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# NOTES

## Ciprofloxacin, Lomefloxacin, or Levofloxacin as Treatment for Chronic Osteomyelitis

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**The efficacy and safety of three oral fluoroquinolones (lomefloxacin, levofloxacin, and ciprofloxacin) for the treatment of chronic osteomyelitis were analyzed. Twenty-seven patients had documented infections with quinolone-sensitive organisms and received either lomefloxacin, levofloxacin, or ciprofloxacin. Levofloxacin was effective therapy for 9 of 15 (60%) patients. Lomefloxacin was effective therapy for five of seven (71%) patients, and ciprofloxacin was effective therapy for two of five patients (40%). Average follow-up was 11.8 months for patients who completed the course of therapy, and the average duration of therapy was 60.6 days. Gram-positive bacteria were isolated from 18 patients, and 11 patients were cured. Oral fluoroquinolones can be safe, effective therapy if they are given for a prolonged course as treatment for infections caused by susceptible gram-positive as well as gram-negative organisms and in combination with adequate surgical debridement.**

This paper describes the outcomes for an additional 27 patients (patients 81 to 107) treated for osteomyelitis in our clinical trials in which we are evaluating quinolone therapy. Our first 80 patients participated in clinical trials in which we evaluated ciprofloxacin therapy and have been described elsewhere (1–3). The objectives of the study were to evaluate the efficacy and safety of ciprofloxacin, high-dose lomefloxacin (800 mg every 12 h), or levofloxacin for the treatment of chronic osteomyelitis caused by susceptible organisms.

Patients were enrolled in either a prospective, randomized, nonblinded trial that compared ciprofloxacin to lomefloxacin or in an open trial with levofloxacin as therapy. All patients were older than 17 years, and for all patients specimens from their infections (specimens obtained at the time of surgical debridement or an aspirate from infected bone) were cultured. Exclusion criteria included pregnancy or breast-feeding, severe disease requiring concomitant antimicrobial therapy, hypersensitivity to any quinolone, resistance of the isolated pathogen to the study drug, or a creatinine clearance rate less than 30 ml/min/1.73 $m^2$.

Patients who failed to respond during therapy were clinical failures. If signs and symptoms were markedly reduced at the end of therapy, the patient was considered improved but not cured. Resolution of infection had to include a healed wound without any drainage or swelling. Patients were monitored for relapsing infection for as long as possible after the end of treatment. Informed consent was given voluntarily by each patient, and the studies were approved by the University of Kentucky Institutional Review Board.

Table 1 details the responses of the 27 patients with chronic osteomyelitis to therapy. There were 20 men (mean age, 37 ± 3 years) and 7 women (mean age, 38 ± 7 years). Quinolone-susceptible organisms were isolated in cultures of specimens from all of the patients. Fifteen patients were treated with oral levofloxacin (500 mg every 24 h), seven patients received oral lomefloxacin dosed at 800 mg every 12 h, which is four times higher than the approved dose, and five patients received oral ciprofloxacin (750 mg every 12 h). All patients were evaluable for the safety of the quinolone, and 24 patients were evaluable for the efficacy of the quinolone.

Levofloxacin was effective therapy for 9 (60%) of 15 patients. Those who failed to respond included one patient with an allergic reaction (rash and tongue swelling), one patient who failed levofloxacin therapy due to inadequate debridement (dead bone at the site of infection was identified during therapy), three patients who had relapses after the end of therapy due to inadequate debridement (dead bone at the infection site was identified after the completion of therapy), and one patient who had a relapse 5 months after the end of therapy. The infections in patients who were cured were caused by the following organisms: *Staphylococcus aureus* ($n$ = 4), members of the family *Enterobacteriaceae* ($n$ = 4), anaerobes ($n$ = 4), other staphylococci ($n$ = 3), streptococci ($n$ = 2), and *Pseudomonas aeruginosa* ($n$ = 2). The one failure not associated with a lack of debridement involved *Staphylococcus aureus* and *Enterococcus faecalis*. Monitoring of cured patients ranged from 3 to 24 months, with a median of 12 months.

High-dose lomefloxacin was effective therapy for five (71%) of seven patients. Those who were not cured included one patient who stopped lomefloxacin after 1 day of therapy because of nausea and dizziness and one patient who was improving but whose therapy was changed because of *Clostridium difficile* diarrheal disease. Cured infections included those due to members of the family *Enterobacteriaceae* ($n$ = 5) and *S. aureus* ($n$ = 2). Monitoring of cured patients ranged from 0 to 17 months, with a median of 8 months. Photosensitivity occurred in one patient who elected to take precautions and continue the lomefloxacin treatment, and photophobia and dyspepsia

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TABLE 1. Results of treatment with other antimicrobial agents[a]

