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Treatment of Acute Uncomplicated Urinary Tract Infections with 3 Days of Lomefloxacin Compared with Treatment with 3 Days of Norfloxacin

L. E. NICOLLE,[1] J. DuBOIS,[2]* A. Y. MARTEL,[3] G. K. M. HARDING,[4] S. D. SHAFRAN,[5] AND J. M. CONLY[6]

University of Manitoba and Health Sciences Centre[1] and St. Boniface General Hospital,[4] Winnipeg, Manitoba, Centre Hospitalier Hotel-Dieu, Sherbrooke,[2] and Laval University, Quebec City,[3] Quebec, University of Alberta, Edmonton, Alberta,[5] and University of Saskatchewan, Saskatoon, Saskatchewan,[6] Canada

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The bacteriologic and clinical efficacies of 3 days of lomefloxacin therapy were compared with those of 3 days of norfloxacin therapy for the treatment of acute uncomplicated urinary tract infections in a prospective, randomized, double-blind study. One hundred sixty-four subjects were enrolled at five Canadian centers; 84 received lomefloxacin, and 80 received norfloxacin. *Escherichia coli* (84%) and *Staphylococcus saprophyticus* (11%) were the most common organisms isolated. Forty subjects (24%) had low quantitative counts in their pretherapy urine specimens. In the intent-to-treat analysis, 76 lomefloxacin subjects (91%) and 76 norfloxacin subjects (95%) were cured or improved at follow-up 5 to 9 days posttreatment and 73 (87%) and 71 (89%) subjects from the lomefloxacin and norfloxacin groups, respectively, were cured or improved at 4 to 6 weeks posttreatment. Bacteriologic eradication occurred in 61 of 63 lomefloxacin subjects (97%) with $\geq 10^8$ CFU/liter in their pretherapy specimens and 56 of 59 norfloxacin subjects (95%) at 5 to 9 days and 55 (87%) and 53 (90%) subjects from the lomefloxacin and norfloxacin groups, respectively, at 4 to 6 weeks. There were no statistically significant differences in outcome. Adverse effects which were potentially related to the study medications were reported by 26% of the subjects who received lomefloxacin and 25% of the subjects who received norfloxacin. There were no severe adverse events, and only one subject discontinued therapy. These data suggest that 3 days of therapy with either lomefloxacin or norfloxacin is effective in the treatment of acute uncomplicated urinary tract infections.

Acute uncomplicated urinary tract infections are among the most common bacterial infections, occurring primarily in young women with healthy genitourinary tracts (11). This syndrome is associated with limited long-term morbidity but may have substantial short-term morbidity because of disruption in a woman's activities by symptomatic episodes. Women with acute uncomplicated urinary tract infections generally respond well to short courses of antimicrobial therapy (14, 19). While short courses of therapy may be minimally less effective than longer courses of therapy of 7 to 14 days, the increased adverse effects associated with longer courses of therapy make short courses of therapy the treatment of choice. For trimethoprim-sulfamethoxazole, single-dose therapy is likely optimal (4, 12, 15). For other antimicrobial agents effective as short courses of therapy, 3 days of therapy has been suggested to be appropriate (6, 8, 9, 16). For the fluoroquinolone antimicrobial agents, in particular, 3 days of therapy seems necessary because of the high failure rates of single-dose therapy of infection with *Staphylococcus saprophyticus*, the second most frequent infecting organism in this syndrome (5, 8, 17). In Canada, norfloxacin has been marketed with an indication for 3 days of therapy for uncomplicated urinary tract infections, making it the only antimicrobial agent marketed with an indication for a short course of therapy for this syndrome.

Lomefloxacin is a fluoroquinolone antimicrobial agent characterized by excellent bioavailability, virtually complete urinary excretion, and a prolonged half-life, permitting once-daily dosing (18). It shares the wide gram-negative spectrum of other quinolones, and thus it should be an excellent antimicrobial agent for the treatment of urinary tract infections (21). Reports of therapeutic studies of both complicated and uncomplicated urinary tract infections with traditional courses of antimicrobial therapy suggest that it is as effective as other regimens in the treatment of urinary tract infections (1, 3, 10). This study was undertaken in order to determine whether 3 days of lomefloxacin therapy was equivalent to 3 days of norfloxacin therapy for the treatment of acute uncomplicated urinary tract infections.

