

SESSION 14

Comparative Studies of Fluoroquinolones in the Treatment of Urinary Tract Infections

R. Malinverni and M. P. Glauser

*From the Medizinische Universitätsklinik, Inselspital, Bern,
and the Division of Infectious Diseases, Department of
Medicine, Centre Hospitalier Universitaire Vaudois,
Lausanne, Switzerland*

The results of comparative trials of fluoroquinolones for the treatment of uncomplicated and complicated urinary tract infections (UTI) were reviewed. Several randomized, comparative trials showed that in uncomplicated UTI norfloxacin, ciprofloxacin, and ofloxacin were at least as effective as trimethoprim-sulfamethoxazole (TMP-SMZ) and amoxicillin and usually more effective than nalidixic acid, pipemidic acid, and nitrofurantoin. Comparative trials of single-dose regimens have, however, been limited. A few randomized, comparative trials have shown that in complicated UTI norfloxacin, ciprofloxacin, and ofloxacin were at least as effective as amoxicillin and TMP-SMZ and usually more effective than pipemidic acid. Moreover, preliminary results indicate that fluoroquinolones might be effective for the oral treatment of complicated UTI that are difficult to treat, especially those due to *Pseudomonas aeruginosa*. Comparative trials are needed to establish the value of fluoroquinolones for chronic bacterial prostatitis. There are no conclusive data on fluoroquinolone treatment of UTI in patients with renal failure. Emergence of resistant pathogens during therapy with fluoroquinolones has been infrequent but might be more frequent in complicated UTI caused by *P. aeruginosa*.

Although highly effective and well-established antibiotic regimens are available for the treatment of urinary tract infection (UTI), there is a need for new antimicrobial agents, especially for the treatment of outpatients with UTI that are difficult to treat and for which most of the drugs available for oral treatment are ineffective.

The fluoroquinolones have several properties that suggest their potential clinical utility for the treatment of UTI, including high activity *in vitro* against virtually all urinary tract pathogens and good absorption after oral administration that results in prolonged high levels of drug in urine [1].

The methodologic problems associated with open and comparative trials evaluating the efficacy of new antibiotics for the treatment of UTI have recently been reviewed [2]. For this review of the efficacy of fluoroquinolones for the treatment of UTI, we have emphasized those studies that have both sufficient data for a clear classification of UTI and data on

follow-up urine cultures 4–6 weeks after the end of treatment (unless otherwise mentioned). In this evaluation, bacteriologic cure (sterile urine) was considered as the end point of antibiotic treatment since the definitions of clinical response, when stated, varied from one study to another and symptoms may disappear in the absence of bacteriologic cure. In table 1, which outlines the efficacy of fluoroquinolone treatment of UTI by infecting organism, only data from studies (noncomparative and comparative) that provided sufficient information to permit a clear classification of UTI were taken into account. We will consider and analyze separately the uncomplicated and the complicated UTI.

Uncomplicated UTI is an infection occurring in a patient without anatomic or functional abnormalities of the urinary tract. Such infections are amenable to either a single dose or to very short-term treatment [3–5]. In contrast, complicated UTI will be considered as those that occur during pregnancy or in patients with anatomic or functional abnormalities of the urinary tract, those in patients with debilitating underlying diseases such as diabetes mellitus, or those in patients presenting with the clinical picture of acute pyelonephritis. The treatment of complicated UTI should be more prolonged than

We thank Mrs. Kathrin Zsirmik and Mrs. Alexandra Bloch for typing the manuscript.

Please address requests for reprints to R. Malinverni, Medizinische Universitätsklinik, Inselspital, CH-3010 Bern, Switzerland.

Table 1. Rates of eradication of organisms after fluoroquinolone treatment of urinary tract infections (UTI).

Type of infection, fluoroquinolone	Percentage of strains eradicated after treatment (total no. isolated before treatment)*						
	Coagulase- negative staphylococci	Enterococci	<i>Escherichia coli</i>	<i>Proteus</i> species	<i>Klebsiella</i> species	<i>Pseudomonas aeruginosa</i>	<i>Enterobacter</i> species
Uncomplicated UTI							
Norfloxacin	94 (32)	...	93 (228)	100 (17)	58 (12)	100 (8)	100 (5)
Ciprofloxacin	87 (15)	100 (7)	96 (266)	100 (10)	100 (6)
Ofloxacin	...	100 (8)	94 (97)	94 (18)	100 (8)
Enoxacin	99 (107)
Pefloxacin	88 (48)	...	100 (5)	100 (5)	...
Complicated UTI							
Norfloxacin	...	100 (5)	96 (27)	81 (36)	...
Ciprofloxacin	100 (5)	100 (5)	98 (93)	100 (35)	85 (27)	54 (112)	100 (10)
Ofloxacin	89 (19)	94 (36)	94 (65)	93 (29)	78 (27)	67 (52)	75 (8)
Enoxacin	...	100 (22)	75 (12)	79 (38)	...
Pefloxacin	100 (5)	...	95 (62)	95 (20)	100 (6)

NOTE. Data are from [10-53] and from data on file, Laboratoire Roger Bellon (Neuilly-sur-Seine, France).

* The minimum number of strains required to be reported in this table was five. The total number of strains isolated before treatment was calculated by summarizing the data from all trials that used one of the fluoroquinolones for the treatment of uncomplicated or complicated UTI. Eradication rates (%) were the number of isolates of one bacterial species eradicated at follow-up divided by the total number of isolates of the same species found before treatment.

that of uncomplicated UTI since relapses frequently occur after short-term treatment [4] and even after courses of therapy longer than 10-14 days [5, 6]. There are suggestions that 6 weeks of antibiotic therapy may be needed to eradicate complicated (relapsing) infections, as shown in women with upper UTI [7], in renal transplant recipients [8], and in men with recurrent UTI [9].

