascitic fluid protein levels

(ie, <15 g/L).[3,4,7,8] In our trial, the results of ascitic fluid proteins levels were available in 66.8% but not 100% of patients with ascites, in part, probably because paracentesis was not used in some patients with small-volume ascites. In any case, we enrolled patients regardless of baseline ascitic fluid protein levels. Our subgroup analysis in patients with low baseline ascitic fluid protein levels showed that 6-month mortality was lower in patients in the norfloxacin group than those in the placebo group. Lower mortality was not observed with norfloxacin in the subgroup of our patients with high ascitic fluid protein levels (ie, ≥15 g/L). Although these results should be interpreted with caution, in particular because of missing data regarding ascitic fluid protein levels in some patients, they strongly suggest, along with previous findings obtained in an independent study,[8] that patients with advanced cirrhosis and low ascitic fluid protein levels are good candidates for prolonged norfloxacin administration to decrease mortality. Importantly, for the first time, our trial assessed norfloxacin effects in patients with advanced cirrhosis and high ascitic fluid protein levels and the results strongly suggest that these patients are not good candidates for prolonged norfloxacin therapy because of the lack of beneficial effect of the antibiotic on survival.

Our trial does have several limitations. The statistical power to detect a reduction in 6-month mortality with norfloxacin was low because only 291 patients were enrolled rather than 392, as planned. This was due to a combination of slow recruitment (which was probably related to a loss of clinical equipoise due to the various guidelines recommending open-label norfloxacin use),[25,26] termination of funding, and the expiration date of the trial drug. In our trial, adherence and retention were lower than in most trials that assess chronic diseases' progression, which reflects the challenges of investigating the effects of long-term treatment in patients with advanced alcoholic cirrhosis. Low adherence and retention have also been found in a previous trial in patients with advanced alcoholic cirrhosis.[3] However, in this previous trial and in our study, treatment was usually discontinued because of death or a medical decision based on the occurrence of an event that had been prespecified as a reason for discontinuation (ie, development of an episode of SBP or liver transplantation). Although one cannot exclude that issues with health insurance could have contributed to low adherence of some patients, this explanation seems unlikely because patients who are included in a clinical study protocol in France are fully covered by law via a basic health insurance during the trial. Together, these findings suggest that because of limitations, a type II error cannot be excluded regarding the lack of significance found in the primary analysis.

In conclusion, in patients with advanced cirrhosis who have not recently received fluoroquinolones and who were enrolled without taking into account the value of ascitic fluid protein levels, long-term norfloxacin therapy did not reduce 6-mortality rate estimated by the Kaplan–Meier method with censoring of data at the time of SBP or of liver transplantation (if there was no episode of SBP before transplantation). Nevertheless, results of competing risk analysis suggest that norfloxacin therapy could reduce the incidence of death among patients with ascitic fluid protein concentrations <15 g/L, but not among those with ascitic fluid protein concentration ≥15 g/L. Norfloxacin may prevent some infections, especially Gram-negative bacterial infections, but not development of SBP and other non-infectious, liver-related complications.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.08.026.

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Conflicts of interest
These authors disclose the following: Christophe Bureau has served as speaker for Gore Norgine. Pierre-Emmanuel Rautou has conducted research for Exalenz, and Conatus. The remaining authors disclose no conflicts.