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MATERIALS AND METHODS

Patient population. Patients were enrolled in five Canadian centers. Recruitment took place through family physician offices, infectious diseases outpatient clinics, and university-affiliated student health centers at different centers. Eligible subjects were female, were 18 to 65 years in age, and had at least two symptoms, including dysuria, frequency, urgency, suprapubic pain, gross hematuria, turbid urine, or malodorous urine of a recent onset. Subjects were excluded from enrollment if they had flank pain or fever, if they were already receiving antimicrobial or antiseptic therapy for a urinary tract infection, if they required concurrent probene-

* Corresponding author.

cid, if concurrent infections which might have confused interpretation of the study results were present, or if mineral antacid therapy had been given within 48 h of the initial dosing or was required during the study.

Therapeutic regimens. The study was blinded and randomized in blocks of 10 by using a computer-generated randomization schedule. Patients were randomized to receive either 3 days of lomefloxacin (400 mg) once daily or three days of norfloxacin (400 mg) twice a day. Subjects randomized to the lomefloxacin group received two 200-mg lomefloxacin capsules in the morning and two placebo capsules in the evening for 3 days. Subjects in the norfloxacin treatment group received one capsule containing 400 mg of norfloxacin and one placebo capsule in the morning and one capsule containing 400 mg of norfloxacin and one placebo capsule in the evening for 3 days.

Microbiologic methods. Specimens for urine culture were obtained by clean-catch midstream collection or straight catheterization. Each study center processed specimens at a single laboratory. Isolation and identification of organisms were by standard methods. Susceptibility testing was performed by the disk diffusion method or the broth dilution method following National Committee for Clinical Laboratory Standards standards. The breakpoint for susceptibility to lomefloxacin was a 15-mm zone diameter or 16 μg/ml, and that for norfloxacin was a 12-mm zone diameter or 16 μg/ml.

Patient monitoring. Within 48 h of a patient's being enrolled in the study, her history, a physical examination, an evaluation of signs and symptoms, a urine specimen for culture and sensitivity, and a blood specimen for biochemical studies were obtained. Patients were subsequently reviewed for clinical and microbiologic assessments at days 2 to 4 following the start of therapy and at 5 to 9 days and 4 to 6 weeks posttreatment. Adverse-event data were obtained by clinical and laboratory monitoring, by voluntary statements made by the study subjects, and by direct questioning.

Data analysis. Three sets of data analyses were performed. The first analysis was an intent-to-treat analysis of all patients randomized for the study. The second analysis was a modified intent-to-treat analysis performed for each randomized patient with a confirmed pretherapy urinary pathogen isolated in quantitative counts of $\geq 10^8$ CFU/liter ($\geq 10^5$ CFU/ml). Finally, an analysis of all evaluable patients was performed. These included all subjects with bacteriologically confirmed urinary tract infections ($\geq 10^8$ CFU/liter) who had complied fully with all enrollment inclusion and exclusion criteria and had completed all follow-up visits.

Outcomes were assessed on both a clinical and a bacteriologic basis at the visit on days 2 to 4 and at the early and late posttreatment visits. Bacteriologic outcomes were defined as follows: cure was defined as eradication of the initial pathogen ($\leq 10^7$ CFU/liter), with no isolation of a new pathogen; reinfection was defined as isolation of a different pathogen ($\geq 10^8$ CFU/liter) posttreatment; and superinfection was defined as isolation of a new pathogen during treatment. Eradication was defined as a cure, reinfection, or superinfection. Relapse was defined as a recurrence of the initial pathogen at either posttreatment visit ($\geq 10^7$ CFU/liter), and failure was defined as isolation of the pretherapy pathogen during therapy. Persistence was defined as either relapse or failure. Subjects were considered unevaluable when they had no bacteriologic information available at baseline and unknown when there was no bacteriologic information available at a follow-up visit.

Clinical outcomes were identified at the early and late posttreatment visits as cure, improvement, failure, unevaluable, and unknown. Cure was the absence of all baseline urinary tract infection signs and symptoms, and improvement was a decrease in severity from the baseline of at least one sign or symptom with no deterioration in any other. Success was either cure or improvement. Failure was a worsening of at least one sign or symptom or no change in any signs or symptoms. A failure at 5 to 9 days posttreatment was considered a failure at 4 to 6 weeks. Subjects were considered unevaluable when there was no pretherapy evaluation of urinary tract infection signs and symptoms and unknown when no clinical evaluation of signs and symptoms was available posttreatment.