Because the treatment of both uncomplicated and complicated UTI are relatively well standardized and because most antibacterial agents that achieve reasonable antibacterial activity in the urine are effective for the treatment of UTI, it is not surprising that the new quinolones have shown good activity in open, noncomparative studies. Even placebo therapy might achieve a cure rate of up to 50% in female patients with acute symptomatic UTI. Thus, this review will consider only those studies that have compared in a prospective, randomized fashion fluoroquinolone therapy with well-established regimens. In addition, we will also consider those studies that have tested in a prospective way various dosages or durations of treatment of fluoroquinolones. Finally, this review will analyze the results of open trials specifically aimed at treating UTI caused by *Pseudomonas aeruginosa*, for which no alternative orally administrable drugs are presently available.

Efficacy of Fluoroquinolone Treatment of UTI, by Organisms

Table 1 summarizes the data on the rates of eradication of different organisms from the urinary tract after treatment with five fluoroquinolones. Obviously, a precise comparison of the eradication rate for one drug with that for another was not possible since the duration of treatment varied considerably from one study to another. Furthermore, although in the majority of studies, follow-up cultures were performed 4-6 weeks after the end of treatment, in some studies such cultures were done as early as 7-9 days after completion of therapy. Finally, only a small number of UTI due to gram-positive organisms were included in these studies, since all studies excluded strains resistant in vitro, a common pattern, especially among enterococci tested against fluoroquinolones.

Randomized Trials with Fluoroquinolones for the Treatment of Uncomplicated UTI

Trials aimed at defining optimal treatment regimens. Rugendorff and Schneider [54] treated 59 women with acute infections with either a single dose of norfloxacin (800 mg) or a 3-day course (800 mg

daily) and reported a slightly, but not significantly, better cure rate after the 3-day regimen (93.7%) than after the single dose (85.2%).

Graeff et al. [55] reported that a 3-day course of ciprofloxacin (200 mg daily) was not significantly superior to a single dose (250 mg) for the treatment of postoperative UTI in 100 gynecologic patients. Garlando et al. [25] recently studied two single-dose regimens of ciprofloxacin (either 100 mg or 250 mg orally) for the treatment of acute UTI in 38 women. The cure rates in the two groups (89% and 84%, respectively) were similar, but two of four episodes due to *Staphylococcus saprophyticus*, as compared with only three of 34 due to gram-negative Enterobacteriaceae, could not be cured. The rate of killing by ciprofloxacin of *S. saprophyticus* in vitro was significantly slower than that of four strains of *Escherichia coli*.

Ludwig [46] treated 43 patients with either a 1-day course (200 mg) or a 3-day course of ofloxacin and reported similar cure rates (91% and 95%) for the two regimens.

Randomized, comparative trials. The results of randomized, comparative trials are summarized in table 2. Norfloxacin was compared with trimethoprim-sulfamethoxazole (TMP-SMZ) in several randomized, comparative trials for the treatment of uncomplicated UTI [10–17, 56, 59]. In each trial, norfloxacin was at least as effective as TMP-SMZ. In a large trial including 323 patients, norfloxacin (800 mg daily for 3–10 days) was significantly more effective (97% cure rate) than TMP-SMZ (90% cure rate) [59]. In the largest randomized, double-blind multicenter study, which included more than 600 patients, two norfloxacin regimens (400 or 800 mg daily) were compared with TMP-SMZ (320/1,600 mg daily) given for 7 days [60]. A minority of the patients had recurrent UTI (~25%) or UTI complicated by factors such as structural abnormalities of the urinary tract, stones, or diabetes mellitus (~15%). The bacteriologic efficacy 4 weeks after the end of treatment was similar in all treatment groups (88%–89%). However, the lower dose of norfloxacin (400 mg) was less effective than the higher dose (800 mg) and than TMP-SMZ for UTI in men and for patients with complicated UTI.

Among those trials that determined bacterial susceptibilities after norfloxacin therapy [10–13, 15–17], only one therapeutic failure was due to superinfection with a resistant group B streptococcal strain [16].

One study compared a single dose of norfloxacin (1,200 mg) to a single dose of TMP-SMZ (480/2,400 mg) for the treatment of uncomplicated UTI in 43 women: the cure rates were similar (88% and 82%, respectively) [17]. The two failures (relapses) after norfloxacin therapy were due to strains of *S. saprophyticus* (that were still susceptible to norfloxacin in vitro). When norfloxacin was compared with nalidixic acid and pipemidic acid, norfloxacin was significantly more effective [18, 61]. Finally, norfloxacin was slightly, but not significantly, more effective than amoxicillin for the treatment of uncomplicated UTI in geriatric patients [62].

Henry et al. [36] treated 65 women in a prospective, randomized, double-blind study with either ciprofloxacin (500 mg daily) or TMP-SMZ (320/1,600 mg daily) for 10 days. They reported a slightly better cure rate after ciprofloxacin (100%) than after TMP-SMZ (94%) therapy. Moreover, ciprofloxacin was significantly less toxic. Newsom et al. [38] reported a higher cure rate after a 5-day course of ciprofloxacin (200 mg daily) than after trimethoprim alone (400 mg daily) in 32 geriatric patients with uncomplicated UTI. In one study of 75 hospital inpatients (50% with complicated UTI), two ciprofloxacin regimens (200 mg and 500 mg daily) given during 5 days were compared with TMP-SMZ (320/1,600 mg daily) [37]. Only the two ciprofloxacin groups included patients with infections due to *P. aeruginosa* or *Acinetobacter* species. In spite of this, both ciprofloxacin regimens were at least as effective as TMP-SMZ. In a further study of 60 patients with uncomplicated and complicated UTI, ciprofloxacin (500 mg daily) was significantly superior to TMP-SMZ (320/1,600 mg daily) given for 7–10 days [63]. In a limited study, ciprofloxacin appeared more effective than nalidixic acid [26].

Several randomized, comparative studies of ofloxacin (usually given for 3–5 days) for the treatment of uncomplicated UTI were performed in Europe [64]. Overall, ofloxacin had an efficacy similar to that of TMP-SMZ. Similarly, one study from the United States compared two regimens of ofloxacin (400 mg and 600 mg daily) to TMP-SMZ (320/1,600) given for 7 days to 39 women with uncomplicated UTI. Bacteriologic cure was achieved in all patients [65]. Ofloxacin was more effective than nitrofurantoin for the treatment of uncomplicated UTI in two studies [66, 67]. When compared with pipemidic acid, ofloxacin was significantly more effective, but

Table 2. Results of randomized comparative trials of fluoroquinolones for the treatment of uncomplicated urinary tract infections.

