

Randomized Trial of Ciprofloxacin Compared with Other Antimicrobial Therapy in the Treatment of Osteomyelitis

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Thirty adults (mean age, 52 years) were enrolled in a randomized, comparative trial of oral ciprofloxacin (750 mg twice daily) and other antimicrobial therapies. Etiologic agents included Enterobacteriaceae (18 isolates), *Pseudomonas aeruginosa* (16 isolates), and *Staphylococcus aureus* (four isolates). Seven of 14 (50 percent) ciprofloxacin-treated infections are cured at up to 13 months follow-up and three infections appear improved. Treatment failure or relapse has occurred in four patients. Sixteen patients received other antimicrobial therapy and 11 patients (65 percent) remain without infection and have healed wounds, with follow-up from one to 13 months. One patient has had a relapse, while improvement is apparent in four patients. Complications that occurred in this group included drug-related neutropenia (two patients), diarrhea (two patients), drug allergy (one patient), and catheter-related staphylococcal cellulitis (one patient). Oral ciprofloxacin therapy for chronic osteomyelitis caused by susceptible organisms appears to be as effective as other antimicrobial therapies.

In a recently reported open trial, we evaluated oral ciprofloxacin treatment in adults with chronic osteomyelitis. Fourteen of 26 (54 percent) patients without metal at the site of infection are without relapse after up to two years of follow-up; healing was achieved in an additional four patients (15 percent) by the end of therapy, but these patients were unavailable for follow-up observation. Relapse occurred in six patients, and treatment failed in two patients. Complications due to therapy were minor except for one drug-related rash and one case of streptococcal sepsis during therapy [1]. These results prompted the current study comparing oral ciprofloxacin with other currently used antimicrobial therapy for the treatment of chronic osteomyelitis.

PATIENTS AND METHODS

This was a prospective, controlled, "non-blinded" trial. Enrollment criteria included growth on bacterial cultures established from blood samples or specimens from the osteomyelitis site, and a history compatible with osteomyelitis. All patients were older than 17 years. Exclusion criteria were presence of malignant otitis externa caused by *Pseudomonas* species, severity of disease that necessitated parenteral antimicrobial therapy, pregnancy or lactation, history of hypersensitivity to any quinolone, or a serum creatinine concentration greater than 3.0 mg/dl (or a creatinine clearance rate of less than 30 ml/minute/1.73 m²).

Patients were randomly assigned to receive 750 mg of oral ciprofloxacin every 12 hours or another appropriate antimicrobial therapy. Drugs were administered for at least six weeks if possible.

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TABLE I Results of Ciprofloxacin Treatment

Patient Number	Duration of Treatment (days)	Infecting Organism (culture obtained)	Outcome	Follow-Up (months)	Adverse Reactions #4
30	50	Klebsiella species, Enterobacter cloacae, Proteus mirabilis (biopsy)	Cure	13	None
31	63	P. aeruginosa (swab)	Cure (reinfection with S. aureus at 13 months)	13	Mild dizziness, constipation
32	56	P. aeruginosa, E. cloacae (biopsy)	Relapse	8	None
33	55	Group A streptococci, M. morgani (swab)	Cure	4	None
34	56	P. mirabilis, coagulase-negative staphylococci (swab)	Failure (superinfection with Pseudomonas maltophilia)	0	None
35	44	Escherichia coli, P. mirabilis, coagulase-negative staphylococci, group D streptococci (swab)	Clinical improvement, microbiologic cure	1	None
36	59	P. aeruginosa (biopsy)	Relapse (metal at infection site)	10	None
37	52	P. aeruginosa (biopsy)	Cure	10	None
38	45	Serratia marcescens (aspirate)	Cure	9	None
39	47	S. marcescens, alpha streptococci (biopsy)	Cure	7	Twofold rise in alkaline phosphatase level
40	54	P. aeruginosa (biopsy)	Clinical improvement, microbiologic cure	6	None
41	68	P. aeruginosa	Failure	—	None
42	65	P. aeruginosa, P. mirabilis (biopsy)	Cure	1	None
43	73	P. aeruginosa, S. marcescens (aspirate)	Improvement, but healing not achieved	0	None

Patients were evaluated clinically and with laboratory studies at least every two weeks. Follow-up evaluations at two- to three-month intervals after the end of therapy were attempted for each patient.

