

# Oral Ciprofloxacin Therapy for Chronic Contiguous Osteomyelitis Caused by Aerobic Gram-Negative Bacilli

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Twenty adult patients with chronic contiguous osteomyelitis caused by aerobic gram-negative bacilli were enrolled in an open, prospective cooperative study to determine the effect of oral ciprofloxacin therapy in a dosage of 750 mg every 12 hours. There were 14 men and six women, with a mean age of 55 years. Fifteen of the 20 patients had undergone previous unsuccessful attempts at therapy; seven of the 20 patients had clinically important underlying diseases. Osteomyelitis involved the sternum in three patients and the bones of the lower extremity in 17 patients. Initial surgical debridement was performed in 15 of 20 patients. The predominant organism isolated was *Pseudomonas aeruginosa*, which was found as a single pathogen in 13 patients and as part of a polymicrobial flora in three patients. Based on posttreatment follow-up of seven to 21 months, clinical cure was achieved in 13 of 20 (65 percent) patients and bacteriologic cure was achieved in 14 of 20 (70 percent) patients. Minimal inhibitory concentrations of ciprofloxacin against *P. aeruginosa* increased during therapy in four of 16 (25 percent) patients. Minor gastrointestinal side effects occurred in five patients. Oral ciprofloxacin was an effective and safe therapy in patients with chronic contiguous osteomyelitis due to aerobic gram-negative bacilli.

Chronic contiguous osteomyelitis caused by aerobic gram-negative bacilli can occur in a variety of clinical settings. The most common setting is one in which the initial event is either a compound fracture or an infection as a complication of "clean" surgery required in the management of closed fractures of the long bones of the extremities. Some patients acquire the disease after a nail puncture wound or as a complication of a peripheral neuropathy with associated pressure necrosis of the skin and subcutaneous tissue overlying bone. Contiguous bone infection can also result from an extension of infection from ischemic ulcers induced by peripheral vascular disease. Sternal osteomyelitis after coronary artery bypass surgery represents yet another subset of cases. Failure to analyze treatment results by patient subgroups may explain, in part, the wide range of reported cure rates for chronic osteomyelitis [1-3].

In addition to an uncertain prognosis, aggressive therapy of chronic contiguous osteomyelitis is expensive, time-consuming, and may require the use of potentially toxic antimicrobial agents. Thus, the prospect of an oral drug, active against aerobic gram-negative bacilli, is appealing.

The possible value of ciprofloxacin for *Pseudomonas aeruginosa* osteomyelitis was assessed in rabbits [4]. Four weeks of subcutaneous ciprofloxacin treatment achieved a bacteriologic cure in 17 of 18 rabbits: four

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weeks of tobramycin treatment achieved bacteriologic cure in one of 18 rabbits. These results prompted the following prospective, open, non-comparative cooperative study. Only patients with chronic contiguous osteomyelitis caused by aerobic gram-negative bacilli were enrolled.

#### PATIENTS AND METHODS

**Patient Selection and Definitions.** Candidates for study enrollment included any adult 18 years of age or older with documented chronic contiguous osteomyelitis due to aerobic gram-negative bacilli that were susceptible, *in vitro*, to ciprofloxacin. Patients were excluded from consideration on the basis of pregnancy, a history of allergy to quinolone drugs, or a serum creatinine concentration above 3 mg/dl. Patients were not excluded based on the presence or absence of associated atherosclerotic peripheral vascular disease.

Chronic was defined as the presence of infection for 14 or more days. Patients were considered to have contiguous infection if there was past or continuing infection in the adjacent skin and subcutaneous tissue adjacent to the infected bone, or if there was historical evidence that the initial infection appeared after an open fracture, a puncture wound, or an elective orthopedic procedure. Bone infection was considered present if any of the following manifested in the patient in association with the performance of a valid culture: pain, soft tissue swelling, purulent drainage, or abnormal radiographic finding. Any of the following were considered valid specimens for the establishment of a bacteriologic etiology: bone collected at the time of surgical debridement, needle aspirate or biopsy of bone, and culture of deep wounds contiguous with visible exposed bone. Sinus tract cultures were not considered valid [5]. Isolated pathogens were tested for *in vitro* susceptibility to ciprofloxacin using standard methods. No patient was enrolled who had received any antibiotic therapy active *in vitro* against pathogens found in the pretreatment culture within the previous two weeks.

**Patient Management.** Patients were enrolled into a standardized protocol by the principal investigators and their colleagues in Portland, Oregon, Tacoma, Washington, and Omaha, Nebraska. Prior to the initiation of ciprofloxacin therapy, all patients provided a complete history and underwent a physical examination, and radiographs of the involved bone were obtained. Performance of baseline isotopic bone scans was optional. A complete blood cell count and a multichemistry screen were performed. Baseline ophthalmologic assessment included determination of visual acuity, color discrimination, and performance of an Amsler grid test.

