ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 1990, p. 65–70
0066-4804/90/010065-06$02.00/0
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Vol. 34, No. 1

Activities of Ciprofloxacin and Ofloxacin against Rapidly Growing Mycobacteria with Demonstration of Acquired Resistance following Single-Drug Therapy

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Received 10 July 1989/Accepted 9 October 1989

The susceptibility to ciprofloxacin of 548 clinical isolates of rapidly growing mycobacteria belonging to eight subgroups or species was determined. The 170 isolates of *Mycobacterium fortuitum* biovar. *fortuitum* were most susceptible; the MIC for 90% of the organisms was 0.125 μg/ml. The other biovariants of *M. fortuitum*, *M. smegmatis*, and the *M. chelonae*-like organisms were less susceptible; the modal MIC was 0.5 μg/ml, and the MIC for 90% of organisms was 1.0 μg/ml. The two subspecies of *M. chelonae* were generally resistant, with only 8% of 206 isolates falling in the moderately susceptible category (MIC, 2 μg/ml) and only 2% falling in the susceptible category (MIC, ≤1 μg/ml). MICs of ofloxacin averaged 1 to 2 dilutions higher than those of ciprofloxacin for all subgroups tested. Three patients with *M. fortuitum* cutaneous disease relapsed after an initial response to therapy with ciprofloxacin, and their isolate was shown to have acquired drug resistance. Mutational frequencies for *M. fortuitum* with ciprofloxacin were relatively high (10^{-5} to 10^{-7}), and MICs for single-step mutants were similar to those for the clinically resistant strains. Thus, despite the excellent activity of ciprofloxacin against rapidly growing mycobacterial groups other than *M. chelonae*, single-drug therapy should be used with caution because of the risk of development of mutational resistance.

The rapidly growing mycobacteria produce a wide spectrum of clinical diseases. The most common is a localized cutaneous infection that follows open trauma or a puncture wound (18). Optimal therapy for these infections appears to be surgical debridement and antimicrobial therapy based on susceptibility testing (3, 17). Drugs that have proven effective in this setting include amikacin, doxycycline, sulfonamides, erythromycin, and cefoxitin (3, 15, 17).

Recent studies have suggested that the newest class of antibiotics—the fluorinated quinolones—has good activity against the rapidly growing mycobacteria, especially *Mycobacterium fortuitum* and *Mycobacterium smegmatis* (2, 5, 12, 13, 16, 21). However, none of these studies included large numbers of isolates, and there have been only three case reports of the clinical use of the newer quinolones as single agents (6, 19; L. W. Rumans and P. G. Anikerholz, Abstr. Annu. Meet. Am. Soc. Microbiol. 1989, U56, p. 164) and one study in which the drug was used in combination (20). We tested the susceptibilities to the quinolones of a large number of isolates of rapidly growing mycobacteria that had been identified to species and subspecies. We report the results of these studies, case studies of four patients with cutaneous infections due to *M. fortuitum* whose isolates were resistant to ciprofloxacin after drug therapy, and the mutational frequency of isolates of *M. fortuitum* to ciprofloxacin resistance.

(Part of this research was presented at the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy, New York, N.Y., 4 to 7 October 1987 [G. Bedsole, R. J. Wallace, Jr., C. V. Sanders, L. C. Steele, and D. R. Graham, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 197, 1987].)

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MATERIALS AND METHODS

Isolates. Clinical isolates of rapidly growing mycobacteria submitted to the University of Texas Health Center laboratory for susceptibility testing were evaluated. Most isolates were identified to species by the Texas Department of Health Laboratories, Austin, by standard methods (9, 16). Isolates of *M. fortuitum* biovar. *peregrinum* and the unnamed third biovariant complex were separated from isolates of *M. fortuitum* biovar. *fortuitum* on the basis of the resistance of *M. fortuitum* biovar. *peregrinum* and the unnamed third biovariant complex to pipemidic acid (10) and the difference in their drug patterns (12). All isolates of *M. fortuitum* biovar. *peregrinum* and the third biovariant complex, as well as selected strains of *M. fortuitum* biovar. *fortuitum*, were submitted to the Mycobacterial Reference Center of the Centers for Disease Control, Atlanta, Ga., for species and subspecies confirmation (9). Drug patterns were used to separate the two subspecies of *M. chelonae*. Isolates for which cefoxitin MICs were >64 μg/ml but which were susceptible to tobramycin (MIC, ≤4 μg/ml) were identified as *M. chelonae* subsp. *chelonae*, whereas isolates susceptible to lower concentrations of cefoxitin and resistant to tobramycin were identified as *M. chelonae* subsp. *abscessus* (16). Selected strains of *M. chelonae*, as well as isolates of *M. smegmatis* and the *M. chelonae*-like organisms, were also submitted to the Centers for Disease Control and identified to species and subspecies by using published standards (9, 16).

