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Use of Ciprofloxacin versus Use of Aminoglycosides for Therapy of Complicated Urinary Tract Infection: Prospective, Randomized Clinical and Pharmacokinetic Study

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The efficacy of oral ciprofloxacin was compared with that of parenteral aminoglycoside for therapy of complicated urinary tract infection in a prospective randomized trial. The setting was a chronic-care Veterans Administration facility in which long-term bladder catheterization and resistant bacteria were common. Sixty-five consecutive patients were stratified for presence and type of bladder catheter, the presence of *Providencia* and *Pseudomonas aeruginosa* organisms versus other urinary pathogens, and renal dysfunction. A pharmacokinetic study of ciprofloxacin concentrations in serum and urine was performed with selected patients. Urinary catheters were present in 94%. All patients were symptomatic, and 58.5% had fever. Ciprofloxacin, 500 mg every 12 h orally, was compared with parenteral aminoglycoside for 7 to 10 days. Clinical response, defined by resolution of symptoms and fever at 5 to 9 days posttherapy (short-term) and 28 to 30 days posttherapy (long-term), was essentially identical for both treatment groups. Bacteriologic response, defined by sterile urine cultures, showed that ciprofloxacin was significantly more efficacious ($P = 0.0005$) than aminoglycoside at 5 to 9 days posttherapy. However, by 28 to 30 days, the response rate was essentially identical. Emergence of resistance to the study antibiotic was seen in 62 and 70% of those who did not show a bacteriological response and were receiving ciprofloxacin and aminoglycosides, respectively. Concentrations of ciprofloxacin and aminoglycoside in the urine substantially exceeded the MIC for the urinary pathogens isolated, although these concentrations did not correlate with short-term bacteriologic response for either antibiotic. Ciprofloxacin was efficacious in complicated urinary tract infection compared with the current standard of parenteral aminoglycoside among catheterized patients with relatively resistant bacteria.

Urinary tract infection has become the leading infection and major cause of morbidity in convalescent-care facilities and nursing homes. Furthermore, because antibiotic therapy is given so frequently for symptomatic bacteriuria, the emergence of resistant organisms is becoming increasingly accepted as a consequence of indwelling bladder catheters in an elderly population (3, 31).

For example, at our convalescent-care facility, 50% of nosocomial infections occur in the urinary tract and 70% of the cases of bacteremia begin in the urinary tract. Furthermore, aerobic gram-negative rods resistant to first-generation cephalosporins, trimethoprim-sulfamethoxazole, and ampicillin constitute a major proportion of the etiologic agents. These organisms include *Enterobacter* species, *Pseudomonas aeruginosa*, *Providencia stuartii*, *Morganella morganii*, and *Proteus* species. Thus, oral antimicrobial agents have become notably less useful, so that parenteral agents are often required for patients with symptomatic bacteriuria and systemic signs of infection.

Aminoglycoside agents have been used increasingly in our institution because organisms are resistant not only to the standard oral agents but often to parenteral beta-lactam agents as well. This poses problems in a convalescent-care facility, including the increased costs and nursing time associated with parenteral administration, the need for drug monitoring, and discomfort to the patient. Furthermore, the aminoglycosides are considerably more toxic than the beta-lactam agents. This toxicity is magnified in the elderly patient, in whom renal dysfunction and hearing problems may occur as a natural consequence of aging.

Ciprofloxacin is a fluoroquinolone antimicrobial agent structurally related to nalidixic acid. It has a broad antibacterial spectrum that includes activity against many aerobic gram-negative rods, including those resistant to aminoglycoside and cephalosporin agents (6, 33). The pharmacokinetic characteristics allow twice-daily oral dosing, which is especially convenient in a convalescent-care facility with limited nursing personnel.

Although ciprofloxacin has been demonstrated to be effective in simple urinary tract infections, the efficacy of this agent in a convalescent-care setting for complicated urinary infection has not been addressed specifically (34). Malinverni and Glauser have commented on the potential usefulness of the fluoroquinolones for oral therapy of complicated urinary tract infection but noted that reported trials have failed to evaluate patients at long-term follow-up (22). Thus, we initiated a controlled, randomized, prospective comparative trial of the use of oral ciprofloxacin versus parenteral aminoglycosides for therapy of complicated urinary tract infection. Endpoints for measurement included both clinical and bacteriologic response, evaluated both short-term and long-term.