The nominal level of significance was at the 0.05 level, with all P values two-sided. Continuous variables were analyzed by nonparametric techniques, with contingency table methods used in the analysis of discrete data. Treatment by center interaction was evaluated, and the data were pooled when no significant differences occurred. Efficacy was determined by treatment group comparisons of bacteriologic eradication and clinical success rates by using confidence intervals, frequency tabulations, and contingency table methods. If the 95% confidence interval associated with a difference included 0, there was no statistical evidence of a difference between the treatments.

RESULTS

Patient characteristics. One hundred sixty-four subjects were enrolled at the five centers; 84 were randomized to receive lomefloxacin, and 80 were randomized to receive norfloxacin. Patient characteristics for all randomized subjects for the two treatment groups are shown in Table 1. Analysis of the baseline demographic data showed the two groups to be equivalent except for median weight. The treatment groups were also similar with respect to all baseline clinical signs and symptoms, apart from turbid urine, which was reported by 74% of the lomefloxacin group and 58% of the norfloxacin group ($P = 0.028$). Observations were similar for subjects retained for the modified intent-to-treat and evaluable analyses.

Twenty-one subjects (25%) randomized to the lomefloxacin group and 21 subjects (26%) randomized to the norfloxacin group did not have $\geq 10^8$ CFU of organisms per liter isolated in pretherapy cultures. There was no statistically significant difference in the distribution of infecting organisms between treatment groups for subjects with pretherapy specimens isolated in quantitative counts of $\geq 10^8$ CFU/liter (Table 1). *Escherichia coli* was the predominant organism, making up 84% of the organisms isolated in the lomefloxacin group and 83% of those isolated in the norfloxacin group. The second most frequently isolated pathogen was *S. saprophyticus*, which was consistent with the expected distribution of organisms for acute uncomplicated urinary tract infections. One organism, an *Enterococcus* species, was susceptible to norfloxacin and resistant to lomefloxacin. All other isolates were susceptible to both study medications.

The numbers of study subjects retained for the different analyses and the reasons for nonevaluation are summarized in Table 2. After their enrollment, 11% of each treatment group (9 of 84 lomefloxacin patients and 9 of 80 norfloxacin patients) were withdrawn by the study investigator prior to completion of the study. The primary reason for withdrawal was treatment failure, which applied to six of nine patients in the lomefloxacin group and seven of nine patients in the norfloxacin group. All withdrawals were maintained in the intent-to-treat and modified intent-to-treat analyses.

TABLE 1. Characteristics of study subjects enrolled in a comparative trial of 3 days of lomefloxacin or 3 days of norfloxacin for treatment of acute uncomplicated urinary tract infections

Characteristic	Value for antimicrobial group[a]	
	Lomefloxacin	Norfloxacin
Total subjects	84	80
Age (yr)	30 (17–78)	30 (17–71)
Ht (cm)	160 (145–177.8)	160 (147.5–178)
Wt (kg)	57 (43.1–109)	59 (45.4–160)[b]
Symptoms		
Dysuria	74 (88)	63 (79)
Frequency	83 (99)	72 (90)
Urgency	73 (87)	68 (85)
Suprapubic pain	55 (65)	60 (75)
Turbid urine	62 (74)	46 (58)
Malodorous urine	30 (36)	19 (24)
Hematuria	44 (52)	38 (48)
Infecting organisms		
Total no.	63	59
E. coli	53 (84)	49 (83)
S. saprophyticus	8 (13)	5 (8.5)
Other members of the *Enterobacteriaceae*[c]	2 (3.2)	4 (6.8)
Pseudomonas aeruginosa	0	1
Staphylococcal species	2	1
Other (gram positive)	1	1

[a] Values for ages, heights, and weights are medians; data in parentheses are ranges. For symptoms, values are numbers of subjects; data in parentheses are percents. Values for infecting organisms are numbers of isolates; data in parentheses are percents.
[b] $P = 0.028$.
[c] Include two *Klebsiella pneumoniae* isolates and one isolate each of *Proteus mirabilis*, *Citrobacter diversus*, *Enterobacter cloacae*, and an *Enterobacter* sp.