Specimens were obtained primarily from surgical biopsy sites or by bone aspiration. Some specimens were swabs from open lesions. All aspirates and biopsy specimens were cultured aerobically and anaerobically. Susceptibility was determined by the Kirby-Bauer method [2] with a 5- μ g ciprofloxacin disk; the susceptible zone was equal to or more than 21 mm and the resistant zone was less than 15 mm.

Cure was defined as complete healing of the wound drainage site at the end of therapy, with no evidence of inflammation and disappearance of fever. Improvement was defined as a marked decrease in inflammation at the infection site, with no evidence of drainage but without total healing. Relapse was defined as the reappearance of signs and symptoms of infection and of the same organism at the infection site after resolution of signs and symptoms.

RESULTS

Thirty patients, 20 men and 10 women (mean age, 52 years), were enrolled in the study. All had chronic osteomyelitis with at least one pathogen being a ciprofloxacin-susceptible gram-negative bacillus. Fourteen patients were treated with oral ciprofloxacin (750 mg every 12 hours) (Table I). Sixteen patients received other antimicrobial therapy (Table II). These patients are numbered

30 to 59 because they followed 29 other patients who were enrolled in our earlier ciprofloxacin trial [1].

With antimicrobial therapy other than ciprofloxacin, cures were apparently achieved in 11 of 16 (69 percent) patients at the end of therapy. One immunosuppressed patient with a renal transplant had a relapse two weeks after the end of treatment. Four patients did not have complete healing of draining sinus tracts, but improvement was observed while they received therapy. Five patients experienced complications and required changes in therapy. Complications included drug-related neutropenia (two patients), diarrhea (two patients), drug allergy (one patient), and a serious staphylococcal cellulitis related to a subcutaneous catheter (one patient).

Cures were achieved in seven of 14 (50 percent) patients treated with ciprofloxacin, and no relapses occurred. The condition of three patients appeared improved. In four patients, either treatment failed or relapse occurred. Reasons for treatment failure or occurrence of relapse were poor compliance (one patient), metal appliance at site of infection (one patient), immunosuppression (one patient), and superinfection with a ciprofloxacin-resistant organism (one patient). The only complications in this group were slight dizziness (one patient) and a minor rise in the level of alkaline phosphatase (one patient); neither problem required a change in therapy.

TABLE II Results of Treatment with Other Antimicrobials

Patient Number	Antimicrobial Drug	Treatment Duration (days)	Infecting Organism (culture obtained)	Outcome	Follow-Up (months)	Adverse Reactions
44	GM, AK	51	<i>P. aeruginosa</i> (aspirate)	Relapse (immunosuppressed patient)	—	None
45	GM, TM, VM	46	<i>P. aeruginosa</i> , group A streptococci, enterococci, <i>S. aureus</i> (swab)	Cure	1	None
46	CT, CZ	19	<i>Proteus rettgeri</i> (biopsy)	Improvement when drugs stopped	—	Pancytopenia caused by antimicrobials that required discontinuation of treatment
47	PI, TM	57	<i>P. aeruginosa</i> (biopsy)	Cure	3	Severe catheter-related cellulitis due to <i>S. aureus</i>
48	TM, CD	42	<i>P. aeruginosa</i> (biopsy)	Clinical improvement, culture negative	4	None
49	CZ, GM, CL	19	<i>P. mirabilis</i> (biopsy)	Cure	6	None
50	MZ, VM, implantable drug pump with AK	150	<i>E. cloacae</i> , <i>S. aureus</i> , <i>E. coli</i> , enterococci (biopsy)	Improvement (lost to follow-up)	—	None
51	TM, CZ, TMP/SFX, AM	37	<i>P. mirabilis</i> (biopsy)	Improvement	—	Diarrhea
52	CZ, TM, TMP/SFX, VM, AZ, CE	53	<i>S. aureus</i> , <i>E. cloacae</i> (aspirate)	Cure	10	Allergies to cefotaxime and vancomycin
53	CF, GM	21	<i>P. aeruginosa</i> (biopsy)	Cure	11	None
54	CD, CZ, CR	42	<i>E. cloacae</i> (biopsy)	Cure	11	None
55	TM, CN	37	<i>P. aeruginosa</i> (aspirate)	Cure	11	None
56	TM, AN, CP	28	<i>P. aeruginosa</i> (swab)	Cure	4	Neutropenia due to azlocillin, diarrhea
57	TM, IM	32	<i>P. aeruginosa</i> (biopsy)	Cure	2	None
58	CF, CR	28	CDC VE-2, alpha streptococci (aspirate)	Cure	1	None
59	TM, PI	37	<i>P. aeruginosa</i> (swab)	Cure	13	None