Agents	No. of patients	Dosage (mg/day)	Duration (days)	Bacteriologic cure rate (%)	Reference(s)
Norfloxacin vs. Trimethoprim-sulfamethoxazole (TMP-SMZ)	816	800*	10†	75-100	10-17, 56-59
Norfloxacin vs. Nalidixic acid	110	800	3	96	18
Norfloxacin vs. Pipemidic acid	197	1,980	10	82	61
Norfloxacin vs. Amoxicillin	91	800	7	91	62
Ciprofloxacin vs. TMP-SMZ	65	750	10	83	36
Ciprofloxacin vs. TMP	32	500	5	100	38
Ciprofloxacin vs. Nalidixic acid	19	200	7	94	26
Ofloxacin vs. TMP-SMZ	72	400	3-5	71	64
Ofloxacin vs. Nalidixic acid	189	2,000	7	80	64
Ofloxacin vs. Nitrofurantoin	123	100	3	94	66, 67
Ofloxacin vs. Pipemidic acid	50	200	7	77	43
Enoxacin vs. Pipemidic acid	252	300	7	78/91	52
		300	7	66/77	
		200	3	81	
		800	5	55	
		300	7	99	
		750		90	

* In two studies [11, 56] the daily dose was 400 mg; one study [17] compared a single dose of norfloxacin (1,200 mg) and TMP-SMZ (480/2,400 mg).

† Duration of treatment was 10 days in seven of 12 trials [10-14, 56, 58], 7-10 days in two trials [15, 16], 7 days in one trial [57], 3-10 days in one trial [59], and a single dose in one trial [17].

the follow-up period was short (1 week) [43]. Moreover, ofloxacin was compared with nalidixic acid for the treatment of uncomplicated UTI and achieved a higher rate of cure [64].

Kamidono et al. [52] compared enoxacin with

pipemidic acid for the treatment of acute uncomplicated cystitis in women and observed a significantly higher cure rate with enoxacin, but no follow-up cultures were performed. In conclusion, fluoroquinolones were at least as effective as other well-

Table 3. Results of randomized comparative trials of fluoroquinolones for the treatment of complicated urinary tract infections.

Agents	No. of patients	Dosage (mg/day)	Duration (days)	Bacteriologic cure rate (%)	Reference(s)
Norfloxacin vs. Amoxicillin	40	800 750	7	95 75	19
Norfloxacin vs. Pipemidic acid	530	800 2,000	5	63/75 48/62	68, 69
Norfloxacin vs. Trimethoprim-sulfamethoxazole (TMP-SMZ)	109	800 320/1,600	28-42	93 80	70
Norfloxacin vs. Parenteral therapy (β -lactam \pm aminoglycoside)	28	800	14-42	100 88	24
Ciprofloxacin vs. TMP-SMZ	61	500 320/1,600	10	63 45	71
Ciprofloxacin vs. Mezlocillin	40	200 (iv) 4,000	Not stated	88 57	72
Ofloxacin vs. TMP-SMZ	425	400 320/1,600	7	82 80	64
Ofloxacin vs. Amoxicillin + clavulanic acid	50	400 1,875	7	96 57	64
Ofloxacin vs. Pipemidic acid	228	600 2,000	5	89 72	42
Enoxacin vs. Pipemidic acid	393	600 2,000	5	89 68	52

established antimicrobial agents, but in the majority of the trials, the duration of therapy for uncomplicated UTI was too long.

Randomized, Comparative Trials for the Treatment of Complicated UTI

The results of some randomized, comparative trials of treatment of complicated UTI are summarized in table 3. When norfloxacin was compared with amoxicillin for the treatment of complicated UTI in geriatric patients, it proved slightly, but not significantly, better than amoxicillin [19]. Norfloxacin was superior to pipemidic acid in two double-blind

randomized studies [68, 69]. However, in both studies the follow-up period may have been inadequate. Sabbaj et al. [70] treated 109 men with recurrent UTI with either norfloxacin or TMP-SMZ for 4-6 weeks and reported a significantly higher cure rate with norfloxacin. In an open, comparative study, 28 patients with complicated UTI due to organisms resistant to aminoglycosides and TMP-SMZ were treated orally with norfloxacin or with a parenteral regimen (usually a β -lactam plus an aminoglycoside) for 2-6 weeks [24]. Norfloxacin cured more patients (100%) than did the parenteral regimens (88%), but the follow-up period may have been inadequate for all patients.

Boerema et al. [71] compared ciprofloxacin with TMP-SMZ for complicated UTI in male and female patients with anatomic or functional disorders of the urinary tract. Four to 6 weeks after therapy, the cure rate among patients treated with ciprofloxacin was higher (63%) than that among those treated with TMP-SMZ (45%). Similarly, Peters [72] found a higher cure rate 4 weeks after the end of therapy in 20 urologic patients treated iv with ciprofloxacin than in patients treated with mezlocillin.

Ofloxacin was compared with TMP-SMZ in several randomized studies of Europe for the treatment of complicated UTI [64]. The cure rates reported for the two regimens were similar. A smaller number of patients were included in trials comparing ofloxacin with a fixed combination of amoxicillin plus clavulanic acid [64]. Bacteriologic cures were observed in more patients treated with ofloxacin than in those treated with amoxicillin plus clavulanic acid. In a large double-blind trial in Japan that compared ofloxacin with piperimic acid for the treatment of UTI complicated by factors such as neurogenic bladder dysfunction, lithiasis, obstruction, or neoplasms, ofloxacin was significantly more effective than piperimic acid [42]. However, it is unclear in that study when follow-up cultures were performed.

Enoxacin was compared with piperimic acid for the treatment of complicated UTI, and a significantly higher cure rate was reported for patients treated with enoxacin, but no follow-up cultures were performed [52].

In conclusion, the new quinolones were at least as effective as TMP-SMZ or amoxicillin for the treatment of complicated UTI. In this setting, however, in some trials the duration of therapy was clearly too short and adequate follow-up cultures often were missing.