TABLE 2. Study subjects retained for different analytical groups and reasons for nonevaluability

Group or characteristic	No. of subjects in antimicrobial group	
	Lomefloxacin	Norfloxacin
Intent to treat	84	80
Modified intent to treat	63	59
Evaluable	55	49
Reasons for exclusion[a]		
Insufficient colony count[b]	20	20
No baseline pathogen[b]	1	1
Baseline evaluation >48 h	2	0
No posttreatment evaluation	1	1
Resistant pathogen	0	1
Insufficient duration of therapy	8	9
Posttreatment evaluation outside 5 to 9 days	1	2
Concomitant antimicrobial therapy	4	3
Concomitant antacid therapy	1	0
Age outside 18 to 65 yr	3	2

[a] Not mutually exclusive.
[b] Excluded from modified intent-to-treat analysis.

Bacteriologic efficacies. Both antimicrobial regimens were highly effective, with more than 95% eradication at 5 to 9 days posttherapy and more than 85% eradication at 4 to 6 weeks posttherapy (Table 3). There were no statistically significant differences between lomefloxacin and norfloxacin for either patient group analyzed at either early or late follow-up. At 5 to 9 days, one *E. coli* infection relapsed in a subject who received lomefloxacin and two *E. coli* infections relapsed in subjects who received norfloxacin. The single subject who failed was infected with an *Enterococcus* species and received norfloxacin. All five relapses at 4 to 6 weeks with lomefloxacin were *E. coli*; for norfloxacin, the four relapses were with *E. coli* and the failure was the *Enterococcus* species. The second most frequently isolated pathogen, *S. saprophyticus*, was uniformly eradicated in both treatment groups.

If subjects with reinfections are considered failures, rather than part of the eradication group, the cure rates remain excellent, with 61 of 63 lomefloxacin subjects (97%) and 55 of 59 norfloxacin subjects (93%) cured at early and 54 of 63 (86%) and 50 of 59 (85%) cured at late follow-up, respectively, for the modified intent-to-treat analysis. The single reinfection at short-term follow-up was a *Klebsiella pneumoniae* and beta-hemolytic streptococcal mixed infection. The organisms isolated from the three norfloxacin reinfections at long-term follow-up were a group D streptococcus, an *E. coli* isolate, and a *Proteus mirabilis* isolate. *Enterobacter cloacae* was isolated in the long-term follow-up reinfection in the lomefloxacin group.

Clinical outcome. The clinical outcomes for study subjects were also good, with cure or improvement for more than 90% of all subjects at 5 to 9 days posttreatment and more than 85% of all subjects in all analyses at 4 to 6 weeks posttreatment (Table 4). No statistically significant differences between the lomefloxacin and norfloxacin treatment groups were detected for any of the analytical groups. For the subjects excluded from the modified intent-to-treat analysis because of low quantitative counts pretherapy, 19 of 20 subjects (95%) who received lomefloxacin were cured and one was unknown, and 20 of 20 who received norfloxacin were cured.

Adverse events. Forty-eight percent of the study subjects who received lomefloxacin and 40% who received norfloxacin reported at least one potential adverse event. These were believed by the investigator to be probably due to the study drug with 26% of the lomefloxacin subjects and 25% of the norfloxacin subjects. No serious adverse events were reported. Moderately severe events were observed with 14% of the patients from the lomefloxacin group and 11% of those from the norfloxacin group. The adverse events most frequently reported were nausea (11% of lomefloxacin patients and 14% of norfloxacin patients) and headaches (12% of lomefloxacin patients and 8% of norfloxacin patients). Four subjects (4.8%) who received lomefloxacin and three subjects (3.8%) who received norfloxacin had symptoms consistent with or a microbiologic diagnosis of vulvovaginal candidiasis. Only one subject, who received lomefloxacin, had the study medication withdrawn because of a potential adverse event due to medication. This patient experienced an earache, a headache, hypoesthesia, and nausea. No clinically significant changes in hematologic or biochemical laboratory parameters were identified in laboratory monitoring.