MATERIALS AND METHODS

The study was conducted at the Pittsburgh Veterans Administration (VA) Medical Center at Aspinwall. The facility is a 432-bed chronic-care center, with 204 beds

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designated for intermediate care and 228 for nursing-home care.

Urinary tract infection was defined as present if a patient showed typical clinical signs and symptoms (e.g., dysuria, frequency and urgency of urination, suprapubic pain) and had a pretreatment urine culture that was positive for bacteria at 10^5 CFU/ml. A urinary tract infection was defined as complicated, for the purposes of this study, if there was documented anatomic or functional abnormality of the urinary tract, including neurogenic bladder. All patients with symptomatic, complicated urinary tract infection were evaluated as candidates for enrollment into this study. For patients with external condom catheters, urine was collected for culture by removing the catheter and collecting urine directly from the bladder by sterile technique and a no. 16 French catheter. A Vacutainer (Becton Dickinson, Rutherford, N.J.) culture kit was used for transport. For patients with an indwelling Foley bladder catheter, urine for culture was aspirated directly from the specimen port of the indwelling catheter with a sterile syringe. It was then injected into a closed Vacutainer culture transport tube.

The criteria for inclusion in the study were (i) presence of symptoms attributable to urinary tract infection, including dysuria, frequency and urgency of urination, and suprapubic pain; (ii) microbiologic confirmation of infection, with pyuria (greater than 8 leukocytes per mm^3) and bacteriuria (at least 10^5 CFU/ml) detected in a "clean-catch" midstream urine specimen (for patients with an external condom or indwelling catheter, urine for culture was obtained by straight catheterization); and (iii) the presence of bacteria susceptible in vitro to the study antibiotics. All patients were required to give informed consent.

The criteria for exclusion were (i) known allergy to nalidixic acid, quinolones, or aminoglycosides; (ii) presence of any gastrointestinal condition which might interfere with absorption of an oral agent; and (iii) administration of any antibacterial therapy within 7 days prior to the current infection.

Study design. Patients were assigned to the study regimens by a random number table. Patient assignments were stratified by presence and type of catheter (Foley, suprapubic nephrostomy, or condom catheter), presence of *Providencia* species or *Pseudomonas aeruginosa* versus other bacteria, and increased creatinine level (>1.8 mg/dl) versus normal renal function. These parameters were presumed to be risk factors for treatment failure following antibiotic therapy, and it was deemed desirable to ensure that patients with these risk factors be comparably distributed between the two treatment groups.

Treatment regimens. Ciprofloxacin was given at 500 mg every 12 h for 7 to 10 days. Compliance was ensured by having the nursing staff administer the medication, and concentrations of the drug in urine were measured for selected patients.

Gentamicin was the aminoglycoside of choice and was administered at a dose of 1 to 1.7 mg/kg intramuscularly or intravenously every 8 h for 7 days; the dosage was adjusted for renal dysfunction. Tobramycin and amikacin were acceptable alternatives. Tobramycin was preferred if *P. aeruginosa* was a suspected pathogen, and amikacin was preferred if the organism(s) was suspected to be gentamicin resistant.

Endpoints for assessment of outcome. Two endpoints at two points in time were used to assess outcome. Clinical cure was defined as resolution of patient symptoms and fever, and bacteriologic cure was defined as sterile urine cultures. Both clinical and bacteriologic assessments were performed short-term (5 to 9 days posttherapy) and long-term (28 to 30 days posttherapy). Fisher's exact test, two-tailed, was used for assessment of outcome endpoints and type of therapy. Significance (alpha) was set at 0.05. A Kaplan-Meier cumulative survival curve was constructed for each treatment group. The starting point was the completion of antibiotic therapy (study drug), and the endpoint was the initiation of antibiotic treatment for recurrent infection. Patients who were re-treated all met the original criteria for urinary tract infection with respect to symptoms and the bacteriologic test. The two cumulative curves were compared by the Gehan-Breslow test. With a sample size of 72, there was a probability of 0.55 (power) of being able to detect a difference as large as 15% between the two treatment groups. It should be noted that a statistically significant difference was ultimately found (Results).