Fluoroquinolones for the Treatment of UTI Due to *P. aeruginosa*

Leigh and Emmanuel [20] observed an 84% cure rate in 19 patients with complicated UTI (paraplegia, multiple sclerosis, or other compromised bladder function; prostatic neoplasia, or indwelling catheters) due to *P. aeruginosa* and to *Pseudomonas fluorescens* after norfloxacin (800 mg daily) given for 5–10 days. However, follow-up cultures were not adequate for all patients. In this study, one of three failures occurred in a patient with a UTI caused by a resistant strain of *P. aeruginosa*. Boerema and Van Saene

[23] treated 16 similar patients with *P. aeruginosa* UTI with norfloxacin (400–800 mg daily) for 3 months and reported a 75% cure rate, but three of four failures were infections due to resistant strains of *P. aeruginosa*. Sauerwein and Bauernfeind [73] reported a 43% cure rate in 52 paraplegic patients with recurrent UTI (due primarily to *P. aeruginosa*) 1 week after the end of a 10-day course of norfloxacin (800 mg daily) and observed the emergence of resistance in three (11%) of 28 *P. aeruginosa* strains after therapy. Westenfelder et al. [74] treated 60 patients (14 of whom were infected with *P. aeruginosa*) with UTI and obstructions of the lower or upper urinary tract, which in most patients were due to malignancy, with norfloxacin (800 mg daily) for 7–9 days and observed a bacteriologic cure rate of 91% after 5–9 days of therapy; in the *P. aeruginosa* infection that did not respond to therapy, resistance developed.

Leigh et al. [39] reported a 63% cure rate in 27 UTI due to *P. aeruginosa* that were treated with ciprofloxacin (400–500 mg daily) for 5 days in patients with abnormalities of the urinary tract and reported development of resistance in three of 10 failures. Brown et al. [40] treated 16 patients with chronic (>2 months duration) *P. aeruginosa* UTI with ciprofloxacin (100–500 mg daily) for 2 weeks and reported a 44% cure rate 8 weeks after the end of treatment, observing emergence of resistance in one case of failure. As a part of a comparative trial, Williams and Grüneberg [37] treated 18 hospital inpatients with *P. aeruginosa* UTI with ciprofloxacin (200–500 mg daily) for 5 days, observing a cure rate of 72% without emergence of resistance. Van Poppel et al. [28] treated 29 patients with UTI (38% of which were due to multiresistant *P. aeruginosa*) and neurogenic bladder dysfunction with ciprofloxacin (200 mg daily) for 7 days and reported a 48% cure rate after 1 week but only a 17% cure rate after 1 month; one *P. aeruginosa* strain developed resistance. Using a higher dose regimen (1,000 mg of ciprofloxacin daily), Saavedra et al. [75] treated 28 patients (20 with pseudomonal infections) with urinary tract obstructions for a mean duration of 12 days, with a cure rate at 4 weeks of 35%. A total of 26 patients with UTI due to *P. aeruginosa* were treated with ciprofloxacin (1,000 mg daily) usually for 10 days in three open studies that included other infections [27, 29, 30]. Ninety-two percent of these patients were cured, but the follow-up period was only 1 week. Kumazawa et al. [31] treated 62 patients with complicated UTI due to *P. aeruginosa* and observed bac-

teriologic cure in 72.6% after ciprofloxacin therapy (400 mg daily for 5–14 days). Unfortunately, it is unclear when follow-up cultures were performed.

In conclusion, the patient's underlying conditions, the dosages, and the durations of administration of the fluoroquinolones varied considerably among these studies, complicating a conclusive interpretation of the results. Nevertheless, the orally administered fluoroquinolones have been effective against urinary *P. aeruginosa* infections, but emergence of resistant strains was observed repeatedly.

Fluoroquinolones for the Treatment of Prostatitis

The results of treatment of bacterial prostatitis with fluoroquinolones are summarized in table 4. Bologna et al. [76] treated 20 patients with chronic relapsing prostatitis with a 10-day course of norfloxacin (800 mg daily). Four weeks after the end of the treatment, bacteriologic cure was observed in 85% of the patients. In a comparative study Sabbaj et al. [70] treated 25 male patients with recurrent UTI and culture-positive prostatic fluid or ejaculate with norfloxacin for 4–6 weeks and reported a 92% cure rate at follow-up cultures at 1–3 weeks. Ciprofloxacin (1,000 mg daily) was tested by Guibert et al. [32] for the treatment of 26 patients with acute (28-day treatment) and chronic (84-day treatment) prostatitis due primarily to *E. coli*. After 6 weeks, bacteriologic cure had occurred in 77% of the patients. Suzuki et al. [77] treated 22 patients (four with acute and 18 with chronic prostatitis) with ofloxacin (300–600 mg daily) for 5–21 days. The segmented urine culture technique was used, and an overall rate of bacteriologic cure of 82% was reported. All eight gram-negative infections were eradicated, whereas only 10 of 14 gram-positive coccal infections were eradicated. No follow-up cultures were performed in this study after the end of the treatment. Finally, pefloxacin

(800 mg daily) was given to 33 patients with acute or recurrent prostatitis for a median duration of 28 days; the bacteriologic cure rate was 63% in patients followed up for up to 3 months (data on file, Laboratoire Roger Bellon, Neuilly-sur-Seine, France).

Treatment of Patients with Renal Failure

The urinary recovery of fluoroquinolones decreases as impairment of renal function progresses, but drug concentrations may remain above the MIC for most urinary pathogens [1, 78]. Thus, fluoroquinolone treatment of UTI in patients with different levels of renal failure is of special clinical interest. However, the vast majority of controlled clinical trials have excluded patients with impaired renal function. Only a few clinical studies [39, 40, 47, 53] involved patients with renal failure. In one study [53], treatment of UTI with enoxacin failed in three of five patients with mild to severe renal failure (plasma creatinine levels, 1.8–3.8 mg/100 mL) and structural abnormalities of the urinary tract; it is notable that the three failures occurred in patients with the highest creatinine levels. Brown et al. [40] described a failure in a patient with chronic UTI due to *P. aeruginosa* and severe renal failure in whom concentrations of ciprofloxacin in urine were similar (1 mg/L) to the MIC for the organism. Schulz and Dörfler [47] observed a 71% cure rate among 15 patients with mild to severe renal failure (plasma creatinine levels, 1.2–10 mg/100 mL), and four patients undergoing hemodialysis, whose doses of ofloxacin were adjusted (100–400 mg daily). Two of the four patients receiving dialysis were cured, but one of these patients was cured only after the dose of ofloxacin was doubled. The therapeutic response was negatively affected by concomitant treatment with antacids, which are known to interfere with the gastrointestinal absorption of fluoroquinolones.