TABLE 3. Bacteriologic outcomes at early and late posttreatment evaluations for subjects randomized to 3 days of lomefloxacin or norfloxacin

Group and time of follow-up with the following agent[a]:	Eradication[b]	No. cured/ no. reinfected	Persistence (no. of subjects)	No. of relapses/ no. of failures	Unknown (no. of subjects)
Modified intent to treat					
5–9 days					
Lom	61/63 (97)	61/0	1	1/0	1
Nor	56/59 (95)	55/1	3	2/1	0
4–6 wk					
Lom	55/63 (87)	54/1	5	5/0	3
Nor	53/59 (90)	50/3	5	4/1	1
Evaluable					
5–9 days					
Lom	54/55 (98)	54/0	1	1/0	0
Nor	47/49 (96)	46/1	2	2/0	0
4–6 wk					
Lom	50/55 (91)	50/0	4	4/0	1
Nor	45/49 (92)	42/3	4	4/0	0

[a] Lom, lomefloxacin; Nor, norfloxacin.
[b] Number of subjects/total number (data in parentheses are percents). For the modified intent-to-treat group, 95% confidence intervals of the difference were −6.8 and 10.6% at 5 to 9 days and −15.4 and 10.4% at 4 to 6 weeks. For the evaluable group, they were −6.2 and 10.8% at 5 to 9 days and −13.7 and 11.8% at 4 to 6 weeks.

TABLE 4. Clinical outcomes of treatment with 3 days of lomefloxacin or 3 days of norfloxacin for acute uncomplicated urinary tract infections

Group and time of follow-up with the following agent[a]:	No. cured or improved (%)[b]	No. of failures (%)	Unknown (%)
Intent to treat			
5–9 days			
Lom	76 (91)	5 (6.0)	3 (3.6)
Nor	76 (95)	2 (2.25)	2 (2.5)
4–6 wk			
Lom	73 (87)	6 (7.1)	5 (6.0)
Nor	71 (89)	6 (7.5)	3 (3.8)
Modified intent to treat			
5–9 days			
Lom	57 (91)	4 (6.3)	2 (3.2)
Nor	56 (95)	2 (3.4)	1 (1.7)
4–6 wk			
Lom	55 (87)	5 (7.9)	3 (4.8)
Nor	51 (86)	6 (10.2)	2 (3.4)
Evaluable			
5–9 days			
Lom	51 (93)	3 (5.5)	1 (1.8)
Nor	48 (98)	1 (2.0)	0
4–6 wk			
Lom	50 (91)	3 (5.5)	2 (3.6)
Nor	43 (88)	5 (10.2)	1 (2.0)

[a] Lom, lomefloxacin; nor, norfloxacin.
[b] For the intent-to-treat group, 95% confidence intervals of the difference were −13.6 and 4.6% at 5 to 9 days and −13.1 and 9.4% at 4 to 6 weeks. For the modified intent-to-treat group, they were −15.2 and 6.4% at 5 to 9 days and −12.8 and 14.5% at 4 to 6 weeks. For the evaluable group, they were −15.1 and 4.6% at 5 to 9 days and −10.7 and 17.0% at 4 to 6 weeks.

DISCUSSION

The characteristics of the subjects enrolled in this study are consistent with those anticipated for a population of individuals experiencing acute uncomplicated urinary tract infections (11). Subjects were relatively young, with a median age of only 30 years; *E. coli* was the principal infecting organism, and *S. saprophyticus* was the second most frequent; and one-quarter of the subjects had quantitative counts of $<10^8$ CFU of organisms per liter in their pretherapy specimens (20). Patient characteristics were consistent in the five study centers, despite the differences in the clinic settings. Thus, the demographic and microbiologic observations are consistent with the population enrolled being the target population of women with acute uncomplicated urinary tract infections.

Both 3-day therapeutic regimens, lomefloxacin (400 mg) daily and norfloxacin (400 mg) twice daily, were highly effective, and the two antimicrobial agents were equivalent in both clinical and bacteriologic efficacies. The outcomes with 3 days of norfloxacin therapy in this study are consistent with the results with this same therapeutic regimen in a previous multicenter Canadian study of uncomplicated urinary tract infections (17). The reported success rates of more than 90% are also consistent with those from other reports of short-term therapy with quinolones or trimethoprim-sulfamethoxazole in the treatment of acute uncomplicated urinary tract infections (4, 8). Thus, lomefloxacin is an appropriate therapy as a 3-day treatment regimen for acute uncomplicated urinary tract infections. The once-daily dosing regimen may provide an advantage for some patients.