Susceptibility testing. Isolates were tested for susceptibility to ciprofloxacin and for susceptibility of selected strains to ofloxacin by using the broth microdilution system as

TABLE 1. Susceptibility of eight subgroups or species of rapidly growing mycobacteria to ciprofloxacin and ofloxacin

Organism	Drug	No. tested	MIC (μg/ml)[a]				% Susceptible
			50%	90%	Mode	Range	
M. fortuitum							
biovar. *fortuitum*	Ciprofloxacin	170	≤0.063	0.125	≤0.063	≤0.063–0.25	100
	Ofloxacin	88	0.25	0.5	0.25	≤0.063–0.5	100
biovar. *peregrinum*	Ciprofloxacin	21	0.125	1.0	≤0.063; 0.5	≤0.063–1.0	100
third biovariant complex	Ciprofloxacin	34	0.5	1.0	0.5	0.25–2.0	100
	Ofloxacin	19	1.0	2.0	1.0	1.0–4.0	100
M. chelonae-like organisms	Ciprofloxacin	62	0.5	1.0	0.5	0.125–2.0	100
	Ofloxacin	18	2.0	4.0	4.0	0.25–4.0	100
M. chelonae							
subsp. *abscessus*	Ciprofloxacin	142	>8	>8	>8	0.5–>8	6
	Ofloxacin	66	>8	>8	>8	4–>8	2
subsp. *chelonae*	Ciprofloxacin	64	4	>8	4	0.5–>8	19
	Ofloxacin	37	>8	>8	>8	4–>8	5
M. smegmatis	Cirpoflocacin	33	0.5	1.0	0.5	0.125–2.0	100
	Ofloxacin	23	1.0	2.0	1.0	0.5–4.0	100
Pigmented isolates	Ciprofloxacin	22	0.125	2.0	≤0.063	≤0.063–>8	95
	Ofloxacin	8	0.25	1.0	0.25	0.125–>8	88

[a] 50% and 90%, MIC for 50 and 90% of isolates tested, respectively.

previously described for rapidly growing mycobacteria (11). Strains isolated prior to ciprofloxacin treatment and during relapse after ciprofloxacin therapy, as well as laboratory-derived ciprofloxacin-resistant mutants, were also tested for resistance to doxycycline, sulfamethoxazole, erythromycin, cefoxitin, imipenem, amoxicillin-clavulanic acid (Augmentin), amikacin, tobramycin, and kanamycin by the same method. This method involved cation-supplemented Mueller-Hinton broth and a 72-h incubation period at 30°C in a moisturized incubator with room air. Susceptibility plates were prepared by using the Mini-Quick Spense II System (Bellco Glass, Inc., Vineland, N.J.) and twofold drug dilutions. Bacterial control strains were *Escherichia coli* ATCC 25922, *E. coli* ATCC 35218 (the organism recommended for testing of clavulanic acid), and *Staphylococcus aureus* ATCC 29213 (7), as well as the type strain *M. fortuitum* ATCC 6841 (12). Plates were tested against all four control strains at the time of preparation and were then tested against three of the strains on a weekly basis after storage at −70°C.

The currently proposed MIC breakpoints of ofloxacin (≥8.0 μg/ml for resistant, 4.0 μg/ml for moderately susceptible, and ≤2.0 μg/ml for susceptible) were used (4). Susceptibility and resistance breakpoints for all other agents including ciprofloxacin were those currently recommended by the National Committee for Clinical Laboratory Standards for aerobic organisms in general (7), except that an MIC of >32 μg/ml rather than >16 μg/ml was used to define resistance to cefoxitin (12). It should be noted that clinical information to establish the validity of these breakpoints for the rapidly growing mycobacteria is limited and has not been specifically addressed by the National Committee for Clinical Laboratory Standards.

Clinical cases. Clinical information which had been provided to the Texas laboratory on selected cases was screened to identify patients who had been treated with ciprofloxacin. In addition, all relapse or repeat isolates were carefully evaluated for a change in susceptibility to the quinolones. Follow-up information on these cases was then sought by telephone.