AK = amikacin; AM = ampicillin; AN = azlocillin; AZ = aztreonam; CD = ceftazidime; CE = cefprozime; CF = cefotaxime; CL = cefadroxil; CN = clindamycin; CP = cefoperazone; CR = ceftriaxone; CT = cefoxitin; CZ = ceftazolin; GM = gentamicin; IM = imipenem; MZ = mezlocillin; PI = piperacillin; TM = tobramycin; TMP/SFX = trimethoprim/sulfamethoxazole; VM = vancomycin.

The susceptibility to ciprofloxacin, by disk testing, of all study isolates was 96 percent (43 of 45 organisms tested). In addition, there were five strains that were not tested. All 16 *Pseudomonas aeruginosa*, 18 Enterobacteriaceae, and four *Staphylococcus aureus* strains tested were susceptible. Also susceptible were CDC VE-2 (one strain), coagulase-negative staphylococci (two strains), *Morganella morganii* (one strain), and group D streptococci (one strain). There were two resistant strains of streptococci, and an additional four streptococcal strains were not tested.

The clinical response to ciprofloxacin in *P. aeruginosa* osteomyelitis was three cures, two relapses, and one failure (38 percent of the patients had cures and were no longer receiving therapy). This compared with eight cures

and one relapse (89 percent) with other antimicrobial therapy. The response to ciprofloxacin in patients infected with Enterobacteriaceae was as follows: six cures, three improvements, one relapse, and one failure (55 percent of the patients had cures and were no longer receiving therapy). Cures were achieved with other therapies in all seven patients infected with Enterobacteriaceae. Ciprofloxacin treatment failed in one *S. aureus* infection, whereas all three such infections were cured with conventional therapies.

COMMENTS

In our randomized trial, 750 mg of oral ciprofloxacin every 12 hours was a successful treatment (cure or improvement at the end of therapy) in 71 percent of patients with

osteomyelitis, which compares with a 94 percent success rate with other therapies. Side effects associated with ciprofloxacin treatment were significantly less serious than those observed with other antimicrobial therapies. Five patients receiving other agents required a change in therapy because of drug-related reactions, whereas none in the ciprofloxacin group required a change. Clearly, the oral administration of ciprofloxacin had advantages over parenteral therapy. Thus, in terms of efficacy and safety, ciprofloxacin appeared to be as effective as conventional therapy, but had fewer side effects and much lower hospitalization-related costs.

On the other hand, compliance with oral therapy was a problem in at least one ciprofloxacin-treated patient. This suggests that therapeutic failures in those patients treated

with oral ciprofloxacin may not always be related to an infected sequestrum or ineffective antimicrobial agent.

Overall, it appears that ciprofloxacin should be considered as an initial therapy in adults with osteomyelitis caused by susceptible organisms. The oral dosing regimen will make this drug especially attractive in the treatment of this type of infection.

REFERENCES

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2. Bauer AW, Kirby WMM, Sherris JC, Turck M: Antibiotic susceptibility testing by a standardized single disk method. *Am J Clin Pathol* 1966; 45: 493-496.

Open Trial and Randomized Trial of Ciprofloxacin vs. Standard Therapy in the Treatment of Osteomyelitis

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ABSTRACT

One of us (RNG) recently completed an open trial with ciprofloxacin treating 29 patients with osteomyelitis. Fourteen of the 29 patients have not relapsed with at least one-year follow-up, and an additional four were cured at end of treatment but lost to follow-up. These results (62% success) suggested the need for a randomized comparison trial with ciprofloxacin versus standard therapy for osteomyelitis.

Our randomized trial has enrolled 50 patients. All patients are adults with a mean age of 52 years; there are 20 males and 10 females. All have chronic osteomyelitis with at least one pathogen being an aerobic gram-negative bacilli. Sixteen were treated with conventional therapy, eleven are currently cured, four were improved but not cured, and one relapsed. Of the fourteen ciprofloxacin-treated patients (750 mg twice daily), seven are currently cured, two are improved, four failed or relapsed, and one remains on therapy. The ciprofloxacin failures or relapses appear to be due to poor compliance (1), metal appliance at site of infection (1), immunosuppression (1), and superinfection with ciprofloxacin-resistant organism (1). Complications in the standard therapy group included drug-related neutropenia (2), drug allergy (1), diarrhea (2), and a serious staphylococcal cellulitis related to an intravenous catheter