Whenever possible, patients were subjected to aggressive surgical debridement with concomitant removal of orthopedic metallic foreign bodies. If immobilization was necessary, external fixation devices were used. Following surgery and performance of the appropriate cultures, oral ciprofloxacin was initiated in a dosage of 750 mg every 12 hours.

During therapy, the condition of patients was assessed on a weekly basis. Assessment included a clinical evaluation with careful attention to symptoms suggesting drug-induced adverse reactions, ophthalmologic evaluation (visual acuity, color discrimination, and Amsler grid), a complete blood cell count, and a multichemistry screen. In the absence of evidence of clinical or bacteriologic failure, patients were treated

for a minimum of six weeks. Treatment was continued beyond six weeks based on the clinical judgment of the individual investigator.

Repeat cultures, radiographs, and isotopic bone scans were obtained during therapy as clinically indicated. Cultures were performed at the termination of therapy, and at the time of follow-up examination, if valid cultures, as defined previously, were possible. All patients were required to have a posttreatment radiograph. Follow-up examinations were conducted at one, two, three, six, nine, and 12 months following termination of drug therapy.

**Response Criteria.** A clinical cure was defined as the absence of pain, drainage, swelling, fever, or progressive radiographic abnormality at the time of the last posttreatment evaluation. A partial response was defined as a definite and persistent improvement in the pattern of the individual patient's osteomyelitis as manifested by reduced drainage, less purulent drainage, less swelling, less pain, and no radiographic evidence of progression. Clinical failure was defined as no change at the time of the last follow-up examination in the amount or character of drainage, the amount of swelling, and the amount of pain, or definite radiographic evidence of progressive bone destruction.

Each patient's bacteriologic response was judged as either cure or failure. Cure was defined as either the absence of drainage with no clinical justification for repeat culture of the involved bone, or the absence of a pathogen in cultures from a persistent open contiguous wound (e.g., neurotrophic ulcer). Bacteriologic failure was defined as culture evidence of persistence of the initial pathogen during or after completion of therapy, documentation that the original pathogen developed *in vitro* resistance to ciprofloxacin, or the appearance of a different pathogen resistant to ciprofloxacin *in vitro* after completion of ciprofloxacin therapy.

The results reported herein indicate the clinical and bacteriologic responses as of the last available posttreatment follow-up evaluation, which ranged from seven to 21 months.

#### RESULTS

**Patient Characteristics.** A total of 27 patients were enrolled in the study. Seven patients were excluded from the data analysis because of an inability to undergo surgical debridement, because it was not possible to obtain a valid pretreatment culture, or because pretreatment cultures indicated the presence of both aerobic gram-positive cocci and aerobic gram-negative bacilli. The 20 patients evaluated included six women and 14 men, who ranged in age from 20 to 75 years. The median age was 59 years.

Duration of chronic osteomyelitis ranged from one month to 56 years. In five patients, ciprofloxacin represented the initial attempt at therapy. Six patients had received one previous course of antibiotic surgical therapy, three patients had received two to five previous courses of combined therapy, and six patients had received more than five previous attempts at treatment of their bone infection.

Potentially important associated disease states were present in seven of the 20 patients. Insulin-dependent dia-

**TABLE I** Precipitating Events and Underlying Diseases in 20 Patients with Contiguous Osteomyelitis

Type of Event (underlying disease)	Number of Patients	Number of Patients with Bacteriologic Cure
Open fracture with initial infection or infection complicating management of long bone fractures	9	6
Nail puncture wound	2	2
Pressure necrosis of overlying skin and underlying neuropathy	2	2
Ischemic necrosis of overlying skin and underlying atherosclerotic peripheral vascular disease	4	1
Sternal infection after aorto-coronary bypass surgery	3	3

betes mellitus was present in four patients. In three of the four patients, there was evidence of concomitant peripheral vascular disease; one of the diabetic patients had peripheral neuropathy. One patient each had peripheral neuropathy due to alcohol consumption and childhood injury. Atherosclerotic peripheral vascular disease sufficient to cause claudication or require physician management was present in one patient. In four of the 20 patients, the concomitant vascular disease was sufficient to classify the patient's disease as chronic osteomyelitis due to vascular insufficiency. There were no pertinent associated or underlying diseases in the remaining 13 patients.

In 17 of the 20 patients, the osteomyelitis involved the bones of the lower extremity: tibia, seven patients; talus, four patients; femur, two patients; metatarsal, two patients; calcaneus, one patient; and phalanx, one patient. The remaining three patients had postoperative infections of the sternum.