Pharmacokinetic study. Blood and urine were collected from 12 patients at steady state during a single 12-h dosing interval between days 3 and 5 of treatment. Ciprofloxacin was administered as a 500-mg oral dose with 120 ml of water following an overnight fast. Food was withheld for an additional 4 h after drug administration. Antacids, if prescribed, were not administered within 24 h of the kinetic dose. Blood samples for ciprofloxacin analysis were collected through an indwelling heparinized venous catheter immediately prior to the study dose and at 0.25, 0.5, 1, 2, 4, 6, and 12 h after administration. Indwelling urinary collection devices were voided prior to drug administration, and urine was collected from 0 to 2, 2 to 4, 4 to 6, and 6 to 12 h thereafter. Cumulative urine samples were also collected at 24- and 48-h intervals following treatment. All samples were frozen at −70°C pending assay. Ciprofloxacin concentrations were determined by high-performance liquid chromatography with a reversed-phase procedure and fluorescence detection, which allows differentiation between ciprofloxacin and its three metabolites (19). The sensitivity of the assay was 0.008 μg/ml. The within-day precision of the fluorometric detection assay was less than 5%, and the between-day precision was 8.3%, expressed as the coefficient of variation.

Noncompartmental methods based on statistical-moment theory were used for pharmacokinetic analysis (13, 25). The best fit of area under the serum concentration-time curve ($AUC_{0-\infty}$) was assessed by logarithmic and linear-trapezoidal methods. $AUC_{0-\infty}$ and total systemic clearance (Cl/F) were calculated by standard methods. Renal drug clearance was calculated by dividing the total amount of unchanged ciprofloxacin excreted in the urine by $AUC_{0-\infty}$. Extrarenal clearance was defined as total systemic clearance minus renal drug clearance. The average steady-state concentration in serum was estimated by dividing $AUC_{0-\infty}$ by the dosing interval.

RESULTS

Seventy-two patients with complicated urinary tract infection were evaluated. Five were excluded because the organisms isolated were resistant to aminoglycoside agents (three patients) or therapy was delayed for 48 h after the urine culture was obtained because of logistic problems (two patients). Two patients were dropped prior to completion of therapy: one was transferred to a nursing home, and another terminally ill patient had all therapy, including antibiotics, discontinued. Both had been randomized to the aminoglycoside group. Thus, the final study group numbered 65 pa-

TABLE 1. Demographics of the two treatment groups were comparable[a]

Characteristic	Ciprofloxacin (n = 37)	Aminoglycoside (n = 28)	P
Mean age (range), yr	71 (20–95)	73 (59–92)	NS[c]
Urinary tract abnormality	100 (37)	100 (28)	NS
Obstruction	11	9	
Stone	2	2	
Neurogenic bladder	21	16	
Chronic pyelonephritis	3	1	
Renal disease	8 (3)	7 (2)	NS
Liver disease (active)	5 (2)	0 (0)	NS
Malignancy	8 (3)	14 (4)	NS
Diabetes mellitus	24 (9)	21 (6)	NS
Immunosuppressed[b]	3 (1)	4 (1)	NS
Paraplegic	30 (11)	18 (5)	NS
Cerebrovascular accident	27 (10)	25 (7)	NS
COPD	11 (4)	36 (10)	0.03
Polymicrobial etiology	56.4 (21)	46.4 (13)	NS
Catheterized	92 (34)	96 (27)	NS
Foley	15	9	
Suprapubic	6	3	
Condom	13	15	
Intermittent	2	0	
Ileal loop	1	0	

[a] Values are percentage (number) of patients in group unless otherwise specified.
[b] Immunosuppressed, prednisone (20 mg daily) given for chronic obstructive pulmonary disease (COPD).
[c] NS, not significant.

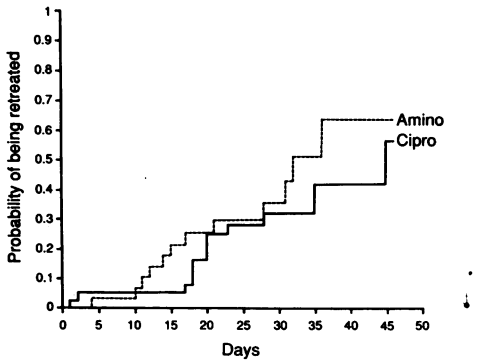

FIG. 1. Kaplan-Meier curves depicting the number of days post-therapy before a patient required retreatment for recurrence of urinary tract infection. Patients who were re-treated met the original criteria for urinary tract infection with respect to symptoms and presence of bacteria (see text). There was no significant difference between the two treatment groups (Gehan-Breslow rank test, P = 0.44). Amino, aminoglycoside; Cipro, ciprofloxacin.

tients. There were 63 males and 2 females, reflecting the male preponderance in the VA hospital system.