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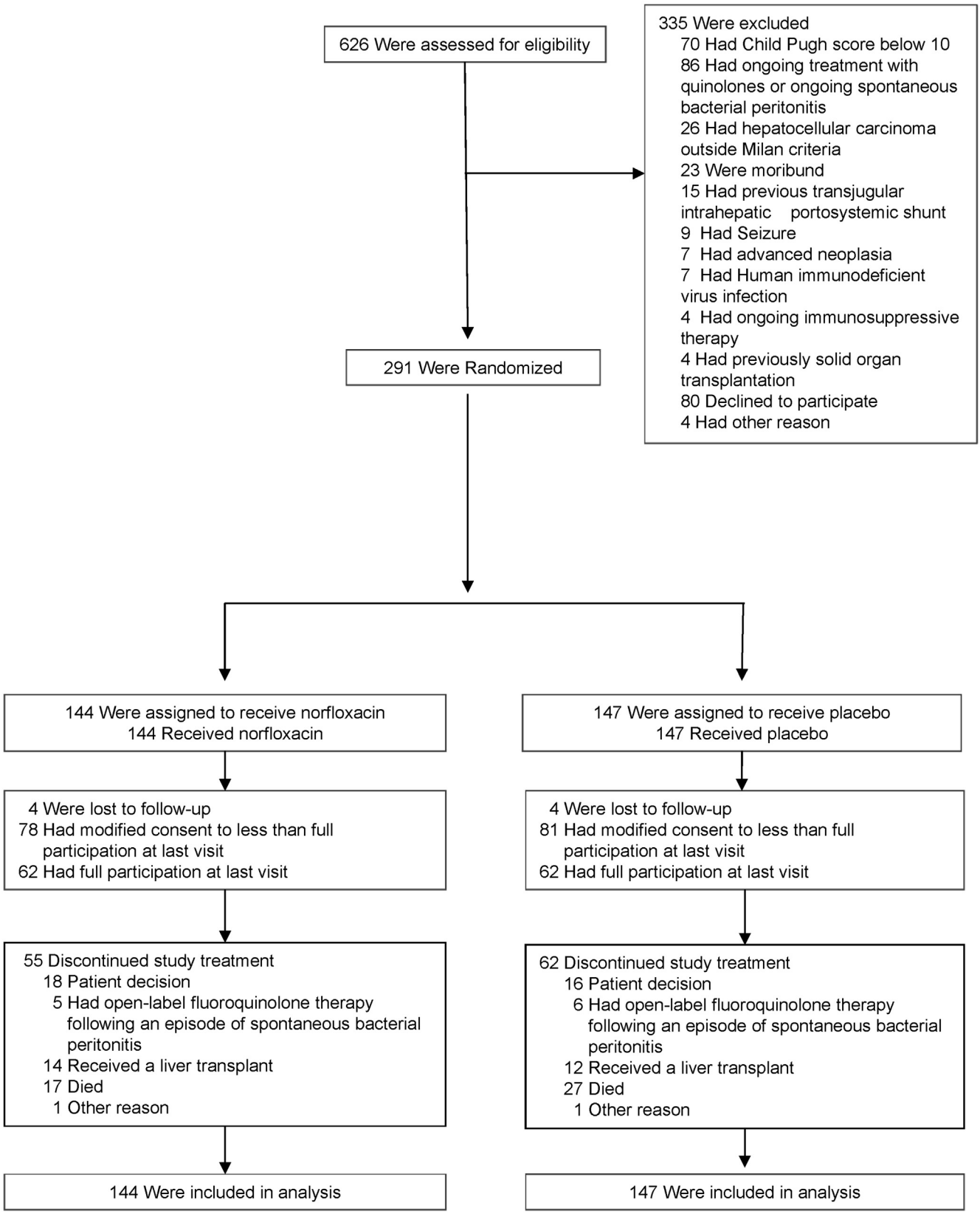
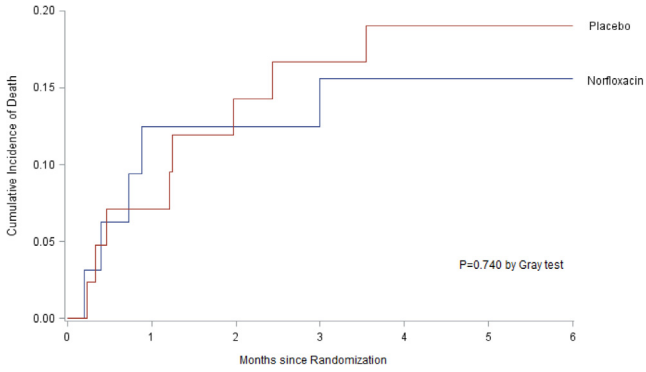
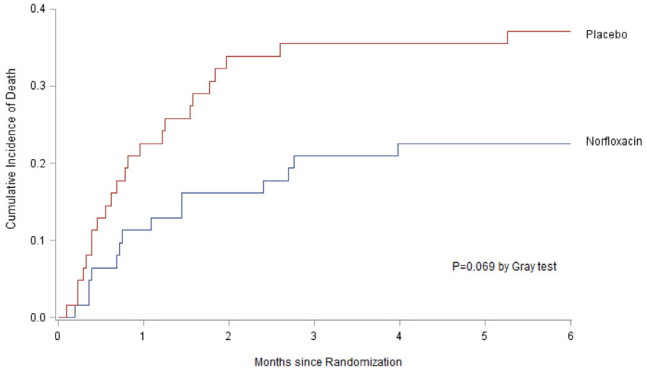