The usual clinical practice in the management of uncomplicated urinary tract infections is often to treat with empiric antimicrobial therapy prior to culture results. In many cases, a pretherapy urine culture may not be obtained. Some antimicrobial trials for therapy of urinary tract infections have excluded patients from enrollment because of their low quantitative counts or pretherapy resistant organisms or, if the patients were enrolled, have excluded these subjects

from outcome analysis (6, 9, 16). Since such subjects would frequently not be identified or excluded in usual clinical practice, the study observations from such trials may not be relevant to actual clinical use of the antimicrobial agent. The intent-to-treat analysis performed for this study, which retained all subjects enrolled, including those with low quantitative counts in pretherapy urine specimens, would be consistent with anticipated clinical practice. Thus, the observations of efficacy of lomefloxacin and norfloxacin in this study are relevant to clinical practice. As has been previously reported (4), subjects with pretherapy urine specimens with low quantitative counts had clinical outcomes similar to those of subjects with significant bacteriuria.

This was a study of two different 3-day regimens, and it did not address a comparison of short and longer courses of therapy. In studies of lomefloxacin therapy of acute uncomplicated urinary tract infections with 7 to 10 days of the antibiotic, clinical and bacteriologic cures of more than 95% at short-term follow-up were reported (1, 10). The observations in this study suggest an efficacy of the 3-day regimen similar to that reported for longer antimicrobial courses. The uniformly high success rates with different durations of therapy suggest that a direct comparative study of long and short courses of therapy in order to document small differences, if any, would require large numbers of subjects. Even if a small difference were documented, with cure or eradication rates of more than 95% for both regimens, it would be unlikely to be clinically meaningful. Thus, the 3-day regimen would seem to be the optimal therapeutic duration for lomefloxacin in treating uncomplicated urinary tract infections.

In a large Scandinavian study of acute uncomplicated urinary tract infections, 3 days of norfloxacin was not as effective as 7 days of therapy (9). The observed bacteriologic success rates of 90% for norfloxacin at long-term follow-up in the study reported here are comparable to the reported 92% success rate for 7 days of therapy in the Scandinavian study, rather than the 81% success rate with 3 days of therapy reported in that study. The reported differences in 3 and 7 days of norfloxacin therapy may reflect study population characteristics. The mean age of the subjects enrolled in the Scandinavian study was 45 years, suggesting that a large number of older women were enrolled. Postmenopausal women do less well with short courses of therapy for urinary tract infections (2, 7, 17), and the high proportion of older women enrolled may explain the observed differences between 3 and 7 days of therapy for that study. In contrast to those from the Scandinavian study, the observations from this and other studies (8, 17) suggest that 3 days is likely the optimal duration for quinolone treatment of acute uncomplicated urinary tract infections in young women.

The outcome of *S. saprophyticus* infections has been identified as a particular concern with quinolone therapy. This organism is the second most frequent cause of acute uncomplicated urinary tract infections and is inadequately treated by very short courses of quinolone therapy (8, 13, 17). In our recent Canadian study comparing a single dose with 3 days of norfloxacin, all subjects infected with *S. saprophyticus* failed single-dose therapy, but 3 days of therapy cured these infections (17). The study reported here confirms the efficacy of 3 days of quinolone therapy with either lomefloxacin or norfloxacin for the treatment of *S. saprophyticus*. Since this duration of therapy is effective, empiric therapy with either of these regimens would be appropriate.

The potential adverse events reported by 25% of the study subjects in both study arms is relatively high. The proportion of subjects reporting adverse events is, however, dependent on the intensity with which potential events are sought. Other clinical studies which used active methods for the identification of adverse events have reported frequencies similar to those observed in this study (8). Serious adverse effects were not identified and, in the entire study population, only one subject (0.6%) discontinued medication because of potential adverse effects. This discontinuation rate is lower than those in some other studies, which have reported rates of discontinuation as high as 2.5% (9).

While this study further confirms the efficacy of 3 days of quinolone therapy in the management of acute uncomplicated urinary tract infections, it does not clarify the role of quinolones relative to those of other antimicrobial agents. The quinolone regimen is expensive compared with other widely used antimicrobial agents such as trimethoprim-sulfamethoxazole, trimethoprim, and nitrofurantoin. Subjects with multiple drug allergies or intolerance or with known or suspected resistant organisms would likely benefit from quinolone therapy. This group would include women who develop infections with prophylactic antimicrobial agents or who have been recently treated for an infection. The more general empiric use of a quinolone for acute uncomplicated urinary tract infections is likely only warranted if the local community prevalence of resistance to first-line agents in common uropathogens is substantial.

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