| Patient no. | Antimicrobial drug | Duration of quinolone treatment (days) | Infecting organism[b] | Site of infection | Outcome | Duration of follow-up (mo) | Adverse reaction |
|---|---|---|---|---|---|---|---|
| 81 | LF | 66 | *Peptostreptococcus magnus*,[c] *Streptococcus epidermidis*,[c] *Staphylococcus simulans*[c] | Left tibia | Cure | 9 | None |
| 82 | LF | 89 | *Enterobacter cloacae*,[c] *Staphylococcus aureus*[c] | Right femur | Cure | 18 | None |
| 83 | LF | 42 | *Peptostreptococcus* species,[c] *Staphylococcus saprophyticus*[a] | Right third metetarsal head | Cure | 24 | None |
| 84 | LF | 38 | Group B streptococcus,[c] *Pseudomonas aeruginosa*,[c] *Flavobacterium adoratum*[c] | Right calcaneous | Relapse (inadequate debridement) | 12 | None |
| 85 | LF | 60 | *Staphylococcus hemolytica*[c] | Right femur | Cure | 10 | None |
| 86 | LF, TC | 51 | *Staphylococcus aureus* (TC-S),[c] Group B streptococcus (TC-R)[c] | Left tibia | Cure | 3 | None |
| 87 | LF | 86 | *Staphylococcus aureus*,[c] *Proteus mirabilis*, *Enterobacter cloacae*, Group B streptococcus, *Klebsiella oxytoca* (aspirate) | Left calcaneous | Failure (inadequate debridement) | | None |
| 88 | LF, MC | 56 | *Staphylococcus epidermidis* (aspirate) | Left fifth metatarsal | Relapse (inadequate debridement) | 5 | None |
| 89 | LF | 52 | *Escherichia coli*,[c] *Pseudomonas aeruginosa*,[c] *Morganella morganii*,[c] *Bacteroides species*[c] | Right tibia | Cure | 21 | None |
| 90 | LF | 2 | *Staphylococcus aureus*[c] | Right media malleolus | Treatment stopped due to tongue swelling and rash | | |
| 91 | LF, MN | 90 | *Bacteroides* (aspirate) | Left second finger | Cure | 18 | None |
| 92 | LF | 75 | *Staphylococcus aureus*,[c] *Pseudomonas aeruginosa*[c] | Right femur | Cure | 12 | None |
| 93 | LF | 44 | *Escherichia coli*[c] | Left calcaneous | Cure | 14 | None |
| 94 | LF | 39 | *Staphylococcus aureus*,[c] *Enterococcus faecalis*[c] | Right great toe | Relapse | 5 | None |
| 95 | LF | 60 | *Staphylococcus aureus*[c] | Right malleolus | Relapse (inadequate debridement) | 3 | None |
| 96 | LM | 28 | *Serratia marcescens*[c] | Right femur | Cure | 1 | None |
| 97 | LM | 55 | *Staphylococcus aureus*[c] | Left femur | Cure | 17 | Photophobia, dyspepsia |
| 98 | LM, MN | 16 | *Staphylococcus aureus*[c] | Left tibia | Improving when MN started and LM stopped | | *Clostridium difficile* associated with diarrhea |
| 99 | LM | 2 | *Staphylococcus aureus*[c] | Right knee | Stopped on day 2 | | Dizziness, nausea |
| 100 | LM | 44 | *Serratia marcescens*[c] | Left ulna | Cure | 8 | Photosensitivity |
| 101 | LM | 28 | *Staphylococcus aureus*,[c] *Eikenella corrodens*, *Klebsiella odytoca* (aspirate) | Right second finger | Cure | 14 | None |
| 102 | LM | 59 | *Escherichia coli*[c] | L4-L5 disc | Cure | 0 | None |
| 103 | CP | 52 | *Staphylococcus aureus*[c] | Right tibia | Failure | | None |
| 104 | CP | 98 | *Staphylococcus aureus*[c] | Left tibia | Failure | | None |
| 105 | CP | 110 | *Staphylococcus aureus*[c] | Left fibula | Cure | 14 | None |
| 106 | CP | 78 | *Staphylococcus aureus*[c] | Left tibia | Relapse | 5 | None |
| 107 | CP | 96 | *Staphylococcus epidermidis* | Right femur | Cure | 36 | None |

[a] Abbreviations: LF, levofloxacin; CP, ciprofloxacin; LM, lomefloxacin; MC, macrodantin; MN, metronidazole; TC, tetracycline for bone marking; TC-R, tetracycline resistant; TC-S, tetracycline susceptible.

[b] The infecting organism was obtained by culture of a clinical specimen.

[c] Obtained by surgical debridement and biopsy.

were reported by another patient, who elected to continue the lomefloxacin treatment.

Ciprofloxacin was effective in two of five patients who were monitored for 14 to 36 months after treatment. The infections in the two patients who failed treatment and the one patient who had a relapse were caused by *S. aureus*. The infections that were cured were caused by *S. aureus* ($n = 1$) and *Staphylococcus epidermidis* ($n = 1$).

These studies intended to explore the efficacies of quinolones for the treatment of chronic osteomyelitis caused by gram-positive bacteria, especially *S. aureus*. For 11 of 18 patients who had staphylococcal infections and who completed their course of quinolone therapy, the infections were resolved. Seven infections involving gram-positive organisms, including four caused by *S. aureus*, were cured with levofloxacin. Two infections due to *S. aureus* were cured with lomefloxacin. One infection due to *S. aureus* and one infection due to *S. epidermidis* were cured with ciprofloxacin. All cured patients had adequate debridement of their infected bone and treatment that lasted until their wounds were closed. The treatment durations for patients whose infections were cured ranged from 28 to 110 days, with a mean of 57 ± 6 days. The durations of treatment for patients who failed treatment or who had relapses were also long (38 to 98 days, with a mean of 63 ± 8 days). The prolonged duration of therapy along with adequate debridement may have been important factors in achieving cures in patients with infections caused by gram-positive organisms (4). Oral quinolone therapy is easier for patients than the traditional parenteral antibiotic treatment for *S. aureus* osteomyelitis and may offer an option for some patients in

whom a quinolone-susceptible gram-positive organism is causing their osteomyelitis (4). The combination of a quinolone with other oral agents active against gram-positive pathogens, such as clindamycin and/or rifampin, offers a reasonable option for use in future studies in an effort to further improve cure rates for chronic osteomyelitis caused by gram-positive pathogens (4).

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