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NOTES

Rapid Emergence of Quinolone Resistance in Cirrhotic Patients Treated with Norfloxacin To Prevent Spontaneous Bacterial Peritonitis

CATHERINE DUPEYRON,[1]* NICOLE MANGENEY,[1] LYRIA SEDRATI,[1] BERNARD CAMPILLO,[2] PAUL FOUET,[2] AND GEORGES LELUAN[1]

Laboratoire de Bactériologie[1] and Service d'Hépatogastroentérologie,[2] Hôpital Albert Chenevier, Créteil, France

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We carried out quantitative culturing of stools from 31 hospitalized alcoholic patients with cirrhosis and ascites, before treatment with 400 mg of norfloxacin per day, weekly for the first month, and then every 2 weeks thereafter for 15 to 229 days (median, 54 days). Members of the family *Enterobacteriaceae* virtually disappeared from the stools ($<10^2$/g), but treatment had little effect on enterococci. No selection of resistant organisms occurred in 15 patients, but the remaining 16 patients developed fecal organisms resistant to fluoroquinolones between days 14 and 43 of treatment (median, 25 days). *Staphylococcus aureus* was isolated four times, coagulase-negative *Staphylococcus* spp. were isolated six times, *Citrobacter freundii* was isolated four times, *Enterobacter cloacae* was isolated three times, *Klebsiella oxytoca* was isolated twice, *Proteus rettgeri* was isolated once, and untypeable streptococci were isolated six times. Some isolates persisted, while others were transient (one to seven consecutively positive cultures). The MICs of four quinolones (nalidixic acid, norfloxacin, ofloxacin, and ciprofloxacin) were determined by use of experimental microwell strips (ATB CMI; Biomerieux S.A.). All the strains isolated before treatment were susceptible to the four quinolones, with low MICs, whereas those isolated during norfloxacin treatment were highly resistant. Long-term norfloxacin administration thus carries a risk of disturbing the bacterial ecology in these patients, suggesting that digestive decontamination should no longer be prescribed routinely to cirrhotic patients with ascites.

Spontaneous bacterial peritonitis (SBP) of ascitic fluid is a very serious and frequent complication in cirrhotic patients; it occurs in 8 to 25% of cases and is the second most frequent cause of death in this setting (11, 12, 13, 15, 26). As SBP is usually caused by commensal enteric organisms, selective digestive decontamination has been recommended (10). This antibiotic prophylaxis is aimed at eliminating members of the family *Enterobacteriaceae* while respecting the other components of the gut flora.

Several recent studies (9, 27) have shown that norfloxacin reduces the frequency of SBP, and this antibiotic is now commonly used prophylactically in these patients. However, the associated risk of selecting resistant bacteria is poorly documented. There have been few studies on the effect of norfloxacin on the gut flora of cirrhotic patients (8, 9).

The aim of this work was to determine the medium-term influence of norfloxacin on fecal flora in hospitalized cirrhotic patients, together with the development of resistance to quinolones during treatment.

The study involved 31 inpatients with alcoholic cirrhosis. All had clinical ascites; they were free of infection at inclusion in the study and had not received antibiotics for at least 2 weeks. They were treated prophylactically with 400 mg of norfloxacin per day by mouth.

* Corresponding author. Mailing address: Laboratoire de Bactériologie, Hôpital Albert Chenevier, 40, rue de Mesly, 94000 Créteil, France. Phone: 49 81 31 09. Fax: 49 81 31 19.

Quantitative stool culturing was carried out just before treatment, weekly during the first month, and every 2 weeks thereafter. Stools were collected in sterile containers and cultured either immediately or after no more than 15 days of storage at −70°C. One gram of feces was homogenized in 9 ml of prereduced peptone broth. Aliquots (0.05 ml) of four 10-fold dilutions were seeded onto the following media: Drigalski agar (Diagnostics Pasteur, Marnes-la-Coquette, France), Chapman mannitol agar, blood agar with nalidixic acid and colistin, blood agar, bile esculin agar, Sabouraud's agar with chloramphenicol (Biomerieux S.A., Marcy l'Etoile, France), Wilkins-Chalgren medium with 5% sheep blood and neomycin (130 μg/ml), Wilkins-Chalgren medium with 5% sheep blood, kanamycin (100 μg/ml), and vancomycin (7.5 μg/ml) (Oxoid, Unipath Ltd., Basingstoke, England), Rogosa agar (Diagnostics Pasteur), and polymyxin sulfite agar (17) prepared in our laboratory.