All patients had documented abnormalities of the urinary tract (Table 1). Ninety-four percent (61 of 65) had had urinary catheters in place for at least 4 months (Table 1). All patients were symptomatic, with dysuria or suprapubic pain (60%, 39 of 65), fever (59%, 38 of 65), urinary frequency (35%, 11 of 31, excluding patients with bladder catheters), chills (14%, 9 of 65), and costovertebral angle tenderness (6%, 4 of 65).

Thirty-seven patients were administered ciprofloxacin, and 28 were given an aminoglycoside (12 gentamicin, 14 tobramycin, and 2 amikacin). The patient groups were comparable with respect to underlying disease and type of urinary tract abnormality, although chronic obstructive pulmonary disease occurred more frequently in the patients randomized to the aminoglycoside group (Table 1).

Factors that were projected to have an adverse effect on outcome were presence of a bladder catheter, type of catheter (Foley, suprapubic, or external condom), *Providencia* species and *P. aeruginosa* as pathogens, and renal dysfunction (creatinine level >1.8 mg/dl). The stratification process performed well except that *Providencia* species were implicated more frequently in the group randomized to ciprofloxacin; this difference was not statistically significant. This occurred on occasion because the pathogen had not been definitively identified by the microbiology laboratory at the time of entry into the study.

Clinical response. Short-term cure, defined as resolution of symptoms by 5 to 9 days posttherapy, was similar to both treatment groups (Table 2). By 28 to 30 days posttherapy, the rate of long-term cure fell for both groups (Table 2). Survival curves also failed to show a significant difference between the antibiotic regimens in the prevention of recurrent urinary tract infection (Fig. 1). The short-term advantage of ciprofloxacin over aminoglycosides was maximal at 2 weeks posttreatment but disappeared by 3 weeks.

Side effects were seen in two patients: nausea in a patient receiving ciprofloxacin, and an erythematous papular rash in a patient receiving an aminoglycoside. In neither of the cases was the antibiotic discontinued, and the side effects resolved following discontinuation of therapy. No significant alterations in hematologic, renal, or hepatic laboratory values were attributed to the study antibiotic during the treatment period.

Bacteriologic response. (i) Short-term. Cultures taken during therapy (2 to 5 days after the first dose) were virtually all sterile for both treatment groups. There were significantly fewer short-term bacteriologic failures (defined as a sterile urine culture 5 to 9 days following completion of therapy) following therapy for patients receiving ciprofloxacin (37%) than for those receiving an aminoglycoside (85%) (P =

TABLE 2. Response to treatment with ciprofloxacin and aminoglycosides in complicated urinary tract infection[a]

Treatment (no. in group)	Clinical response (% of patients)						Bacteriologic response (% of patients)					
	Short-term		P	Long-term		P	Short-term		P	Long-term		P
	Cure	Failure		Cure	Failure		Eradication	Failure		Eradication	Failure	
Ciprofloxacin (37)	81	19	NS[b]	69	31	NS	63	37	0.0005	21	79	NS
Aminoglycoside (28)	82	18		58	42		15	85		23	77	

[a] See text for definitions of clinical response, bacteriologic response, short-term, long-term, failure, and eradication. Values are percentages of patients in each group. P values compare results for ciprofloxacin with those for aminoglycosides.
[b] NS, not significant.

TABLE 3. Bacteriologic response subclassified by etiology

Organism	Treatment group[a]	No. of patients	Etiology (no. of patients)		% of patients				
					Short-term follow-up		Long-term follow-up		
			Single agent	Multiagent	Eradication	Persistence	Eradication	Persistence	Recurrence
Providencia stuartii	C	18	5	13	100	0	79	0	21
	A	7	3	4	29	71	40	60	0
Pseudomonas aeruginosa	C	8	3	4	75	25	43	14	43
	A	8	6	2	75	25	71	14	14
Proteus mirabilis	C	8	3	5	100	0	100	0	0
	A	7	1	6	100	0	100	0	0
Enterococcus faecalis	C	6	0	6	33	67	50	25	25
	A	6	0	6	16	83	17	83	0
Escherichia coli	C	5	2	3	100	0	100	0	0
	A	3	1	2	67	33	67	33	0
Morganella morganii	C	3	0	3	67	33	67	33	0
	A	3	0	3	67	33	100	0	0
Providencia rettgeri	C	2	1	1	100	0	100	0	0
	A	2	1	1	0	100	0	100	0
Enterobacter sp.	C	3	1	2	100	0	67	33	0
	A	0	0	0					

[a] C, ciprofloxacin; A, aminoglycoside.