Supplementary Figure 1. Study design. The trial included blinded treatment and post-treatment periods. During the treatment period, patients were allocated to receive either norfloxacin (1 tablet of 400 mg daily) or a placebo for 6 months . Patients were followed up for an additional 6 months (double-blind post-treatment period). Patients were seen monthly for the first 6 months and at 9 months and 12 months thereafter. During each follow-up visit (*short arrows*), the investigator collected information on any prespecified liver-related complications that had occurred since the last visit (infections, including the site of infection, the isolated pathogen(s), and the presence of septic shock; kidney dysfunction; hepatic encephalopathy; or gastrointestinal hemorrhage; all defined in Supplementary Table 3).

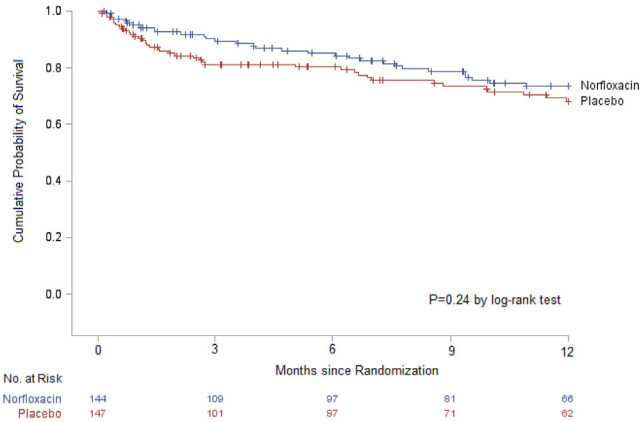
Supplementary Figure 2. Enrollment, randomization, and follow-up of the study participants during the double-blind treatment period. The planned duration of the double-blind treatment period was 6 months. There were 2 deaths among patients of the norfloxacin group who withdrew their consent to participate. As a result, the number of deaths in the norfloxacin group shown in the Figure 1 (17 deaths) differs from the number of deaths in the norfloxacin group reported in Table 2 (19 deaths).



Supplementary Figure 4. Post-hoc analyses of the primary outcome of 6-mo mortality in patients who had had a prior episode of infection unrelated to SBP. Post-hoc analyses were performed in 74 patients (32 in the norfloxacin group and 42 in the placebo group) who had had a prior episode of infection unrelated to SBP before enrollment. The figure shows cumulative incidence of death when liver transplantation was taken into account as a competing risk of death and survival data of patients with SBP were not censored. At 6 months, the estimated cumulative incidence of death was 15.6% (95% CI, 5.6%–30.3%) in the norfloxacin group and 19.0% (95% CI, 8.8%–32.2%) in the placebo group ($P = .74$ by Gray test). The subdistribution hazard ratio for death at 6 months was 0.83 (95% CI, 0.27–2.50) with norfloxacin vs placebo.



Supplementary Figure 3. Post-hoc per-protocol analysis of the primary outcome of 6-mo mortality in patients with full participation at last visit. Post-hoc per-protocol analyses were performed in 124 patients with full participation at last visit (62 patients in each of the 2 study groups). The figure shows cumulative incidence of death when liver transplantation was taken into account as a competing risk of death and survival data of patients with SBP were not censored. At 6 months , the estimated cumulative incidence of death was 22.6% (95% CI, 13.1%–33.7%) in the norfloxacin group and 37.1% (95% CI, 25.2%–49.0%) in the placebo group ($P = .069$ by Gray test). The subdistribution hazard ratio for death at 6 months was 0.54 (95% CI, 0.28–1.05) with norfloxacin vs placebo.