Media were inoculated by use of the Spiral System (Spiral System Inc.). Aerobic media were incubated for 24 h at 37°C, and anaerobic media were incubated for 4 days at 37°C in an anaerobic chamber (GasPak; BBL Microbiology Systems, Cockeysville, Md.). The different types of colonies were counted by use of the special Spiral System grid. Aerobic and facultatively aerobic organisms were identified by their biochemical characteristics.

Antibiotic susceptibility testing was carried out on all identified isolates by the semisolid agar dilution method (ATB; Biomerieux).

TABLE 1. Quinolone MICs for fecal isolates before norfloxacin treatment

Patient(s)	Species	MIC (μg/ml) of:			
		Nalidixic acid	Norfloxacin	Ofloxacin	Ciprofloxacin
1, 2, 3, 4, 5, 6, 8, 9, 11, 14, 15, 16, 21, 22, 24, 26, 28, and 29	*E. coli*	<4	<0.5	<0.25	<0.25
7	*E. coli*	256	<0.5	1	<0.25
18	*E. coli*	>512	64	>16	16
12, 13, 17, 25, and 27	*K. pneumoniae*	<4	<0.5	<0.25	<0.25
10	*K. oxytoca*	8	<0.5	<0.25	<0.25
20	*E. cloacae*	<4	<0.5	<0.25	<0.25
23 and 30	*C. freundii*	<4	<0.5	<0.25	<0.25
31	*C. freundii*	16	<0.5	<0.25	<0.25
19	*C. freundii*	>512	64	>16	>16
19 and 30	*S. aureus*	>512	>64	>16	>16
31	*Staphylococcus* species	>512	>64	>16	>16

The MICs of the four quinolones were then determined by use of the experimental microwell strips (ATB CMI; Biomerieux) (25) prepared especially for this study. The system consists of 32 wells containing the following quinolone concentrations: nalidixic acid, 4, 8, 16, 32, 64, 128, 256, and 512 μg/ml; norfloxacin, 0.5, 1, 2, 4, 8, 16, 32, and 64 μg/ml; and ofloxacin and ciprofloxacin, 0.25, 0.5, 1, 2, 4, 8, and 16 μg/ml. Each well was inoculated with 135 μl of Mueller-Hinton broth containing 10^6 CFU/ml. After 18 h of incubation at 35°C, an automated tray reader (ATB 1520; Biomerieux) records the turbidity in each well, which is then interpreted by a computer (ATB 1545; software 1.7.6.; Biomerieux) as indicating an MIC in the susceptible, moderately susceptible, or resistant category. The breakpoints recommended by the 1992 statement of the Antibiogram Committee of the French Society for Microbiology (1) were as follows: nalidixic acid, ≤8 and >16; norfloxacin, ≤1 and >8; ofloxacin, ≤1 and >4; and ciprofloxacin, ≤1 and >2. MICs for the following reference strains were determined concomitantly: *Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853, and *Enterococcus faecalis* ATCC 29212 (recommended by the National Committee for Clinical Laboratory standards [18]) and *Staphylococcus aureus* ATCC 25923 (recommended by the Antibiogram Committee of the French Society for Microbiology [1]). The results were consistent with the values recommended by these two organizations.

Before treatment with norfloxacin, the aerobic and facultatively anaerobic fecal flora was essentially made up of members of the family *Enterobacteriaceae* and enterococci (10^6 to 10^8/g of feces). The anaerobic flora (10^9/g) was mainly composed of *Bacteroides*, *Lactobacillus*, and *Clostridium* spp. Most of the isolates of the *Enterobacteriaceae* were susceptible to the quinolones (Table 1). Only seven isolates were resistant to nalidixic acid (two *E. coli*, two *Citrobacter freundii*, two *S. aureus*, and one *Staphylococcus* sp.), and five of these were resistant to the fluoroquinolones (one *E. coli*, one *C. freundii*, two *S. aureus*, and one *Staphylococcus* sp.).