0.0005, Fisher's exact test) (Table 2). Patients who experienced short-term clinical cures, as defined above, were somewhat more likely to also experience short-term bacteriologic eradication ($P = 0.13$).

The most frequently isolated causative organisms are listed in Table 3, subclassified by bacteriologic response. Other organisms included *Serratia marcescens* (two patients), *Staphylococcus aureus* (one patient), *Streptococcus* group B (one patient), and *Staphylococcus epidermidis* (one patient). More than one organism was isolated from 56.8% (21 of 37) of the ciprofloxacin group and 46.4% (13 of 28) of the aminoglycoside group.

Among the 13 patients who had short-term bacteriologic failures in the ciprofloxacin group, 6 developed superinfection with an organism sensitive in vitro to ciprofloxacin, 5 developed superinfection with an organism resistant in vitro to ciprofloxacin, 3 had persistent infection with the original organism with resistance emerging following therapy, and 4 had persistent infection with a sensitive organism. (The numbers total greater than 13 because polymicrobial failures fell into more than one category.) Of the failures in the ciprofloxacin group, 69.2% (9 of 13) were polymicrobial. *Enterococcus faecalis* and *P. aeruginosa* were implicated in 76.9% (10 of 13) and 46.2% (6 of 13) of the failures, respectively. Organisms that were resistant in vitro following therapy included *P. aeruginosa* (one case), *Pseudomonas maltophila* (one case), *Staphylococcus aureus* (one case), *E. faecalis* (two cases), and *Alcaligenes odorans* (two cases).

There were 23 short-term bacteriologic failures in the aminoglycoside group; 10 were superinfection with a resistant organism, 3 were superinfection with a sensitive organism, 8 were persistent infection with the original organism resistant in vitro to aminoglycosides, and 6 were persistent infection with a sensitive organism. (The numbers total greater than 23 because polymicrobial failures fell into more than one category.) Of the failures in the aminoglycoside group, 39% (9 of 23) were polymicrobial. *E. faecalis* (43%, 10 of 23), *Providencia stuartii* (39%, 9 of 23), and *Morganella morganii* (17%, 4 of 23) were the most frequently implicated organisms in bacteriologic failure with an aminoglycoside.

(ii) Long-term. The bacteriologic response long-term (defined as a sterile urine culture 28 to 30 days following completion of antibiotic therapy) was similar between the groups (Table 2 and Fig. 1). The organisms isolated in the short-term failures were usually present 28 to 30 days later. Infections with polymicrobial etiology had a higher frequency of bacteriologic failure (short-term and long-term) than infections with single-organism etiology, but statistical significance was not attained (data not shown). *Providencia* species responded better to ciprofloxacin than to an aminoglycoside (Table 3). Neither antibiotic did well against *E. faecalis*.

In vitro susceptibility results. The MIC ranges of ciprofloxacin for organisms isolated posttherapy were 0.016 to 0.125 μg/ml for *P. stuartii*, 0.25 to 8.0 μg/ml for *P. aeruginosa*, 0.125 μg/ml for *M. morganii*, 32 μg/ml for *P. maltophila*, 0.125 μg/ml for *Escherichia coli*, 64 μg/ml for *Alcaligenes odorans*, 0.125 μg/ml for *Enterobacter cloacae*, and 0.25 to 64 μg/ml for *E. faecalis*. The organisms isolated after aminoglycoside therapy (MIC range) were *P. stuartii* (0.25 to 64 μg/ml for gentamicin and tobramycin and 0.25 to 4 μg/ml for amikacin), *E. faecalis* (64 to >512 μg/ml for all aminoglycosides), *M. morganii* (16 to 128 μg/ml for gentamicin, 8 to 16 μg/ml for tobramycin, and 2 to 8 μg/ml for amikacin), *Proteus rettgeri* (0.5 to 16 μg/ml for all aminoglycosides), *S. aureus* (32 to 256 μg/ml for gentamicin, 8 to 128 μg/ml for tobramycin, and 1 to 8 μg/ml for amikacin), *E. coli* (0.25 to 0.50 μg/ml for gentamicin and tobramycin and 1 to 4 μg/ml for amikacin), *Acinetobacter* spp. (128 to 512 μg/ml for gentamicin and tobramycin and 8 μg/ml for amikacin), *Serratia marcescens* (8 to 12 μg/ml for gentamicin and tobramycin and 2 μg/ml for amikacin), *Klebsiella pneumoniae* (8 to 16 μg/ml for gentamicin and tobramycin and 1 μg/ml for amikacin), and *P. aeruginosa* (2 to 8 μg/ml for all aminoglycosides).