The precipitating events and underlying disease states in the 20 evaluated patients are summarized in Table I. The heterogeneity of the patient population is evident. The largest number of patients acquired chronic osteomyelitis as a result of initial environmental contamination from an open fracture or as a complication of surgical procedures necessary in the management of a closed fracture. Generally, the bones infected were the femur or tibia, and the patients had received multiple previous courses of antibiotic therapy. The nail puncture injuries did not result in fracture and involved the small bones of the feet. These patients had not received previous antimicrobial therapy, but their disease met the duration of illness criterion we had established for chronic osteomyelitis. Patients with underlying peripheral neuropathy and/or underlying pe-

ripheral vascular disease had osteomyelitis of the bones of the ankle or feet.

**Bacteriologic Results.** The bacteriologic data are summarized in Table II. Pretreatment cultures were established from bone collected at the time of surgical debridement in 15 patients, from percutaneous needle aspiration or bone biopsy in one patient, and from material obtained from open wounds with contiguous exposed bone in four patients.

In 15 of the 20 patients, only a single pathogen was isolated in the pretreatment culture. It is notable that *P. aeruginosa* was the only pathogen isolated in 13 of the 15 patients. Four patients had multiple pathogens present in the pretreatment culture. Although mixed gram-negative rods were present, *P. aeruginosa* was present as part of the mixed flora in three of the four patients. Polymicrobial cultures were established from material obtained from open wounds in two patients and from surgical debridement specimens in two patients.

*P. aeruginosa* persisted in the contiguous drainage from infected bones in five of the 13 patients who had *P. aeruginosa* as the only pretreatment pathogen. Therapy was continued for as long as results of in vitro sensitivity tests indicated continued susceptibility to ciprofloxacin. After six to 14 weeks of therapy, four of the original 13 patients with *P. aeruginosa* as the sole pathogen had culture results that demonstrated the emergence of in vitro resistance or intermediate susceptibility to ciprofloxacin. Drug treatment was discontinued, and these cases were classified as bacteriologic and clinical failures of treatment. In one patient, *P. aeruginosa* was present on cultures performed eight months after completion of therapy. The organism was susceptible in vitro to ciprofloxacin. The sixth patient had positive culture results three months after the completion of therapy, but the isolate was inadvertently discarded before in vitro susceptibility testing was performed.

Of the four patients with pretreatment polymicrobial cultures, two patients had positive results for potential pathogens during therapy. At the end of seven to 11 weeks of therapy and after seven to 21 months of follow-up, the condition of all four patients had improved, and no suitable specimen was available, or indicated, for a valid culture. Inexplicably, one patient demonstrated persistent drainage from the site of infection, but results of repeated aerobic and anaerobic cultures were negative. Technically bacteriologic cure was achieved in the patient, but the case was considered to be a clinical failure. Thus, after a follow-up of seven to 21 months, bacteriologic cure was achieved in 14 of the 20 (70 percent) patients evaluated.

The bacteriologic response of clinical subsets of patients is included in Table I. A bacteriologic cure was achieved in all patients in whom osteomyelitis developed after a nail puncture wound of the foot, who had an underlying peripheral neuropathy, or who had an infected sternum after aorto-coronary bypass surgery.

**TABLE II** Summary of all Bacteriologic Cultures Performed before, during, and after Ciprofloxacin Therapy

Pretreatment		During Treatment		Posttreatment*	
Pathogen(s)	Number of Patients	Pathogen(s)	Number of Patients	Pathogen(s)	Number of Patients
Single pathogen					
P. aeruginosa	13	P. aeruginosa	5	P. aeruginosa	6†
Proteus mirabilis	2				
Serratia marcescens	1				
Polymicrobial					
P. aeruginosa	1	Staphylococcus aureus	1		
Enterobacter cloacae		Alcaligenes species			
P. aeruginosa	1	P. mirabilis	1		
Escherichia coli		Staphylococcus epidermidis			
P. aeruginosa	1				
P. mirabilis					
E. coli					
Bacteroides fragilis					
Klebsiella pneumoniae	1				
E. cloacae					
P. mirabilis					
Culture negative	0		13		14‡
Total	20		20		20

\*Posttreatment: bacteriologic status at time of last follow-up examination.

†In vitro susceptibility to ciprofloxacin: three isolates were resistant, one isolate was intermediate, one was sensitive, and one was not tested.

‡One patient had persistent drainage but negative culture results.

Bacteriologic cure was achieved in two thirds of the nine patients with infection as a complication of fracture of the tibia or femur. Underlying atherosclerotic vascular disease, with associated diabetes in three patients, was the most difficult subset to treat, since bacteriologic cure was considered to have been achieved in only one of four patients.