Table 4. Results of the treatment of bacterial prostatitis with fluoroquinolones.

Agent	No. of patients	Dosage (mg/day)	Duration (days)	Follow-up (weeks)	Bacteriologic cure rate (%)	Reference
Norfloxacin	20	800	10	4	85	76
Norfloxacin	25	800	28–42	1–3	92	70
Ciprofloxacin	26	1,000	28/84	6	77	32
Ofloxacin	22	300–600	5–21	End of treatment	82	77
Pefloxacin	33	800	28	12	63	*

* Data on file, Laboratoire Roger Bellon (Neuilly-sur-Seine, France).

Conclusions

For the treatment of uncomplicated UTI, randomized comparative trials of norfloxacin, ciprofloxacin, and ofloxacin have conclusively shown these drugs to be at least as effective as TMP-SMZ and amoxicillin and usually superior to nalidixic acid, pipemidic acid, and nitrofurantoin. In some trials, however, the duration of treatment was >3 days, thus raising the question of whether such relatively prolonged treatment was actually necessary—considering that conventional short-term treatment has been effective in such conditions.

Comparative trials of single-dose regimens have been limited, and in two studies, treatment failures have been attributed to the poor susceptibility of gram-positive cocci such as *S. saprophyticus* after single doses of norfloxacin or ciprofloxacin. Clearly, the use of short-term treatment for uncomplicated UTI requires careful, additional studies, but some authors have questioned the interest of the sponsors of such studies for the short-term approach in the management of uncomplicated UTI [79].

For the treatment of complicated UTI, norfloxacin, ciprofloxacin, and ofloxacin have demonstrated good efficacy and were at least as effective as amoxicillin and TMP-SMZ and were usually superior to pipemidic acid. In these trials, however, the duration of treatment was relatively short when one considers the necessity for prolonged administration of antibiotics for complicated UTI.

The few published reports of the outcome of clinical trials of oral treatment of complicated UTI due to *P. aeruginosa* have indicated that the fluoroquinolones may be remarkably effective in this setting. Unfortunately, too many trials that include complicated infections lack the data on follow-up 4–6 weeks after the end of the treatment that are critical in evaluating efficacy. This follow-up period might be especially important when considering the possibility of emergence of resistant organisms during fluoroquinolone treatment, as has been observed in other clinical settings such as osteoarticular or pulmonary infections.

The pharmacokinetic characteristics of fluoroquinolones suggest a possible role for the treatment of chronic bacterial prostatitis [1]. Limited, noncomparative clinical trials suggest that the fluoroquinolones are effective in this condition. Clearly, careful confirmatory clinical trials with microbiologically well-documented infections and follow-up cultures

for several months after discontinuation of treatment are urgently needed to conclusively establish a role for the fluoroquinolones in the treatment of this chronic condition.

The development of resistance to the fluoroquinolones might be related in part to the presence at the infected site of concentrations of the antibiotic that are barely inhibitory and that thus may permit the growth of more resistant bacterial subpopulations. Fluoroquinolones produce very high concentrations of drug in the urine, and the emergence of resistance in pathogens of the urinary tract during therapy with fluoroquinolones has been observed only infrequently among organisms other than *P. aeruginosa*. However, preliminary data have indicated that emergence of resistant *P. aeruginosa* during fluoroquinolone therapy for complicated UTI might be a significant problem.

Since the fluoroquinolones are excreted, in part, by the kidney and their urinary recovery decreases as renal function decreases, the treatment of UTI in patients with renal failure should be investigated carefully. The excellent activity of these compounds in vitro and their lack of significant nephrotoxicity make them potentially usable and safe in this setting. However, at present only a few anecdotal reports of the use of these agents in this setting are available, and it is not possible to make a valid conclusion. Controlled trials involving patients with different stages of renal failure are needed, and special attention should be paid to the emergence of resistance. Whether the widespread use of these agents for the treatment of UTI will select resistant strains at other body sites, as has been observed in some French institutions after the widespread use of pefloxacin, is uncertain [80].

References

1. Hooper DC, Wolfson JS. The fluoroquinolones: pharmacology, clinical uses, and toxicities in humans. *Antimicrob Agents Chemother* 1985;28:716–21
2. Brumfitt W, Hamilton-Miller JMT. A review of the problem of urinary infection management and the evaluation of a potential new antibiotic. *J Antimicrob Chemother* 1984;13(Suppl B):121–33
3. Grüneberg RN, Brumfitt W. Single-dose treatment of acute urinary tract infection: a controlled trial. *Br Med J* 1967;3:649–51
4. Ronald AR, Boutros P, Mourtada H. Bacteriuria localization and response to single-dose therapy in women. *JAMA* 1976;235:1854–6