Among the five patients who initially had resistant isolates, three had received antibiotics, either amoxicillin-clavulanic acid (patients 18 and 31) or ceftazidime (patient 19), 3 to 4 weeks before inclusion in the study. Among the remaining 26 patients, 5 had received antibiotics, either amoxicillin-clavulanic acid (patient 20), ceftriaxone (patients 8 and 27), ceftazidime and ciprofloxacin (patient 27), or ofloxacin (patients 4 and 24), 3 to 6 weeks before inclusion.

Follow-up lasted between 15 and 229 days, with a median of 54 days. Stool sampling was stopped either when the patient was discharged or because of the onset of septicemia, with infection of the ascitic fluid caused by methicillin-resistant *S. aureus* (patients 21 and 24), a coagulase-negative *Staphylococcus* sp. (patients 19 and 31), or *P. aeruginosa* (patient 30), which led to death in all five cases.

Members of the family *Enterobacteriaceae* were no longer detectable during norfloxacin treatment (<10^2/g), while no effect was observed on enterococci or anaerobes. No resistant organisms were isolated from 15 patients at any time during the study. In contrast, 16 patients developed organisms resistant to fluoroquinolones between days 12 and 43 of treatment (median, 25 days) (Table 2). *S. aureus* was isolated four times, coagulase-negative staphylococci were isolated six times (two *S. haemolyticus*, two *S. epidermidis*, and two other *Staphylococcus* spp.), *C. freundii* was isolated four times, *Enterobacter cloacae* was isolated three times, *Klebsiella oxytoca* was isolated twice, *Proteus rettgeri* was isolated once, and untypeable streptococci were isolated six times. These isolates disappeared spontaneously from some patients but usually persisted until the end of follow-up. The staphylococci were methicillin resistant, while the isolates of the *Enterobacteriaceae* were also resistant to aminoglycosides and beta-lactams. Three *Citrobacter* (patients 1, 3, and 6), one *Enterobacter* (patient 23), and two *Klebsiella* (patients 11 and 28) spp. were high-level penicillinase producers. One *Citrobacter* (patient 2) and two *Enterobacter* (patients 10 and 12) spp. were high-level cephalosporinase producers. The *P. rettgeri* isolate was a high-level penicillinase producer.

Norfloxacin has been recommended for selective digestive decontamination for the following reasons: poor intestinal absorption, strong activity against gram-negative facultative aerobes and anaerobes, weak activity against anaerobes, and few side effects when given for long periods (30). Few studies of fecal microbial ecology in cirrhotic patients treated prophylactically with norfloxacin have been done. Preliminary work in this setting (8) showed that oral norfloxacin administration for 1 week led to the disappearance of gram-negative bacteria from the gut without significantly affecting anaerobes. Gines et al. (9), in a study which showed the beneficial effects of norfloxacin in preventing SBP in cirrhotic patients with ascites, analyzed the fecal flora of six patients monthly for 1 year and compared the results with those for six control patients. With regard to the disappearance of members of the family *Enterobacteriaceae* and the lack of effect on enterococci and anaerobes, our findings concur with those of Gines et al. (9). They are also in keeping with data published by authors who