**Clinical Response.** None of the 20 patients was considered to be acutely ill. A maximum temperature elevation to 101°F was present prior to therapy in two patients. The temperature returned to within normal limits within the first week of drug administration in both patients.

The overall clinical response is summarized in Table III. Only the clinical status at the time of the last available posttreatment follow-up examination is presented. After a posttreatment period of one to 15 months, 13 of 20 (65 percent) patients were considered to have clinical cure, and seven patients were considered to have clinical failure. The patient with persistent sterile drainage was mentioned previously.

**Adverse Effects.** Various gastrointestinal complaints of mild severity were encountered in four patients. Postprandial and nocturnal, modest volume, watery diarrhea developed in a fifth patient after three weeks of therapy. Testing for Clostridium difficile enterotoxin yielded negative results. No ova or parasites were present. A stool culture for pathogens was reported as a "pure" culture of yeast. The diarrhea promptly resolved but returned each time clotrimazole treatment was discontinued. Subsequently, the dos-

**TABLE III** Clinical Response of Patients Given Ciprofloxacin as Assessed at the Time of the Last Posttreatment Follow-Up Evaluation

Response	Duration of Therapy (weeks)	Number of Patients	Duration of Follow-Up (months)
Cure*	6-12	13	7-21
Failure†	6-16	7	Not applicable

\*Cure: no fever, drainage, or pain at last follow-up evaluation.

†Failure: no change in fever, drainage, or pain at last follow-up evaluation. May have had transient change during therapy.

age frequency of clotrimazole was gradually reduced to twice a day, which controlled the diarrhea until the course of therapy was completed.

#### COMMENTS

The patients enrolled in this study were part of a non-randomized, "non-blinded phase III clinical evaluation of oral ciprofloxacin therapy for the treatment of osteomyelitis. It was our objective to define, prior to retrospective evaluation of the clinical records, a relatively homogeneous group of patients. Thus, only patients with chronic contiguous infection caused by aerobic gram-negative rods were included.

The results indicate that considerable heterogeneity existed within the group of 20 patients evaluated despite

the pre-evaluation criteria. Oral ciprofloxacin was 100 percent effective in resolving the aerobic gram-negative-rod chronic contiguous osteomyelitis due to nail puncture wounds, pressure necrosis complicating peripheral neuropathy, or sternal infection after coronary artery bypass surgery. Most of these patients received ciprofloxacin as the first course of antibiotic treatment for chronic osteomyelitis. Oral ciprofloxacin was only moderately successful in patients with post-traumatic or postoperative osteomyelitis of the tibia or femur. Most of these patients had previously received multiple unsuccessful courses of antimicrobial therapy. Oral ciprofloxacin was least successful in the patients with underlying peripheral atherosclerotic vascular disease and diabetes mellitus. Although the number of patients in each subset is small, the data strongly suggests the value of analyzing the clinical and bacteriologic responses of subgroups of patients with chronic osteomyelitis.

Because of the apparent difference in the prognosis of subsets of patients with chronic osteomyelitis, it is not possible to compare our results with the reported efficacy of other new antimicrobial agents. A review of several recent publications indicates an occasional separation of patients into groups with acute and chronic osteomyelitis [6–10]. However, there has been little attempt to perform subset analysis of the patients with chronic infection.

Emergence of resistance during therapy with quinolone antibiotics is a concern [11]. Resistance was detected in four of our patients with bone infection due to *P. aeruginosa*. An increase in the minimal inhibitory concentrations of ciprofloxacin was not detected until after six weeks of therapy. In contrast, acquired resistance was observed in *P. aeruginosa* after only 10 days of ciprofloxacin therapy in patients with cystic fibrosis who had airway infections

[12]. Resistant strains of *P. aeruginosa* were found in 14 of 37 treated patients, and in several other patients in the same hospital who were not treated. Perhaps the greater frequency and speed of emergence of resistance in these patients is a reflection of the greater density of bacteria in patients with cystic fibrosis. In our patients, there was no systematic attempt to identify the time of appearances of resistant organisms. Repeat cultures were performed at the discretion of the investigator. Oral ciprofloxacin was well tolerated. Gastrointestinal complaints occurred in 25 percent of the patients. In no instance were the problems severe enough to cause an interruption of therapy.

Many of our patients had previously received a treatment regimen consisting of several weeks of parenteral antibiotic therapy. These patients were very enthusiastic at the prospect of a twice-daily oral drug in lieu of round-the-clock intravenous antibiotic therapy.

In this small group of patients, oral ciprofloxacin was a safe and effective therapy for chronic contiguous osteomyelitis caused by aerobic gram-negative bacilli. Emergence of resistant organisms occurred in 20 percent of the patients but was not detected until after several weeks of therapy. The drug was least effective in patients with underlying atherosclerotic peripheral vascular disease.

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