5. Fang LST, Tolkoff-Rubin NE, Rubin RH. Efficacy of single-dose and conventional amoxicillin therapy in urinary-tract infection localized by the antibody-coated bacteria technic. *N Engl J Med* 1978;**298**:413-6
6. Gargan RA, Brumfitt W, Hamilton-Miller JMT. Antibody-coated bacteria in urine: criterion for a positive test and its value in defining a higher risk of treatment failure. *Lancet* 1983;**2**:704-6
7. Turck M. Importance of localization of urinary tract infection in women. In: Kass EH, Brumfitt W, eds. *Infections of the urinary tract*. Chicago: University of Chicago Press, 1978:114-21
8. Rubin RH, Fang LST, Cosimi AB, Herrin JT, Varga PA, Russell PS, Tolkoff-Rubin NE. Usefulness of the antibody-coated bacteria assay in the management of urinary tract infection in the renal transplant patient. *Transplantation* 1979;**27**:18-20
9. Gleckmann R, Crowley M, Natsios GA. Therapy of recurrent invasive urinary-tract infections of men. *N Engl J Med* 1979;**301**:878-80
10. Guerra JG, Falconi E, Palomino JC, Benavente L, Antunez de Mayolo E. Clinical evaluation of norfloxacin versus cotrimoxazole in urinary tract infections. *Eur J Clin Microbiol* 1983;**2**:260-5
11. Giamarellou H, Tsagarakis J, Petrikos G, Daikos GK. Norfloxacin versus cotrimoxazole in the treatment of lower urinary tract infections. *Eur J Clin Microbiol* 1983;**2**:266-9
12. Panichi G, Pantosti A, Testore GP. Norfloxacin (MK-0366) treatment of urinary tract infections in hospitalized patients. *J Antimicrob Chemother* 1983;**11**:589-92
13. Haase DA, Harding GKM, Thomson MJ, Kennedy JK, Urias BA, Ronald AR. Comparative trial of norfloxacin and trimethoprim-sulfamethoxazole in the treatment of women with localized acute, symptomatic urinary tract infections and antimicrobial effect on periurethral and fecal microflora. *Antimicrob Agents Chemother* 1984;**26**:481-4
14. Schaeffer AJ, Sisney GA. Efficacy of norfloxacin in urinary tract infections: biological effects on vaginal and fecal flora. *J Urol* 1985;**133**:628-30
15. Watt B, Chait I, Kelsey MC, Newsom SWB, Newsom RA, Smith J, Toase PD, Deaney NB, Round EM, Vogel R, Currie WJC. Norfloxacin versus cotrimoxazole in the treatment of uncomplicated urinary tract infections—a multicentre trial. *J Antimicrob Chemother* 1984;**13**(Suppl B):89-94
16. Goldstein EJC, Alpert ML, Ginsberg BP. Norfloxacin versus trimethoprim-sulfamethoxazole in the therapy of uncomplicated, community-acquired urinary tract infections. *Antimicrob Agents Chemother* 1985;**27**:422-3
17. deVevey P, Darioli R, Bille J, Glauser MP. Traitement à dose unique de l'infection urinaire simple par norfloxacine versus cotrimoxazole [abstract no. 23]. In: *Résumés de la 54ème Assemblée annuelle de la Société Suisse de Médecine Interne*. *Schweiz Med Wochenschr [Suppl]* 1986;**20**:12
18. Reeves DS, Lacey RW, Mummery RV, Mahendra M, Bint AJ, Newsom SWB. Treatment of acute urinary infection by norfloxacin or nalidixic acid/citrate: a multi-centre comparative study. *J Antimicrob Chemother* 1984;**13**(Suppl B):99-105
19. Leigh DA, Smith EC, Marriner J. Comparative study using norfloxacin and amoxicillin in the treatment of complicated urinary tract infections in geriatric patients. *J Antimicrob Chemother* 1984;**13**(Suppl B):79-83
20. Leigh DA, Emmanuel FXS. The treatment of *Pseudomonas aeruginosa* urinary tract infections with norfloxacin. *J Antimicrob Chemother* 1984;**13**(Suppl B):85-8
21. Kirby CP. Treatment of simple urinary tract infections in general practice with a 3-day course of norfloxacin. *J Antimicrob Chemother* 1984;**13**(Suppl B):107-12
22. Bailey RR, Peddie BA, Blake E. Norfloxacin for the treatment of uncomplicated urinary tract infections [letter]. *NZ Med J* 1983;**96**:446
23. Boerema JBJ, Van Saene HKF. Norfloxacin treatment in complicated urinary tract infection. *Scand J Infect Dis [Suppl]* 1986;**48**:20-6
24. Cherubin C, Stilwell S. Norfloxacin versus parenteral therapy in the treatment of complicated urinary tract infections. *Scand J Infect Dis [Suppl]* 1986;**48**:32-7
25. Garlando F, Täuber MG, Flepp M, Meier B, Lüthy R. Einmalig Ciprofloxacin zur Behandlung des unkomplizierten Harnwegsinfektes der Frau [abstract no. 24]. In: *Autorreferate der 54. Jahresversammlung der Schweiz. Gesellschaft für Innere Medizin*. *Schweiz Med Wochenschr [Suppl]* 1986;**20**:12
26. Ball AP, Fox C, Brown IRF. Clinical efficacy and kinetics of ciprofloxacin in UTI [abstract no. 627]. In: *Proceedings of the Fourth Mediterranean Congress of Chemotherapy*, Rhodes, 1984
27. Ramirez CA, Bran JL, Mejia CR, Garcia JF. Open, prospective study of the clinical efficacy of ciprofloxacin. *Antimicrob Agents Chemother* 1985;**28**:128-32
28. Van Poppel H, Wegge M, Dammekens H, Chysky V. Ciprofloxacin in the treatment of urinary tract infection in patients with multiple sclerosis. *Eur J Clin Microbiol* 1986;**5**:251-3
29. Eron LJ, Harvey L, Hixon DL, Poretz DM. Ciprofloxacin therapy of infections caused by *Pseudomonas aeruginosa* and other resistant bacteria. *Antimicrob Agents Chemother* 1985;**28**:308-10
30. Scully BE, Neu HC, Parry MF, Mandell W. Oral ciprofloxacin therapy of infections due to *Pseudomonas aeruginosa*. *Lancet* 1986;**1**:819-22
31. Kumazawa J. Clinical evaluation of the use of ciprofloxacin in urological infections in Japan. In: Daikos GK, Mashimo K, eds. *Ciprofloxacin: antimicrobial activity, pharmacokinetics and clinical evaluation*. Tokyo: Tokyo University Press, 1986:51-5
32. Guibert J, Destrée D, Konopka C, Acar J. Ciprofloxacin in the treatment of urinary tract infection due to enterobacteria. *Eur J Clin Microbiol* 1986;**5**:247-8
33. Boerema J, Boll B, Muyltjens H, Branolte J. Efficacy and safety of ciprofloxacin (Bay O 9867) in the treatment of patients with complicated urinary tract infections. *J Antimicrob Chemother* 1985;**16**:211-7
34. Giamarellou H, Galanakis N, Dendrinis C, Stefanou J, Daphnis E, Daikos GK. Evaluation of ciprofloxacin in the treatment of *Pseudomonas aeruginosa* infections. *Eur J Clin Microbiol* 1986;**5**:232-5
35. Mehtar S, Drabu Y, Blakemore P. Ciprofloxacin in the treatment of infections caused by gentamicin-resistant gram-negative bacteria. *Eur J Clin Microbiol* 1986;**5**:248-51
36. Henry NK, Schultz HJ, Grubbs NC, Muller SM, Ilstrup DM,