ABSTRACT - continued

(1). Only slight dizziness (1) and a minor rise in alkaline phosphatase (1) were noted in the ciprofloxacin treated group. Overall, of the 26 patients cases currently cured or improved with ciprofloxacin, the etiologic agents include *Pseudomonas aeruginosa* (13), *Staphylococcus aureus* (7), *Enterobacter sp* (6), *Klebsiella sp* (5), *Proteus mirabilis* (4), *Serratia marcescens* (4), *Escherichia coli* (2), *Providencia sp* (2), coagulase-negative *Staphylococcus* (2), and others (4).

In summary, oral ciprofloxacin therapy appears to be a safe and effective therapy for chronic osteomyelitis due to susceptible organisms.

CONCLUSIONS

1. Oral ciprofloxacin, 750 mg twice daily, appears to be effective therapy for chronic osteomyelitis due to susceptible organisms.
2. Oral ciprofloxacin dosing is better tolerated and has fewer complications than conventional parenteral therapy for chronic osteomyelitis.

OPEN STUDY: SUMMARY

In this open study there were 29 patients, who ranged in age from 15 to 85 years (mean 39). There were 24 males and 5 females. All had chronic osteomyelitis with pathogen determined by bone aspirate or biopsy, and received ciprofloxacin (500 or 750 mg) twice daily. Three of the 29 patients had metal appliances at the infection site, all three showed significant improvement, but relapsed once the study drug was discontinued.

There were two failures, both had infection with a ciprofloxacin-susceptible, methicillin-resistant *Staphylococcus aureus*, which became ciprofloxacin-resistant while on therapy. The six relapsing patients probably still have an

OPEN STUDY: SUMMARY - continued

infected nidus of dead bone that was not adequately debrided at the time of the study (Tables 1 and 2).

One patient developed a *Streptococcus salivarius* sepsis during treatment due to severe dental problems; he responded to the addition of penicillin. Another patient (enrolled but not evaluated) had ciprofloxacin discontinued on study day 6 due to a pruritic maculopapular truncal rash. Other adverse reactions did not require a change in treatment and included bad taste in mouth (4), calcium oxalate crystalluria (3), minor rises in liver function tests (3), and nausea (1).

TABLE 1

Osteomyelitis Isolates and Clinical Response (from 29 Cases in Open Study)

Organism	Total	Without		
		Relapse	Relapsed	Failure
<i>Pseudomonas aeruginosa</i>	13	8	5	0
MSSA	6	5	1	0
MRSA	6	2	2	2
<i>Staphylococcus epidermidis</i>	1	1	0	0
Enterobacteriaceae	23	16	7	0

MSSA = methicillin-susceptible *Staphylococcus aureus*.

MRSA = methicillin-resistant *Staphylococcus aureus*.

TABLE 2

Results of Treatment in Open Study

Number	Treatment Duration (Days)	Infection Organism(s) (Serum Bactericidal Duration)	Outcome	Follow-up in Months	Additional Therapy
1	45	<i>E. coli</i> (2)	C	0*	OAP
2	50	<i>P. aeruginosa</i> MSSA	C	14	
3	54	<i>P. aeruginosa</i>	C	22	
4	43	<i>E. coli</i> (1)	C	12	
5	53	<i>P. aeruginosa</i> (1) <i>P. mirabilis</i> (1)	C	21	
6	47	<i>P. mirabilis</i> MSSA	C	13	
7	45	<i>E. coli</i> (1) <i>P. aeruginosa</i>	C	16	
8	48	<i>Providencia sp</i> (1) <i>P. aeruginosa</i> (1)	C	16	
9	140	<i>S. marcescens</i> , <i>Abstrusella sp</i>	C	12	
10	129	<i>P. aeruginosa</i> (1)	C	12	
11	68	<i>E. coli</i> (1) MSSA (1) <i>Abstrusella sp</i> (1)	C	15	V
12	50	<i>Providencia sp</i> <i>Enterobacter sp</i> MSSA	C	15	
13	116	<i>P. aeruginosa</i> (1)	C	12	
14	191	<i>Abstrusella sp</i> (1) <i>P. aeruginosa</i> (1) <i>Enterobacter sp</i>	C	12	
15	42	MSSA (1)	C	18	
16	29	MSSA	C	10	
17	63	<i>S. pneumoniae</i> (1)	C	3	
18	17	<i>Providencia sp</i> (1) MSSA (1)	C	0	
19	45	MSSA (1) (1)	H	27	
20	63	<i>E. coli</i> (1) <i>P. aeruginosa</i> (1)	H	16	
21	50	<i>P. aeruginosa</i> MSSA	H	12	MI
22	51	<i>P. aeruginosa</i> (1) <i>S. marcescens</i> (1)	H	13	P-MT
23	56	<i>P. mirabilis</i> (1) <i>E. coli</i> (1)	H	9	
24	68	<i>P. mirabilis</i> <i>E. coli</i>	H	9	
25	33	MRSA (1)	F	-	
26	67	MRSA (1)	F	-	
27	63	MRSA <i>S. marcescens</i> (1)	H	1	
28	67	<i>P. aeruginosa</i> (1)	H	1	
29	67	<i>P. aeruginosa</i> (1)	H	1	