TABLE 2. Quinolone MICs for fecal isolates during norfloxacin treatment

Patient	Species[a]	No. of bacteria/g of feces on the indicated day of follow-up[b]:														MIC (μg/ml) of:			
		7	15	21	30	45	60	75	90	105	120	135	150	165	180	Nalidixic acid	Norfloxacin	Ofloxacin	Ciprofloxacin
1	*C. freundii*	0	0	0	0	4×10^4										>512	16	>16	8
2	*C. freundii*	0	8×10^6	5×10^6	4×10^6											>512	>64	>16	>16
	Streptococcus NT	0	4×10^7	0	0											256	>64	>16	>16
3	*S. aureus*	0	8×10^4	2×10^6												256	>64	>16	>16
	C. freundii	0	0	4×10^4												>512	16	16	8
	P. rettgeri	0	0	2×10^6												>512	>64	>16	>16
5	*S. epidermidis*	0	0	1×10^4	0	0	0									512	64	8	16
	Streptococcus NT	0	0	0	0	4×10^6	0									512	4	2	0.5
6	*C. freundii*	0	0	0	3×10^4	4×10^5	0	8×10^4	0							>512	64	>16	>16
	P. fluorescens	0	0	0	6×10^4	8×10^5	0	2×10^5	0							>512	>64	>16	>16
	Streptococcus NT	0	0	0	0	0	2×10^8	0	0							128	4	4	1
10	*E. cloacae*	0	0	0	4×10^5	2×10^5	8×10^6	4×10^3								>512	>64	>16	>16
	S. haemolyticus	0	0	2×10^4	4×10^4	0	0	0								>512	>64	>16	>16
11	*K. oxytoca*	0	4×10^5	0	0	0	0	0	0							>512	32	16	8
12	*E. cloacae*	0	0	0	2×10^5	8×10^4	0	0	0	0	0	0	0	2×10^7	0	>512	>64	>16	>16
	Streptococcus NT	0	0	0	2×10^6	0	3×10^8	3×10^6	4×10^5	3×10^5	0	0	0	0	0	256	4	4	2
14	*Staphylococcus* species	0	0	0	4×10^4	4×10^4	0	0								>512	>64	>16	>16
	Streptococcus NT	0	0	0	0	8×10^4	8×10^4	0								512	>64	>16	>16
17	*S. haemolyticus*	0	2×10^5	6×10^4	2×10^4	0	4×10^4	4×10^3	4×10^2							512	>64	16	>16
	Streptococcus NT	0	3×10^8	2×10^8	2×10^7	8×10^6	2×10^7	8×10^7	8×10^6							512	>64	>16	>16
21	*S. aureus*	0	0	4×10^6												512	>64	>16	>16
23	*E. cloacae*	0	0	2×10^7	4×10^6	8×10^4	8×10^4									>512	>64	>64	>16
24	*S. aureus*	0	0	0	0	8×10^7										512	>64	>16	>16
26	*S. aureus*	0	0	0	0	1×10^4										512	>64	>16	>16
	Staphylococcus species	0	0	0	3×10^5	0										256	>64	>16	>16
27	*S. epidermidis*	0	0	0	0	0	4×10^4									256	8	2	2
28	*K. oxytoca*	0	2×10^5	2×10^7												>512	32	16	16

[a] NT, nontypeable.
[b] 0, not selected. Blank spaces indicate the end of follow-up.

studied the effects of norfloxacin on the fecal flora of healthy volunteers (6, 21, 28) and experimental animals (20). In contrast, our results differ from those of Gines et al. (9) with regard to the selection of resistant organisms, since 16 of the 31 patients that we monitored for several weeks developed resistant isolates, whereas Gines et al. only observed transient carriage of three *Pseudomonas* spp. and one *Aeromonas* sp. This difference may be explained by the types of patients studied: Gines et al. investigated outpatients, while we studied only seriously ill cirrhotic patients requiring hospitalization. In addition, our sampling interval was shorter.

The strains that we isolated showed high-level resistance to the four quinolones tested, and this result was confirmed with consecutive samples (Table 2). To our knowledge, this is the first time that quinolone MICs have been determined for strains isolated from cirrhotic patients. Our results are in keeping with those obtained by other authors studying long-term treatment with quinolones in other clinical settings with regard to the emergence of resistant strains of *S. aureus* (3), the family *Enterobacteriaceae* (4, 16, 22, 29), *Campylobacter* spp. (2, 23, 31), and other gram-negative bacteria (24).

These data provide further arguments in the controversy surrounding selective digestive decontamination (5), confirming that even prophylactic use of antibiotics can lead to selection of resistant strains in the digestive (and cutaneous) bacterial flora (7, 14, 19).

The question raised by our findings is whether it is justifiable to take the risk of creating and disseminating bacteria with high-level resistance in a hospital unit receiving patients with weakened immunity. Indeed, what is intended as a preventive measure may "backfire" and lead to infections by multiresistant members of the family *Enterobacteriaceae* or methicillin-resistant staphylococci. A study of the clinical implications is under way in our gastroenterology unit to more accurately determine the consequences of this measure. In any event, we believe that digestive decontamination should no longer be prescribed routinely for cirrhotic patients with ascites.

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