- Wilson WR. Comparison of ciprofloxacin and co-trimoxazole in the treatment of uncomplicated urinary tract infection in women. *J Antimicrob Chemother* 1986;**18** [Suppl D]:103-6
37. Williams AH, Grüneberg RN. Ciprofloxacin and co-trimoxazole in urinary tract infection. *J Antimicrob Chemother* 1986;**18**(Suppl D):107-10
 38. Newsom SWB, Murphy P, Matthews J. A comparative study of ciprofloxacin and trimethoprim in the treatment of urinary tract infections in geriatric patients. *J Antimicrob Chemother* 1986;**18**(Suppl D):111-5
 39. Leigh DA, Emmanuel FXS, Petch VJ. Ciprofloxacin therapy in complicated urinary tract infections caused by *Pseudomonas aeruginosa* and other resistant bacteria. *J Antimicrob Chemother* 1986;**18**(Suppl D):117-21
 40. Brown EM, Morris R, Stephenson TP. The efficacy and safety of ciprofloxacin in the treatment of chronic *Pseudomonas aeruginosa* urinary tract infection. *J Antimicrob Chemother* 1986;**18**(Suppl D):123-7
 41. Scully BE, Neu HC. Oral ciprofloxacin therapy of infection caused by multiply resistant bacteria other than *Pseudomonas aeruginosa*. *J Antimicrob Chemother* 1986;**18**(Suppl D):179-85
 42. Kishi H, Nito H, Saito I, Nishimura Y, Nijjima T, Ohmori H, Tanaka H, Fujita Y, Deguchi K, Ogawa N. Comparative studies of DL-8280 and pipemidic acid in complicated urinary tract infections by double-blind method. *Hinyokika Kyo* 1984;**30**:1307-55
 43. Wittenberger R. Ofloxacin versus Pipemidsäure und Cotrimoxazol. *Infection* 1986;**14**(Suppl 1):S93-6
 44. Kishi H, Tominaga T, Oshi M, Kaneko H, Nijjima T. DL-8280 treatment of patients with urinary tract infections. In: Spitzky KH, Karrer K, eds. *Proceedings of the 13th International Congress of Chemotherapy*. Vol. 5. Vienna: Verlag H Egermann, 1983:125/27
 45. Sanefuji T, Kanetake H, Shindo K, Saitoh Y. Clinical experience with DL-8280 in urinary tract infections. *Chemotherapy (Tokyo)* 1984;**32**:778-87
 46. Ludwig G. Therapie unkomplizierter Harnwegsinfektionen mit Ofloxacin-Wirksamkeit bei unterschiedlicher Therapiedauer. *Referate zur antimikrobiellen und antineoplastischen Chemotherapie* 1985;**1-2**:67-8
 47. Schulz W, Dörfler A. Ofloxacin Behandlung bei nephrologischen Problempatienten mit unterschiedlich ausgeprägter chronischer Niereninsuffizienz (inkl. Dialyse-Behandlung). *Vorläufige Ergebnisse*. *Infection* 1986;**14**(Suppl 1):S97-101
 48. Guibert J, Acar JF. Ofloxacin (RU 43280): évaluation clinique dans les infections urinaires et prostatiques. *Pathol Biol (Paris)* 1986;**34**:494-7
 49. Guibert J, Boutelier R. Pefloxacin (1589RP): clinical assessment in urinary tract infections. In: Spitzky KH, Karrer K, eds. *Proceedings of the 13th International Congress of Chemotherapy* Vol 5. Vienna: Verlag H Egermann, 1983:110/52
 50. Wolff M, Vittecoq D, Régnier B, Modai J, Vachon F, Sarrazin C, Bure A. Preliminary trial of pefloxacin in the treatment of urinary tract infections and in seriously ill patients treated in hospital. In: Spitzky KH, Karrer K, eds. *Proceedings of the 13th International Congress of Chemotherapy* Vol 5. Vienna: Verlag H Egermann, 1983:110/60
 51. Boerema JBJ, Pauwels R, Scheepers J, Crombach W. Efficacy and safety of pefloxacin in the treatment of patients with complicated urinary tract infections. *J Antimicrob Chemother* 1986;**17**(Suppl B):103-9
 52. Kamidono S, Ishigami J, Nishiura T. Randomized multicenter double-blind studies of enoxacin and pipemidic acid in acute uncomplicated cystitis and complicated urinary tract infection. In: *Proceedings of the Fourth Mediterranean Congress of Chemotherapy*, Rhodes, 1984:503-4
 53. Bailey RR, Peddie BA. Enoxacin for the treatment of urinary tract infection. *NZ Med J* 1985;**98**:286-8
 54. Rugendorff EW, Schneider HJ. Randomized comparison of single-dose norfloxacin vs short-term therapy in acute lower urinary tract infection (abstract no. P-39-107). In: *Proceedings of the 14th International Congress of Chemotherapy*, Kyoto, 1985
 55. Graeff H, Loos W, v Hugo R, Machka K, Fischbach F. Ciprofloxacin in the treatment of patients with symptomatic and asymptomatic urinary tract infections: a comparative study of single-dose application versus three days treatment concerning efficacy and safety (abstract no. S-50-9). In: *Proceedings of the 14th International Congress of Chemotherapy*, Kyoto, 1985
 56. Bologna M, Vaggi L, Martini E, Tomei E. Norfloxacin in the treatment of urinary tract infections. *European Journal of Chemotherapy and Antibiotics* 1983;**3**:41-6
 57. Newsom SWB, Newsom RA, Toase D. Norfloxacin versus cotrimoxazole for urinary tract infection in general practice (abstract no. 519). In: *Program and abstracts of the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy*. Washington DC: American Society for Microbiology, 1983
 58. Bendall MJ. A review of urinary tract infection in the elderly. *J Antimicrob Chemother* 1984;**13**(Suppl B):69-78
 59. Sabbaj J, Hoagland VL, Shih WJ. Multiclinic comparative study of norfloxacin and trimethoprim-sulfamethoxazole for treatment of urinary tract infections. *Antimicrob Agents Chemother* 1985;**27**:297-301
 60. The Urinary Tract Infection Study Group. Coordinated multicenter study of norfloxacin versus trimethoprim-sulfamethoxazole treatment of symptomatic urinary tract infections. *J Infect Dis* 1987;**155**:170-7
 61. Kamidono S, Tomioka O, Hikosaka K, Ishigami J, Nijjima T. A comparative double-blind study of norfloxacin (AM-715) and pipemidic acid in the treatment of acute simple cystitis. *Chemotherapy (Tokyo)* 1982;**30**:1159-81
 62. Vogel R, Deaney NB, Round EM, VandenBurg MJ, Currie WJC. Norfloxacin, amoxicillin, cotrimoxazole and nalidixic acid: a summary of 3-day and 7-day therapy studies in the treatment of urinary tract infections. *J Antimicrob Chemother* 1984;**13**(Suppl B):113-20
 63. Kosmidis J, Macrygiannis E, Aboudabash B. A prospective, randomized comparison of ciprofloxacin and cotrimoxazole in urinary tract infections: in vitro, pharmacokinetics and therapeutic evaluations [abstract no. 634]. In: *Proceedings of the Fourth Mediterranean Congress of Chemotherapy*, Rhodes, 1984
 64. Blomer R, Bruch K, Zahlten RN. Zusammengefasste Ergebnisse der klinischen Phase II- und III-Studien mit Ofloxacin (HOE280) in Europa. *Infection* 1986;**14**(Suppl 1):S102-7
 65. Latham RH, Hooten TM, Wong ES, Stamm WE. Randomized comparison of ofloxacin (ORF 18489) and trimethoprim-sulfamethoxazole in the treatment of uri-