C = cured; H = better end of treatment; F = failed; H = healed.

OAP = osteomyelitis; P-MT = penicillin-resistant *Streptococcus pneumoniae*.

MI = metal appliance present.

MSSA = methicillin-susceptible *Staphylococcus aureus*.

MRSA = methicillin-resistant *Staphylococcus aureus*.

In the randomized study there are 30 patients, all are adults with a mean age of 52 years (20 males, 10 females). All initially had chronic osteomyelitis with at least one pathogen being an aerobic gram-negative bacilli. The patient are summarized in Table 3, the isolates in Table 4. Each patient received either oral ciprofloxacin, 750 mg twice daily, or an appropriate parenteral therapy.

Conventional Therapy (16 patients)

- 11 currently are cured (0-13 months follow-up)
- 4 improved but not cured
- 1 relapse

Adverse Reactions or Problems:

Major

- 2 drug-related neutropenia
- 1 *Staphylococcus aureus* cellulitis at catheter site

Minor

- 1 drug allergy to two treatment agents
- 2 diarrhea

TABLE 3

Results of Treatment in Randomized Study

Case Number	Treatment and Duration (days)	Pathogen Isolated (Antibiotic Resistance)	Outcome	Follow-up in Months	Notes on Outcome
01	CIPRO	Staphylococcus aureus (Methicillin resistant)	Cured	12	
02	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
03	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
04	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
05	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
06	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
07	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
08	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
09	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
10	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
11	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
12	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
13	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
14	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
15	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
16	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
17	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
18	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
19	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
20	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
21	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
22	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
23	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
24	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
25	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
26	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
27	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
28	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
29	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	
30	CIPRO	Staphylococcus aureus (Methicillin resistant)	Improved	12	

Ciprofloxacin Therapy (14 patients)

- 7 currently are cured (1-13 months follow-up)
- 2 improved but not cured
- 4 failure or relapse
 - 1 poor compliance
 - 1 metal at site of infection
 - 1 immunosuppression
 - 1 superinfection with ciprofloxacin-resistant organism
- 1 is on treatment

Adverse Reactions or Problems:

Major

- None

Minor

- 1 slight dizziness
- 1 minor rise in alkaline phosphatase

TABLE 4

Osteomyelitis Isolates from Cases 30 to 59, Ciprofloxacin Susceptibility, and Clinical Response

	Ciprofloxacin Sensitivities		
	Susceptible	Resistant	Unknown
<i>Pseudomonas aeruginosa</i>	16	0	1
<i>Enterobacteriaceae</i>	18	0	0
<i>Staphylococcus aureus</i>	4	0	0
Others†	5	2	4
Total	43	2	5

* Ciprofloxacin treated - Conventional treatment
 † Streptococci (7), VE-2 (1), *Morganella morganii* (1), Coagulase negative Staphylococci (2)

Clinical Response (CIP - Conventional Treatment)

	Cure	Relapse	Failure	On
				Therapy
<i>Pseudomonas aeruginosa</i>	4- 8*	2-1*	1-0*	1-0*
<i>Enterobacteriaceae</i>	8- 7	1-0	1-0	1-0
<i>Staphylococcus aureus</i>	0- 3	0-0	1-0	0-0
Others†	5- 5	0-0	1-0	0-0
Total	17-21	3-1	4-0	2-0

* Ciprofloxacin treated - Conventional treatment
 † Streptococci (7), VE-2 (1), *Morganella morganii* (1), Coagulase negative Staphylococci (2)