Pharmacokinetic analyses. Ciprofloxacin concentrations in serum and cumulative concentrations in urine within a 12-h dosing interval were determined for 12 randomly selected patients. The mean peak concentration in serum was 1.4 (range, 0.9 to 1.8) μg/ml, determined at 2 h following a 500-mg oral dose. Concentrations in serum declined to 0.3

TABLE 4. Ciprofloxacin pharmacokinetic parameters in response to therapy in 12 patients[a]

Response	$AUC_{0-\infty}$ (μg · h/ml)	Total systemic clearance (ml/min)	Renal clearance (ml/min)	Extrarenal clearance (ml/min)
Failure (n = 6)	10.8 ± 4.6	773.0 ± 120.2	245.8 ± 63.5	527.2 ± 100.3
Cure (n = 6)	8.9 ± 2.7	913.7 ± 281.8	215.4 ± 117.8	698.3 ± 180.0

[a] Values are means ± standard deviations.

(0.1 to 0.5) μg/ml at 12 h, consistent with a half-life of 4.1 (2.2 to 5.9) h.

AUC values from the assessed best fit were 10.3 ± 2.3 μg · h/ml for all patients. Mean concentrations in serum at steady state were 0.9 ± 0.2 μg/ml, determined from $AUC_{0-\infty}$ and the dosing interval. Total systemic clearance (Cl/F) was 843.4 ± 217.3 ml/min. A mean of 25% of the drug was excreted in the urine over a 12-h dosing interval, and concentrations in urine ranged from 100 to 300 μg/ml during treatment. The calculated value for renal clearance of 226.8 ± 96.6 ml/min was 26.9% of the total systemic clearance value, in close agreement with the cumulative excretion data within a single dosing interval. There were no significant differences between mean values for $AUC_{0-\infty}$, total systemic clearance, or renal and extrarenal clearance for patients who failed or responded to therapy (Table 4).

Urine specimens for determination of ciprofloxacin concentration were obtained separately at 24-h intervals following discontinuation of therapy from 27 additional patients; 14 patients had sterile urine cultures, and 13 patients had positive urine cultures short-term. The mean ciprofloxacin concentration in urine at 48 h posttherapy for all patients was 14 (range, 8 to 54) μg/ml. There was no correlation between ciprofloxacin concentration in urine and short-term bacteriologic response (data not shown).

Aminoglycoside concentration in urine was measured for 20 patients at 24-h intervals following discontinuation of therapy. The mean concentrations in urine at 48 h posttherapy were 38.4 and 30.8 μg/ml for gentamicin and tobramycin, respectively. Again, there were no apparent correlations between aminoglycoside concentrations in urine and short-term bacteriologic response (data not shown).

DISCUSSION

Controlled comparative studies of the use of quinolones for complicated urinary tract infection are few (22, 34), and most studies performed have used oral antibiotics as the standard for comparison (1, 21, 27). However, if organisms are generally susceptible to commercially available oral agents, we believe that these agents should be preferred over ciprofloxacin and other quinolone agents because of lower costs and established safety profiles. However, with the emergence of bacteria resistant to oral agents in symptomatic patients with complicated urinary tract infections, potent beta-lactam and aminoglycoside agents have emerged as mainstays of therapy. Results from noncomparative, open studies have suggested that ciprofloxacin may be useful in this area (5, 11, 16, 20, 24, 26, 30).