- nary infections in ambulatory women [abstract no. 714]. In: Program and abstracts of the 25th Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington DC: American Society for Microbiology, 1985
66. Porpacz P. Comparison of ofloxacin with co-trimoxazole and nitrofurantoin in urinary tract infections [abstract no. S-45-8]. In: Proceedings of the 14th International Congress of Chemotherapy, Kyoto, 1985
 67. Ludwig G. Clinical experience with ofloxacin in upper and lower urinary tract infections—a comparison with co-trimoxazole and nitrofurantoin [abstract no. WS-9-13]. In: Proceedings of the 14th International Congress of Chemotherapy, Kyoto, 1985
 68. Kamidono S, Tomioka O, Hikosaka K, Ishigami J, Nijijima T. A comparative double-blind study of norfloxacin (AM-715) and pipemidic acid in the treatment of complicated urinary tract infection. *Chemotherapy (Tokyo)* 1982;70:1182-211
 69. Kumamoto Y, Ishigami J. Clinical experience with norfloxacin in urinary tract infections. *European Journal of Chemotherapy and Antibiotics* 1983;3:31-9
 70. Sabbaj J, Hoagland VL, Cook T. Norfloxacin versus co-trimoxazole in the treatment of recurring urinary tract infections in men. *Scand J Infect Dis [Suppl]* 1986;48:48-53
 71. Boerema JBJ, Domen WBM, Branolte JH. Comparative efficacy and safety of ciprofloxacin and co-trimoxazole in the treatment of patients with complicated urinary tract infections [abstract no. S-50-7]. In: Proceedings of the 14th International Congress of Chemotherapy, Kyoto, 1985
 72. Peters HJ. Comparison of intravenous ciprofloxacin and mezlocilin in treatment of complicated urinary tract infection. *Eur J Clin Microbiol* 1986;5:253-5
 73. Sauerwein D, Bauernfeind A. Klinische Erfahrungen bei Behandlung von Harnwegsinfekten bei Querschnittgelähmten mit Norfloxacin. *Fortschritte der Antimikrobiellen und Antineoplastischen Chemotherapie* 1984;3-5:759-64
 74. Westenfelder W, Pelz K, Frankenschmidt A. Efficacy and tolerance of norfloxacin in the treatment of patients with complicated urinary tract infections [abstract no. S-45-14]. In: Proceedings of the 14th International Congress of Chemotherapy, Kyoto, 1985
 75. Saavedra S, Ramírez-Ronda CH, Nevárez M. Ciprofloxacin in the treatment of urinary tract infections caused by *Pseudomonas aeruginosa* and multiresistant bacteria. *Eur J Clin Microbiol* 1986;5:255-7
 76. Bologna M, Vaggi L, Flammini D, Carlucci G, Forchetti CM. Norfloxacin in prostatitis: correlation between HPLC tissue concentrations and clinical results. *Drugs Exp Clin Res* 1985;11:95-100
 77. Suzuki K, Tamai H, Naide Y, Ando K, Moriguchi R. Laboratory and clinical study of ofloxacin in the treatment of bacterial prostatitis. *Hinyokika Kijo* 1984;30:1505-18
 78. Eandi M, Viano I, Di Nola F, Leone L, Genazzani E. Pharmacokinetics of norfloxacin in healthy volunteers and patients with renal and hepatic damage. *Eur J Clin Microbiol* 1983;2:253-9
 79. Bailey RR. Single-dose therapy for uncomplicated urinary tract infections. *NZ Med J* 1985;98:327-9
 80. Wolff M, Bure A, Pathé JP, Pangon B, Régnier B, Rouger-Barbier D, Vachon F. Evolution des résistances bactériennes à la pefloxacin dans le service de réanimation de l'hôpital Claude Bernard. In: Pocardalo JJ, Vachon F, Régnier B, eds. *Les nouvelles quinolones*. Paris: Editions Arnette 1985:213-26