Supplementary Figure 5. Analyses of the secondary outcome of 12-month mortality. The estimated cumulative incidence of death at 12 months after randomization and based on the Kaplan–Meier method was 26.4% (95% CI, 18.6%–34.8%) in the norfloxacin group and 31.8% (95% CI, 23.5%–40.5%) in the placebo group. Censoring of the data is indicated by the *vertical bars*. Data for patients with SBP were censored at the date of infection. Data for patients who received a liver transplant were censored at the date of liver transplantation (if there was no SBP before transplantation). Data for patients who were lost to follow-up were censored at the date of their last follow-up visit.

Supplementary Table 1. Characteristics of Previous Double-Blind, Randomized, Placebo-Controlled Clinical Trials of Oral Fluoroquinolone Therapy in Patients With Cirrhosis

Characteristics	First author			
	Rolachon[1]	Grangé[2]	Fernandez[3]	Terg[4]
Intervention	Ciprofloxacin (750 mg, once/wk, for 6 mo)	Norfloxacin (400 mg/d, for 6 mo)	Norfloxacin (400 mg/d, for 12 mo)	Ciprofloxacin (500 mg/d, for 12 mo)
Inclusion criteria	AF protein concentration ≤15 g/L No prior episode of SBP during the 3 mo before inclusion	AF protein concentration <15 g/L No history of infection (including SBP) No active infection	AF protein concentration ≤15 g/L Advanced cirrhosis[a] No history of SBP	AF protein concentration <15 g/L No history of SBP
Primary outcomes	Prevention of SBP[b]	Primary prevention of Gram-negative bacterial infections	3-mo and 1-y probability of survival	Primary prevention of SBP
No. of patients				
Quinolone	28	53	35	50
Placebo	32	54	33	50
Bacterial infection during follow-up (% of patients)				
Any				
Quinolone	14	13	40	16
Placebo	34	24	58	32[c]
SBP				
Quinolone	4	0	6	4
Placebo	22[c]	9	30[c]	14
Caused by Gram-negative bacteria				
Quinolone	4	0	37	NA
Placebo	0	11	18	NA
Mortality rate, %				
By 3 mo				
Quinolone	—	—	6	—
Placebo	—	—	30[d]	—
By 6 mo				
Quinolone	14	15	—	—
Placebo	19	18	—	—
By 1 y				
Quinolone	—	—	29	12
Placebo	—	—	39[e]	28[f]

AF, ascitic fluid; NA, not available.
[a]Advanced cirrhosis was defined as follows: advanced liver failure (Child-Pugh score ≥9 points with serum bilirubin level ≥3 mg/dL) or impaired renal function (serum creatinine level ≥1.2 mg/dL, blood urea nitrogen level ≥25 mg/dL, or serum sodium level ≤130 mEq/L).
[b]Two (7%) patients in the ciprofloxacin group and 5 (16%) in the placebo group had a prior episode of SBP.
[c]$P < .05$, quinolone vs placebo.
[d]The Kaplan–Meier estimate 3-mo mortality was 6% in the norfloxacin group and 38% in the placebo group ($P = .003$).
[e]The Kaplan–Meier estimate of 1-y mortality was 40% in the norfloxacin group and 52% in the placebo group ($P = .05$).
[f]The Kaplan–Meier estimate of 1-y mortality was 14% in the ciprofloxacin group and 34% in the placebo group ($P = .04$).