Mutational frequencies. Selected strains of *M. fortuitum* were grown to turbidity in broth. Serial 10-fold dilutions were made, and then 0.5 ml of each dilution was added in duplicate to control plates (containing Mueller-Hinton agar only) or to Mueller-Hinton agar plates containing ciprofloxacin at approximately eight times the MIC for the test organism. For isolates of *M. fortuitum* biovar. *fortuitum* a 0.5-μg/ml concentration was used, whereas for the third biovariant complex a 1.0-μg/ml concentration was used. For one isolate of *M. fortuitum* biovar. *fortuitum* and two isolates of the third biovariant complex a 5-μg/ml concentration was also tested. The plates were allowed to dry and were then incubated for 10 days at 35°C in a moisturized incubator. Colony counts of surviving organisms were performed, and selected single-colony resistant mutants were saved for testing of susceptibility to the quinolones as well as the other drugs known to be active against *M. fortuitum* (12).

RESULTS

Isolates. A total of 548 clinical isolates belonging to eight different species or subgroups were tested for susceptibility to ciprofloxacin. Approximately 40% of these isolates had their species or subgroup confirmed at the Centers for Disease Control, whereas the subgroup of the remainder was based on susceptibility patterns as previously described. The numbers of isolates in the seven groups are shown in Table 1.

Susceptibility results. The largest group of rapidly growing mycobacteria studied for quinolone susceptibility contained the 225 isolates of *M. fortuitum*. There was a difference in susceptibility among biovariants. Isolates of *M. fortuitum* biovar. *fortuitum* were the most susceptible (modal MIC, ≤0.063 μg/ml), whereas isolates of the third biovariant complex were the most resistant (the modal MIC was ≥eightfold higher at 0.5 μg/ml). Isolates of *M. fortuitum*

TABLE 2. Clinical information on patients infected with *M. fortuitum* whose disease was successfully treated with ciprofloxacin monotherapy

Case	Patient	Organism	Ciprofloxacin MIC (μg/ml)	Disease	Outcome
1	Adult female	*M. fortuitum* biovar. *fortuitum*	≤0.063	Bacteremia, infected Hickman catheter	Cure
2	Adult male	*M. fortuitum* biovar. *fortuitum*	0.25	Chest wall infection	Cure
3	Adult female	*M. fortuitum* third biovariant complex	0.5	Augmentation mammaplasty wound infection	Cure

biovar. *peregrinum* had a bimodal distribution, with MICs for 11 isolates of ≤0.063 or 0.125 μg/ml and MICs for a second group of 10 isolates of 0.5 or 1.0 μg/ml. Ciprofloxacin MICs showed that all 325 isolates of *M. fortuitum* were in the susceptible (≤1 μg/ml) or moderately susceptible (2 μg/ml) category (Table 1). The MICs of ofloxacin averaged 1 to 2 dilutions higher, with all 107 isolates of *M. fortuitum* being susceptible (≤2 μg/ml) or moderately susceptible (4 μg/ml).

Ciprofloxacin MICs for the 33 isolates of *M. smegmatis* fell in a single cluster similar to those for the third biovariant complex of *M. fortuitum*. Results for 22 of these isolates have been published previously (16).

The 62 isolates of *M. chelonae*-like organisms also produced a tightly clustered set of ciprofloxacin MICs. MICs for 45 of the 62 isolates (73%) were 0.5 or 1.0 μg/ml, with the remaining isolates differing by only 1 or 2 dilutions.

The *M. chelonae* isolates were generally resistant to ciprofloxacin; the MICs for only 9 of 142 isolates of *M. chelonae* subsp. *abscessus* (6%) and 12 of 64 isolates of *M. chelonae* subsp. *chelonae* (19%) were 2 μg/ml or lower. Overall, only 8% of these 206 isolates were moderately susceptible (MIC, 2 μg/ml) and only 2% were susceptible (MIC, ≤1 μg/ml).

Clinical cases. Seven patients were known to have received ciprofloxacin therapy. Three patients were treated successfully with monotherapy, and their case summaries are shown in Table 2. Isolates from two patients acquired ciprofloxacin resistance following monotherapy, an isolate from a third patient became resistant after therapy in which ciprofloxacin was combined with a weakly active drug, and an isolate from a fourth patient became resistant after therapy with an unknown therapeutic agent(s). Their case summaries are given below. The MICs for the isolates from the first three cases are included in Table 3, while those for case 4 are in the text.