We therefore conducted a prospective, comparative trial pitting ciprofloxacin against parenteral aminoglycosides, a most potent class of antibacterial agents against aerobic gram-negative rods. All patients had anatomic or functional abnormalities of the urinary tract, including neurogenic bladder (Table 1). It should be emphasized that for all patients with external condom catheters, urine was obtained by straight catheterization to avoid contamination within the urine bag. In order to minimize the possibility of confounding factors biasing the treatment outcome, we stratified the patients prior to randomization by four risk factors: presence of a urinary catheter, type of catheter (indwelling versus external condom), presence of *P. aeruginosa* or *Providencia* species, and renal function.

The most frequently isolated organisms were *Providencia* species and *P. aeruginosa*, as is common for patients with complicated urinary tract infection and bladder catheters. It should be noted that these organisms are resistant to oral agents such as ampicillin, cephalexin, and trimethoprim-sulfamethoxazole.

Assessment of treatment outcome in antibiotic trials of urinary tract infections has long been problematic. Inconsistent definitions of clinical cure, differing criteria for bacteriologic cure (sterile or less than 10^5 CFU/ml), and the subjective all-encompassing criterion of investigator assessment have prevented a rigorous comparison of published studies. We used two criteria at two points in time: clinical and bacteriologic response and short-term and long-term response.

The clinical response, judged by patient symptoms and fever, was nearly identical short-term for both treatment groups (81 and 82%) (Table 2). Although ciprofloxacin gave a slightly better clinical response long-term (69%) than the aminoglycoside agents (58%), this difference was not statistically significant. For bacteriologic eradication (defined as sterile urine cultures), ciprofloxacin (63%) was significantly better than the aminoglycosides (15%) short-term. The primary reason for the improved short-term efficacy of ciprofloxacin was the higher number of failures seen for *P. stuartii* in the aminoglycoside-treated group despite the in vitro sensitivity of these organisms pretherapy to the aminoglycosides (Table 3). However, it is noteworthy that by 30 days posttherapy, the efficacy rate was almost identical (Table 2 and Fig. 1). Persistent infection or superinfection with an enterococcus was common in both groups.

The bacteriologic response to ciprofloxacin in our study, both short-term and long-term, is notably poorer than that in other published studies. There are a number of possible reasons. (i) We used sterile cultures as endpoints rather than $<10^5$ CFU of bacteria per ml. (ii) Many investigators did not perform long-term evaluation (11, 21), while we performed clinical and bacteriologic evaluation both short-term and long-term. (iii) Some studies experienced a predominance of *E. coli*, which tends to be antibiotic susceptible (21), while most of our organisms were notably resistant to most antibiotics. (iv) Our patients were more severely ill (58.5% had fever) and more prone to develop resistant organisms (75.4% had a history of urinary tract infection requiring therapy in the past 12 months).

Concentrations of ciprofloxacin in the urine at a dosage of 500 mg every 12 h ranged from 100 to 300 μg/ml, well above the MICs for the pathogens isolated. In addition, high

concentrations of ciprofloxacin in urine persisted in all patients for at least several days following multiple-dose therapy. However, neither short-term bacteriologic response nor frequency of superinfection correlated with the concentration of ciprofloxacin in urine measured during treatment or within 48 h of completion of treatment.

Although concentrations in urine were very high during treatment, peak concentrations of ciprofloxacin in serum (0.9 to 1.8 μg/ml) following a 500-mg dose were notably lower than those reported for normal volunteers in previous studies (8, 15), likely reflecting impaired absorption. Renal clearance of ciprofloxacin as a fraction of total clearance was also lower than that observed in normal volunteers (15) but consistent with previous studies of ciprofloxacin clearance in patients with renal disease (12). Total systemic clearance (Cl/F) of ciprofloxacin was very high compared with that in normal volunteers (12, 15). This likely reflects the reduced bioavailability of oral ciprofloxacin in chronically ill patients. Thus, in bacteremic patients with complicated urinary tract infection caused by more-resistant organisms, a 500-mg dose every 12 h may be suboptimal. This is pertinent in that one patient with *Proteus mirabilis* urinary tract infection was also found to be bacteremic with the same organism, although he responded to oral ciprofloxacin. Gasser et al. and Boelaert et al. have suggested that oral doses of less than 500 mg of ciprofloxacin may be appropriate for the treatment of urinary tract infection in patients with renal dysfunction (4, 12), but given our results, lowering the dose may not be advisable in certain patient populations.