Supplementary Table 2. Inclusions Per Study Center

ID–study center	All patients, n (%) (n = 291)	Norfloxacin, n (%) (n = 144)	Placebo, n (%) (n = 147)
01–Beaujon	105 (36.1)	52 (36.1)	53 (32.1)
03–St Antoine	1 (0.3)	1 (0.7)	0 (0.0)
04–Jean Verdier	9 (3.1)	4 (2.8)	5 (3.4)
06–Paul Brousse	20 (6.9)	10 (6.9)	10 (6.8)
07–Pitié	4 (1.4)	2 (1.4)	2 (1.4)
08–Tenon	2 (0.7)	1 (0.7)	1 (0.7)
09–Angers	9 (3.1)	5 (3.5)	4 (2.7)
10–Besançon	29 (10.0)	15 (10.4)	14 (9.5)
11–Caen	12 (4.1)	6 (4.2)	6 (4.1)
12–Gonesse	3 (1.0)	1 (0.7)	2 (1.4)
13–Lille	9 (3.1)	5 (3.5)	4 (2.7)
14–Nancy	1 (0.3)	0 (0.0)	1 (0.7)
16–Toulouse	38 (13.1)	19 (13.2)	19 (12.9)
18–Tours	30 (10.3)	14 (9.7)	16 (12.9)
19–Nice	7 (2.4)	3 (2.1)	4 (2.7)
20–Montpellier	3 (1.0)	1 (0.7)	2 (1.4)
23–Lariboisière	4 (1.4)	2 (1.4)	2 (1.4)
24–Foch	5 (1.7)	3 (2.1)	2 (1.4)

Supplementary Table 3. Prespecified Definitions for Liver-Related Complications

Complication	Definition
Infection	Patients were considered to have infection if they had proven or suspected infection. Diagnosis of other infections was made according to conventional criteria and included any syndrome associated with a high risk of infection (eg, ascending cholangitis). Infections were classified as bacterial and non-bacterial (ie, viral and fungal) infections. Bacterial infections were classified as Gram-negative, Gram-positive, and non-documented bacterial infections.
SBP	Neutrophil count in the ascitic fluid of $>250/mm^3$, in the absence of findings suggestive of secondary peritonitis.[5]
Spontaneous empyema	Positive pleural fluid culture and neutrophil count of $>250/mm^3$ or negative pleural fluid culture and neutrophil count of $>500/mm^3$ in the absence of pneumonia.[5]
Pneumonia	Newly acquired respiratory symptoms (cough, sputum production, and/or dyspnea) and chest radiography showing lung infiltrate.[6]
Urinary tract infection	More than 10 leukocytes per high-power field in urine and positive urine cultures.[7]
Spontaneous bacteremia	Positive blood cultures with no cause of bacteremia.[7]
Multidrug-resistant bacteria	ESBL-producing *Enterobacteriaceae*, vancomycin-susceptible *Enterococcus faecium*, methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Stenotrophomonas maltophilia,* and *Achromobacter spp.*[8]
Septic shock	Sepsis with persistent hypotension requiring vasopressors despite adequate volume rescusitation.[9]
Kidney dysfunction	An increase in serum creatinine level >1.5 mg/dL (133 μmol/L).[10]
Hepatic encephalopathy	Presence of attention disorders and asterixis, confusion, or coma.[11]
Gastrointestinal hemorrhage	Any hematemesis or melena in a patient who, on endoscopy, had active bleeding from esophageal or gastric varices or signs of recent bleeding.[12]

ESBL, extended-spectrum β-lactamase.

Supplementary Table 4. Events that Occurred During the Double-Blind, Post-Treatment Period of the Trial

Event	No. of events	
	Norfloxacin	Placebo
Deaths	12	12
SBP	2	4
Liver transplantation	13	7
Lost to follow-up	4	2
Consent withdrawal	3	2

Supplementary Table 5. Chronological Analysis of Infectious Episodes and Total Numbers That Occurred During the Double-Blind Treatment Period of the Trial