Case 1. A 74-year-old male with severe peripheral vascular disease and chronic renal failure was on long-term chronic ambulatory peritoneal dialysis. In September 1988 he developed purulent peritoneal catheter exit site drainage which grew *M. fortuitum* (third biovariant complex). The catheter was removed, and the patient was placed on hemodialysis for 1 month. He was treated with intravenous amikacin (MIC for *M. fortuitum*, 32 μg/ml) and ciprofloxacin (MIC, 0.25 μg/ml). The drainage site healed, and the patient did well. Approximately 2 weeks later a second peritoneal catheter was inserted. The patient developed clinical peritonitis, and peritoneal fluid grew *M. fortuitum* (third biovariant complex) that was resistant to ciprofloxacin. The catheter was removed, and the patient was placed back on hemodialysis. This led to resolution of many of his symptoms. He was also placed on therapy with oral sulfamethoxazole.

Case 2. A 34-year-old homosexual male who was known to be human immunodeficiency virus positive presented in June 1986 with a mass on the right side of his neck. Therapy with ceftriaxone and cephalexin was unsuccessful. On 2 September he underwent an excisional biopsy of a right posterior cervical lymph node that grew *M. fortuitum* biovar. *fortuitum*. He was placed on trimethoprim-sulfamethoxazole (TMP-SMX), doxycycline, and metronidazole therapy for several weeks, and then the TMP-SMX therapy was discontinued because of a rash. Cytomegalovirus retinitis developed, which required therapy with ganciclovir. The biopsy site, which had healed initially, reopened and drained purulent material that persisted despite further debridement. Under a compassionate-use protocol, the patient was started on oral ciprofloxacin at 750 mg every 12 h. Peak levels in blood on two consecutive days were 0.4 and 2.6 μg/ml (90 min postdose), whereas trough levels were 0.4 and 0.5 μg/ml (30 min predose), respectively. (The reason for the low peak level of 0.4 μg/ml is unknown.) The lesion underwent marked healing over the first few weeks, but by 8 weeks it had broken down and was draining again. An aspirate of the lesion was culture positive for *M. fortuitum* biovar. *fortuitum* that was now resistant to ciprofloxacin. Over the next 2 months the patient developed several complications of acquired immunodeficiency syndrome and then died of a central nervous system lymphoma. No evidence of disseminated *M. fortuitum* was found at autopsy.

Case 3. A 39-year-old male developed swelling on the dorsum of the left foot in February 1985. Two and one-half years previously, he had sustained a puncture wound at that site that had healed spontaneously. The swollen area was excised, with the pathologic report showing only "granulation tissue." The operative incision did well until it was reinjured by an object that had been dropped on the foot. The wound became swollen again, with persistent drainage, and did not respond to further debridement. In December 1985 the cultures were positive for *M. fortuitum* biovar. *fortuitum*. The patient was placed on compassionate-use oral ciprofloxacin and treated for 4.5 months, with improvement in the swelling and cessation of drainage. One month after discontinuation of therapy the area swelled again and drainage recurred. Cultures were positive for *M. fortuitum* biovar. *fortuitum* that was resistant to ciprofloxacin. The patient was placed on therapy with amikacin plus TMP-SMX and then TMP-SMX alone and has done well.

Case 4. A 64-year-old female sustained a puncture wound injury with a piece of metal to her left leg. She developed a draining, indurated area in May 1988, for which she received several courses of unknown oral antimicrobial agents. In June 1988 a wound culture was positive for *M. fortuitum*. On susceptibility testing, the culture consisted of two populations of the third biovariant complex of *M. fortuitum* that were identical except that one was susceptible (MIC, 1.0 μg/ml) and one was resistant (MIC, >8 μg/ml) to ciprofloxacin. In the interim the patient was placed on ciprofloxacin therapy and showed minimal clinical response over the next 2 months (the lesion remained ulcerated and continued to drain). She was then placed on TMP-SMX therapy and has subsequently done well. Although this had not been documented, the patient was presumed to have been treated with a quinolone or some agent which selected for quinolone

TABLE 3. Mutational frequencies and quinolone susceptibility of clinical strains of *M. fortuitum*