What are the weaknesses of this study? A double-blind allocation would have been ideal but was not deemed feasible given the oral route of administration for ciprofloxacin versus the parenteral route for the aminoglycoside. Although an oral placebo agent could have been administered to the aminoglycoside group, we felt it was unethical to administer an intramuscular placebo agent to the ciprofloxacin group. However, objective criteria were used in the assessment of endpoints, so bias should not have been a problem.

P. stuartii was a more frequent pathogen in the ciprofloxacin group than in the aminoglycoside group despite the stratification process (Table 3) (since therapy was often initiated empirically prior to definitive bacteriologic identification), although the difference was not statistically significant. This difference should have biased therapy in favor of the aminoglycoside group, since aminoglycosides performed poorly against *Providencia* species. We did not attempt to differentiate relapse from reinfection in treatment failures; infections in which the same bacterial species was isolated pre- and posttherapy were labeled persistent. It should be noted that differentiation of relapse (treatment failure with original infecting strain) from reinfection (treatment failure with new organism) by serotyping or biotyping may not be altogether reliable (9).

We did not attempt to localize infection to the upper or lower tract. Upper tract disease is more recalcitrant to therapy. This is pertinent in that the fever, chills, and costovertebral angle tenderness considered typical (but not diagnostic) of upper tract disease occurred in some patients. Unfortunately, there are no universally accepted noninvasive methods for localization (14), and they are not generally available in the convalescent-care setting. In any case, this possibility existed for both antibiotic regimens.

Stark and Maki have shown that the definition of bacteriuria as 10^5 CFU of organisms per ml may be too high for catheterized patients (29). Two of our patients with polymicrobial etiology had less than 10^5 CFU of organisms per ml in pretherapy cultures (susceptibilities unknown), which progressed to 10^5 CFU/ml during therapy, one patient with *Alcaligenes* infection receiving ciprofloxacin and another patient with *P. stuartii* infection receiving an aminoglycoside.

It may also be argued that the 7- to 10-day protocol that we used is an insufficient duration for complicated urinary tract infection. However, it is also well known that relapse is common even if therapy is prolonged (7, 10). Consequently, short-term therapy has been deemed reasonable for chronically catheterized patients (14). In any case, this weakness existed for both antibiotic regimens.

Finally, although lower-than-expected concentrations of ciprofloxacin were found in serum, studies of bioavailability were not performed. Given the implications of oral therapy in ill patients who have unsuspected bacteremia, we recommend that our pharmacokinetic results be confirmed in a population of ill and elderly patients rather than normal volunteers.

Implications. Emergence of resistance to ciprofloxacin was seen in 62% of the bacteriologic failures among the patients receiving ciprofloxacin versus 70% of those among the patients receiving an aminoglycoside. The most common organisms to emerge as resistant were *E. faecalis*, *P. stuartii*, and *M. morganii* for the aminoglycosides and *E. faecalis* and *P. aeruginosa* for ciprofloxacin. Despite its initial in vitro susceptibility, both ciprofloxacin and the aminoglycosides proved to be particularly unreliable against *E. faecalis* in this patient population. We also showed that recurrence was frequent in this patient population; 30 to 40% had recurrence of symptoms and bacteriuria 30 days following therapy (Fig. 1).

Despite the problems of recurrence and superinfection (which occurred equally frequently in the aminoglycoside group), we noted some distinct advantages for ciprofloxacin. Oral therapy was clearly better tolerated by the patients. The pain from parenteral injections should not be overlooked in this study, which concentrated on objective parameters. The costs of the ciprofloxacin regimen were also lower if nursing time and injection paraphernalia are taken into account (28). Finally, dosage modification for mild renal failure may not be necessary for ciprofloxacin (2). Given the increasing geriatric population and the concomitant increase in the number of nursing-home patients with indwelling urinary catheters, ciprofloxacin may be particularly useful.

It has been suggested that the emergence of ciprofloxacin-resistant organisms might be minimal given the lack of plasmid-mediated resistance and the lack of resistant bacteria in fecal flora (23). Furthermore, resistance to quinolone agents did not increase dramatically despite increased usage in two large-scale bacteriologic surveys conducted in Europe (17, 32). However, given the ready emergence of organisms resistant to ciprofloxacin in this study (62% of treatment failures), we predict that emergence of resistance will prove to be a major drawback with increased use, as has been seen for other antibacterial agents.

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