Characteristics	Chronological analysis		*P* value
	Norfloxacin (n = 144)	Placebo (n = 147)	
First infectious episode			
Patients, n (%)	31 (21.5)	46 (31.3)	.06[a]
Site of infection, no. of patients (%)			
Ascites	9 (29.0)	16 (34.8)	.60[a]
Lung	4 (12.9)	8 (17.4)	.75[b]
Urine	4 (12.9)	6 (13.0)	1.00[b]
Blood	3 (9.7)	5 (10.9)	1.00[b]
Soft tissue	5 (16.1)	6 (13.0)	.75[b]
Documented pathogen, no. of patients (%)			
Gram-negative bacteria	3 (9.7)	15 (32.6)	.02[a]
Gram-positive bacteria	4 (12.9)	7 (15.2)	1.00[b]
Mixed bacteria	1 (3.2)	3 (6.5)	.64[b]
Multidrug-resistant bacteria	2 (6.5)	1 (2.2)	.56[b]
Other	2 (6.5)	0 (0.0)	.16[b]
Second infectious episode			
Patients, n (%)	7 (4.9)	6 (4.1)	.75[a]
Site of infection, no. of patients (%)			
Ascites	2 (28.6)	4 (66.7)	.29[b]
Lung	1 (14.3)	0 (0.0)	1.00[b]
Urine	2 (28.6)	0 (0.0)	.46[b]
Blood	0 (0.0)	2 (33.3)	.19[b]
Soft tissue	1 (14.3)	0 (0.0)	1.00[b]
Documented pathogen, no. of patients (%)			
Gram-negative bacteria	1 (14.3)	2 (33.3)	.56[b]
Gram-positive bacteria	1 (14.3)	3 (50.0)	.27[b]
Mixed bacteria	0 (0.0)	0 (0.0)	—
Multidrug-resistant bacteria	0 (0.0)	0 (0.0)	—
Other	0 (0.0)	0 (0.0)	—
Third infectious episode			
Patients, n (%)	2 (1.4)	1 (0.7)	.62[b]

Supplementary Table 5. Continued

Characteristics	Chronological analysis		*P* value
	Norfloxacin (n = 144)	Placebo (n = 147)	
Site of infection, no. of patients (%)			
Ascites	2 (100.0)	0 (0.0)	—
Lung	0 (0.0)	0 (0.0)	—
Urine	0 (0.0)	0 (0.0)	—
Blood	0 (0.0)	1 (100.0)	.33[b]
Soft tissue	0 (0.0)	0 (0.0)	—
Documented pathogen, no. of patients (%)			
Gram-negative bacteria	0 (0.0)	0 (0.0)	—
Gram-positive bacteria	0 (0.0)	1 (100)	.33[b]
Mixed bacteria	0 (0.0)	0 (0.0)	—
Multidrug-resistant bacteria	0 (0.0)	0 (0.0)	—
Other	0 (0.0)	0 (0.0)	—
Fourth infectious episode			
Patients, n (%)	1 (0.7)	0 (0.0)	—
Site of infection, no. of patients (%)			
Ascites	1 (100.0)	0 (0.0)	—
Lung	0 (0.0)	0 (0.0)	—
Urine	0 (0.0)	0 (0.0)	—
Blood	0 (0.0)	0 (0.0)	—
Soft tissue	0 (0.0)	0 (0.0)	—
Documented pathogen, no. of patients (%)			
Gram-negative bacteria	0 (0.0)	0 (0.0)	—
Gram-positive bacteria	0 (0.0)	0 (0.0)	—
Mixed bacteria	0 (0.0)	0 (0.0)	—
Multidrug-resistant bacteria	0 (0.0)	0 (0.0)	—
Other	0 (0.0)	0 (0.0)	—
Total no. of infectious episodes	41	53	—
No. of infectious episodes per patient, mean ± SD	0.28 ± 0.63	0.36 ± 0.58	.29[c]
Sites of infection, n (%)			
Ascites	14 (34.1)	20 (37.7)	.72[a]
Lung	5 (12.2)	8 (15.1)	.69[a]
Urine	6 (14.6)	6 (11.3)	.63[a]
Blood	3 (7.3)	8 (15.1)	.34[a]
Soft tissue	6 (14.6)	6 (11.3)	.63[a]
Documented pathogens, n (%)			
Gram-negative bacteria	4 (9.8)	17 (32.1)	.01[a]
Gram-positive bacteria	5 (12.2)	11 (20.8)	.27[a]
Mixed bacteria	1 (2.4)	3 (5.7)	.63[b]
Multidrug-resistant bacteria	2 (4.9)	1 (1.9)	.58[b]
Other	2 (4.9)	0 (0.0)	.19[b]

[a]*P* value obtained by χ^2 test.
[b]*P* value obtained by Fisher's exact test.
[c]*P* value obtained by unpaired *t* test.