Isolate	Organism	Single-test mutational frequency	Source	MIC (μg/ml)	
				Ciprofloxacin	Ofloxacin
1. Mf 411 (case 2)	*M. fortuitum* biovar. *fortuitum*	1.4×10^{-5}	Pretherapy	0.125	
			Relapse	4.0	
2. Mf 360 (case 3)	*M. fortuitum* biovar. *fortuitum*	2.4×10^{-5}	Pretherapy	0.125	0.25
			Relapse	1.0	1.0
			Laboratory mutant	1.0	1.0
3. Mf 557	*M. fortuitum* biovar. *fortuitum*	1.4×10^{-7}	Pretherapy	0.125	0.5
			Laboratory mutant	4.0	8.0
4. Mf 566	*M. fortuitum* biovar. *fortuitum*	2.0×10^{-5}	Pretherapy	0.25	0.5
			Laboratory mutant	4.0	8.0
5. Mf 570	*M. fortuitum* biovar. *fortuitum*	2.0×10^{-9}	Pretherapy	0.063	0.063
			Laboratory mutant	4.0	4.0
6. Mf 485	*M. fortuitum* third biovariant complex	7.6×10^{-6}	Pretherapy	0.25	
			Laboratory mutant no. 1	4.0	>8.0
			Laboratory mutant no. 2	>8.0	8.0
7. Mf 533 (case 1)	*M. fortuitum* third biovariant complex	2.9×10^{-7}	Pretherapy	0.5	1.0
			Relapse	4.0	4.0
			Laboratory mutant	8.0	8.0

resistance before the first culture was obtained in June of 1988.

Mutational frequencies. Four isolates of *M. fortuitum* biovar. *fortuitum* and two isolates of the third biovariant complex were examined. These included two isolates of *M. fortuitum* biovar. *fortuitum* and two isolates of the third biovariant complex from patients treated with ciprofloxacin whose isolate had become drug resistant. The mutational frequencies with the low drug concentrations (0.5 to 1.0 μg/ml) ranged from 10^{-5} to 10^{-7} for six of the seven strains tested (Table 3). The resistant mutants all had low-level quinolone resistance; MICs were comparable for the clinically acquired resistant strains and the laboratory mutants (Table 3). MICs of other drugs, including amikacin, doxycycline, cefoxitin, cefmetazole, and imipenem, were unchanged between the parent or pretreatment isolate and the subsequent quinolone-resistant strains. No mutants were obtained at 5 μg of ciprofloxacin per ml for the isolate of *M. fortuitum* biovar. *fortuitum* or for one of two isolates of the third biovariant complex. One strain of the third biovariant complex that grew colonies resistant to 5.0 μg of ciprofloxacin per ml (strain Mf 485) had a mutational frequency (6.0×10^{-9}) that was almost 3 logs lower than the frequency at 1.0 μg/ml (7.6×10^{-6}).

DISCUSSION

Previous reports of monotherapy of diseases caused by rapidly growing mycobacteria with the fluorinated quinolones have been limited to three case reports. Woods et al. (19) reported a male with chronic renal failure who developed a cutaneous infection at the site of a peritoneal catheter. The patient clinically improved after ciprofloxacin therapy, but cultures were still positive several months later. The repeat culture was still susceptible to ciprofloxacin. Ichiyama and Tsukamura (6) described a 58-year-old male with a right-upper-lobe infiltrate and multiple positive sputa for *M. fortuitum* who was treated with ofloxacin at 300 mg/day. On this therapy the patient was culture negative for 9 months of follow-up and the chest radiograph showed marked clearing. Rumans and Ankerholz (Abstr. Annu. Meet. Am. Soc. Microbiol. 1989) described four patients with cutaneous infections (two with soft tissue disease, one with abdominal wound infection, and one with infected sternotomy incision and osteomyelitis) who were treated with an average of 1,500 mg of ciprofloxacin per day for 6 months. One patient died on day 5 of therapy (but with negative cultures), and another two patients had culture-positive relapses that responded to an increase in the dosage of ciprofloxacin. Repeat susceptibilities of the relapse isolates to ciprofloxacin were not reported.

The current studies suggest that ciprofloxacin monotherapy is effective for cutaneous infections due to *M. fortuitum*, with the apparent limitation of acquired drug resistance. Foreign bodies (catheter, mammaplasty prosthesis) were removed when possible, and this plus surgical debridement is clearly important if not essential management principles as well (17). We are unaware of any experience with the quinolones as therapy for *M. smegmatis* or the *M. chelonae*-like organisms, and the in vitro MICs suggest that the drugs are unlikely to be of much use as monotherapy against most isolates of *M. chelonae*.