Supplementary Table 6. Secondary Efficacy Outcomes at 12 Months, According to Study Group

Outcomes	Norfloxacin (n = 144)	Placebo (n = 147)	*P* value	Hazard ratio (95% CI)
Death[a]				
Patients, n	31	39	—	—
Estimated rate, % (95% CI)	26.4 (18.6–34.8)	31.8 (23.5–40.5)	.24	0.76 (0.47–1.21)
Liver transplantation[b]				
Patients, n	31	23		
Cumulative incidence, % (95% CI)	26.3 (18.6–34.7)	20.9 (13.8–29.0)	.38	1.27 (0.74–2.18)
Liver-related complications[c]				
Infection				
SBP				
Patients, n	12	21	—	—
Cumulative incidence, % (95% CI)	10.2 (5.5–16.7)	18.8 (12.0–26.8)	.09	0.54 (0.27–1.10)
Any infection				
Patients, n	39	56	—	—
Cumulative incidence, % (95% CI)	31.8 (23.5–40.3)	45.4 (36.0–54.3)	.03	0.63 (0.42–0.95)
Any bacterial infection				
Patients, n	38	53	—	—
Cumulative incidence, % (95% CI)	31.0 (22.8–39.5)	43.7 (34.3–52.7)	.04	0.65 (0.43–0.99)
Gram-negative bacterial infection				
Patients, n	8	17	—	—
Cumulative incidence, % (95% CI)	7.6 (3.5–13.8)	14.1 (8.5–21.1)	.04	0.43 (0.19–1.00)
Gram-positive bacterial infection				
Patients, n	4	13	—	—
Cumulative incidence, % (95% CI)	3.4 (1.1–7.9)	11.8 (6.5–18.8)	.02	0.28 (0.09–0.86)
Multidrug-resistant bacteria				
Patients, n	3	1	—	—
Cumulative incidence, % (95% CI)	2.6 (0.7–6.9)	0.7 (0.1–3.7)	.33	2.92 (0.30–28.12)
Septic shock				
Patients, n	11	11	—	—
Cumulative incidence, % (95% CI)	9.5 (4.9–15.8)	10.0 (5.1–16.8)	.99	0.99 (0.43–2.29)
Kidney dysfunction	22	16	—	—
Patients, n	18.1 (11.7–25.5)	13.4 (7.9–20.3)	.32	1.39 (0.73–2.64)
Cumulative incidence, % (95% CI)				
Hepatic encephalopathy	36	38	—	—
Patients, n	30.6 (22.2–39.3)	30.7 (22.6–39.1)	.63	0.89 (0.57–1.41)
Cumulative incidence, % (95% CI)				
Gastrointestinal hemorrhage				
Patients, n	12	14	—	—
Cumulative incidence, % (95% CI)	11.1 (6.0–18.1)	12.2 (6.9–19.1)	.61	0.82 (0.38–1.77)

NOTE. *P* values were derived from log-rank tests. The hazard ratios and 95% confidence limits were derived from Cox regression models.

[a]For the analysis of the outcome of death, data for patients with first SBP (12 in the norfloxacin group and 21 in the placebo group) were censored at the date of infection; data for patients who received a liver transplant and had no SBP before liver transplantation (27 and 19, respectively) were censored at the date of transplantation; and data for non-transplanted patients who had no SBP but were lost to follow-up (8 and 6, respectively) were censored at the date of last follow-up.

[b]For the analysis of incidence of liver transplantation, data for 22 patients in the norfloxacin group and 36 in the placebo group were censored at the date of death.

[c]Prespecified definitions for liver-related complications are provided in the Supplementary Table 3. For the analysis of the incidence of each liver-related complication, data for patients who received a liver transplant were censored as of the date of liver transplantation (if there was no occurrence of the event of interest before liver transplantation) and data for patients who died were censored as of the date of death (if there was no occurrence of the event of interest before death).

Supplementary Table 7. Nonfatal Adverse Events Other Than Liver-Related Complications at 6 Months

Event	Norfloxacin (n = 144)	Placebo (n = 147)	*P* value	Hazard ratio (95% CI)
Dermatologic event				
Patients, n	2	1	—	—
Cumulative incidence, % (95% CI)	1.7 (0.3–5.5)	0.8 (0.1–4.0)	.57	1.97 (0.18–21.75)
Cardiovascular or pulmonary event				
Patients, n	3	5	—	—
Cumulative incidence, % (95% CI)	2.4 (0.6–6.3)	4.4 (1.6–9.4)	.45	0.58 (0.14–2.43)
Digestive event				
Patients, n	6	5	—	—
Cumulative incidence, % (95% CI)	5.1 (2.1–10.2)	4.3 (1.6–9.2)	.82	1.15 (0.35–3.77)
Hematologic event				
Patients, n	8	6	—	—
Cumulative incidence, % (95% CI)	7.0 (3.3–12.7)	4.9 (2.0–9.9)	.64	1.28 (0.45–3.70)
Neuropsychiatric event				
Patients, n	8	6	—	—
Cumulative incidence, % (95% CI)	6.9 (3.2–12.5)	4.8 (1.9–9.6)	.63	1.29 (0.45–3.72)
Endocrine event				
Patients, n	4	6	—	—
Cumulative incidence, % (95% CI)	3.4 (1.1–7.9)	4.8 (1.9–9.5)	.51	0.65 (0.18–2.32)
Malignant condition†				
Patients, n	4	7	—	—
Cumulative incidence, % (95% CI)	3.3 (1.1–7.7)	5.8 (2.5–11.1)	.34	0.55 (0.16–1.89)

NOTE. The nature of and date that each serious adverse event occurred were declared by the investigator using a document that was faxed to the Département de la Recherche Clinique de l'Assistance Publique-Hôpitaux de Paris. The *Medical Dictionary for Regulatory Activities* was used to classify the safety events. Coding was performed at the coordinating center, and up to 5 codes were assigned to each safety event. Further classification into different categories was made by 2 members of the steering committee blinded to study treatment allocation. The accountability of serious adverse events to norfloxacin was blindly reviewed by the sponsor.

Supplementary Table 8. Nonfatal Adverse Events Other than Liver-related Complications at 12 Months

Event	Norfloxacin (n = 144)	Placebo (n = 147)	*P* value	Hazard ratio (95% CI)
Dermatologic event				
Patients, n	2	1	—	—
Cumulative incidence, % (95% CI)	1.7 (0.3–5.5)	0.8 (0.1–4.0)	.57	1.97 (0.18–21.75)
Cardiovascular or pulmonary event				
Patients, n	4	5	—	—
Cumulative incidence, % (95% CI)	3.4 (1.1–7.8)	4.4 (1.6–9.4)	.69	0.77 (0.21–2.86)
Digestive event				
Patients, n	9	8	—	—
Cumulative incidence, % (95% CI)	8.6 (4.1–15.1)	8.6 (3.9–15.7)	.88	1.08 (0.42–2.80)
Hematologic event				
Patients, n	12	7	—	—
Cumulative incidence, % (95% CI)	11.5 (6.2–18.5)	6.2 (2.7–11.8)	.27	1.67 (0.66–4.25)
Neuropsychiatric event				
Patients, n	12	11	—	—
Cumulative incidence, % (95% CI)	11.7 (6.3–19.0)	10.6 (5.5–17.6)	.90	1.05 (0.47–2.39)
Endocrine event				
Patients, n	4	6	—	—
Cumulative incidence, % (95% CI)	3.4 (1.1–7.9)	4.8 (1.9–9.5)	.51	0.65 (0.18–2.32)
Malignant condition				
Patients, n	8	8	—	—
Cumulative incidence, % (95% CI)	8.2 (3.7–14.9)	7.1 (3.2–13.0)	.93	0.96 (0.36–2.54)

NOTE. These events were assessed on the basis of the adverse events in the corresponding Medical Dictionary for Regulatory Activities System Organ Class (www.meddra.org).