The number of patients treated successfully by monotherapy with ciprofloxacin is not known. This drug is very popular at present (R.J.W., unpublished observation), and we suspect that it has been used successfully in many cases not reported here. In our laboratory, physicians usually contact us if therapy is unsuccessful, but follow-up of successfully treated patients is rarely provided, except on request. Hence, we suspect that the four patients whose isolates of *M. fortuitum* acquired resistance to ciprofloxacin may represent most of the patients who were treatment failures with this drug, whereas a much larger but unknown number of patients were treated successfully. The readers should not, in our opinion, interpret the case summaries to mean that four of seven treated isolates acquired drug resistance. The successfully treated cases were included to

demonstrate that the drug is an effective agent in vivo if acquired drug resistance does not occur.

Previous studies have suggested that acquired drug resistance in *M. fortuitum* and *M. chelonae* is related to the selection of spontaneously resistant mutants rather than the acquisition of R plasmids (14). The mutational frequency for resistance to individual drugs such as doxycycline, amikacin, and erythromycin seemed to correlate with the frequency with which acquired resistance occurred after monotherapy of clinical human infections. Acquired resistance was most commonly seen with amikacin, and mutational frequencies were the highest with this aminoglycoside. In addition, the level of resistance to amikacin and the degree of cross-resistance with other aminoglycosides was identical for the laboratory-derived mutants and the clinically acquired drug-resistant strains. The current study demonstrates that the mutational frequencies with ciprofloxacin are relatively high and that the levels of resistance and degrees of cross-resistance to nonquinolones are identical for the laboratory-derived mutants and the strains with clinically acquired resistance.

The mutational frequencies for *M. fortuitum* with ciprofloxacin (10^{-5} to 10^{-7}) were higher than those reported for enteric gram-negative bacilli (10^{-7} to 10^{-8}). However, as with most mutants selected in this latter group, cross resistance was seen only within the family of quinolones and the increase in MICs was modest (8- to 16-fold) (8).

Studies of in vitro drug combinations that include ciprofloxacin or ofloxacin against *M. fortuitum* have not, to our knowledge, been performed. Since the clinical and laboratory-derived isolates showed no cross-resistance between ciprofloxacin and other classes of antimicrobial agents, combination therapy should delay or prevent the development of quinolone resistance. Logical candidates for inclusion with the quinolone include amikacin, doxycycline, sulfonamides, cefoxitin, or imipenem. Yew et al. (20) recently reported 10 patients with sternal wound infections that had been successfully treated with the combination of ofloxacin and amikacin. Amikacin MICs for all isolates were 8 μg/ml or lower. Of interest, one patient in the current study with acquired ciprofloxacin resistance also received amikacin. However, the infecting isolate was a third biovariant complex isolate and had a very high amikacin MIC (32 μg/ml, which is at the limits of safely achievable levels in serum). MICs for most isolates of *M. fortuitum* are in the 0.5- to 1.0-μg/ml range (12). Whether any of these combinations would have theoretical advantages over others (synergism, enhanced killing, etc.) must await additional studies. However, at this point we recommend that initial quinolone therapy of an *M. fortuitum* infection should always include another agent, whose activity should be determined by susceptibility testing.

There is a definite difference among *M. fortuitum* subspecies in the degree of susceptibility to ciprofloxacin. MICs for isolates of the third biovariant complex and for about 50% of the isolates of *M. fortuitum* biovar. *peregrinum* are ≥8-fold higher than those for the isolates of *M. fortuitum* biovar. *fortuitum*. Previous studies have shown that susceptibility to pipemidic acid by a disk diffusion method separates isolates of *M. fortuitum* from *M. chelonae* (1). *M. fortuitum* strains all produced zones of inhibition and were considered susceptible, whereas *M. chelonae* strains did not. Subsequent studies, however, showed that isolates of the third biovariant complex and about 50% of isolates of *M. fortuitum* biovar. *peregrinum* were resistant to pipemidic acid by this method and hence could be misidentified as *M. chelonae* if only that test were used (10). Of interest, all of the isolates of *M. fortuitum* biovar. *peregrinum* and the third biovariant complex in the current study for which ciprofloxacin MICs were high (but which were susceptible to ciprofloxacin) were resistant to pipemidic acid (9; R.J.W. unpublished results). This is not surprising, since pipemidic acid is a quinolone and previous studies had shown that *M. fortuitum* isolates that were pipemidic acid resistant had smaller zones of inhibition by disk diffusion to ciprofloxacin than did isolates of *M. fortuitum* biovar. *fortuitum* and *peregrinum* that were pipemidic acid susceptible (10).

ACKNOWLEDGMENTS

We acknowledge the physicians who provided care and information for some of the patients. They are Charles S. Bryan, Ed Goodman, and William Sutker.

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