THE JOURNAL OF INFECTIOUS DISEASES • VOL. 152, NO. 3 • SEPTEMBER 1985
 0022-1899/85/5203-0009$01.00

Treatment of Nonpulmonary Infections Due to *Mycobacterium fortuitum* and *Mycobacterium chelonei* on the Basis of in Vitro Susceptibilities

Richard J. Wallace, Jr., Jana M. Swenson, Vella A. Silcox, and Michael G. Bullen

From the Department of Microbiology, The University of Texas Health Center at Tyler; Corpus Christi Hospitals, Corpus Christi, Texas; Antimicrobics and Infection Mechanisms Branch, Hospital Infections Program, and the Mycobacterial Reference Section, Division of Bacterial Diseases, Center for Infectious Diseases, Centers for Disease Control, Atlanta, Georgia

One hundred twenty-three patients with nonpulmonary infections due to *Mycobacterium fortuitum* or *Mycobacterium chelonei* were treated by wound debridement and with chemotherapy on the basis of in vitro susceptibilities of the organism. Of 76 patients with infections caused by *M. fortuitum*, 13 required no therapy or were adequately treated with surgery alone. Patients with active localized disease received single drug therapy (usually with a sulfonamide) for a mean period of 10.6 weeks for cellulitis and seven months for osteomyelitis. Patients with extensive disease received amikacin or amikacin plus cefoxitin (mean, four weeks) followed by a sulfonamide (mean, six months). The 47 patients with infections caused by *M. chelonei* received no therapy or were treated with surgery alone (6); with amikacin (10), erythromycin (6), doxycycline (3), or cefoxitin (1); or with amikacin plus cefoxitin followed by cefoxitin alone for a total of 10–12 weeks (20); or other multiple-drug regimens (1). Surgery was performed on 74 (60%) patients. Schlichter tests or serum drug levels were determined for 81 (66%) patients. Response to therapy was excellent; 68 (90%) infections with *M. fortuitum* and 34 (72%) with *M. chelonei* were successfully treated. Cultures became negative within six weeks of chemotherapy, except for sternal osteomyelitis, for which cultures were not negative until up to 14 weeks. Follow-up for a mean period of 12 months following therapy was possible in 80% of cases. Relapses were rare except in patients with disseminated disease, and drug resistance developed in only one patient. These studies demonstrate the value of routine susceptibility testing of these mycobacterial species and the benefit of chemotherapy on the basis of in vitro susceptibilities.

Mycobacterium fortuitum and *Mycobacterium chelonei* are environmental mycobacteria that only rarely infect and produce disease within the lung. They are responsible for a surprising number of primary skin and soft tissue infections, especially in Texas [1]. They have also been identified as a cause of sporadic postsurgical infections, as well as of outbreaks of nosocomial disease that involve dialysis (hemodialysis and peritoneal dialysis) [2, 3], specific types of surgery (augmentation mammaplasty, median sternotomy) [4–6], and postinjection abscesses [7, 8]. Surgical debridement, when possible, has been the mainstay of therapy of infections involving the skin and soft tissue, although without additional chemotherapy many infections persist for months to years. Isolates of the organisms are resistant to the antituberculosis agents—little or no efficacy has

Received for publication 15 January 1985, and in revised form 22 March 1985.

An abstract of part of this work was presented at the 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, in New Orleans, on 23 September 1980, and at the American Thoracic Society, in Los Angeles, California, in April 1982.

This study was funded in part by the Texas Medical Center, Inc. Financial support for production of the color photographs was provided by Bristol Laboratories (Syracuse, New York) and Merck Sharp & Dohme Laboratories (West Point, Pennsylvania).

The authors thank the laboratory personnel who helped us with this study. Special thanks go to Joe Steadham of the Texas Department of Health, Austin, Texas; the Microbiology Section of the Houston Health Department, Houston, Texas; and the members of the laboratory staff at University of Texas Health Center at Tyler. The authors also thank the numerous physicians who collaborated with us, without whose cooperation this study could not have been done.

Please address requests for reprints to Dr. Richard J. Wallace, Jr., Department of Microbiology, The University of Texas Health Center at Tyler, P. O. Box 2003, Tyler, Texas 75710.

been noted when these agents have been used to treat infections. Despite this, the latest recommendations of the American Thoracic Society on therapy of mycobacterial diseases [9] still suggest the use of antituberculosis agents when chemotherapy is indicated.

Recent in vitro studies have revealed the activity against these organisms of a number of traditional antibacterial agents at achievable serum levels [10–17]. Since 1978 we have performed susceptibility tests with these agents against clinically significant isolates of *M. fortuitum* and *M. chelonei* and have managed these infections on the basis of in vitro susceptibilities. We used this approach to treat 123 patients, and the results obtained are the basis for this report.

Patients and Methods

Case selection. The patients or cultures of their infective organism were referred to R. J. W. between July 1978 and December 1983. Patients were either seen by R. J. W. or the primary physician was contacted by telephone. Most patients were contacted within four weeks of isolation of the organism. The nature and extent of disease were evaluated by using the clinical history and physical findings and results of biopsies, acid-fast smears, and cultures.

Therapy. Patients with serious or extensive disease were treated empirically with amikacin alone or amikacin plus cefoxitin, since prior studies have shown these two agents to be active against >90% of isolates, except *M. chelonei* ssp. *chelonei*, which is always cefoxitin resistant. Patients seen early in the study received only amikacin, as the activity of cefoxitin was not appreciated at that time. Therapy for patients with less serious disease was usually withheld pending susceptibility testing of the organism.

Drug dosages for adults were as follows: amikacin or kanamycin, 15 mg/kg per day in divided doses; cefoxitin, 12 g/day in divided doses plus 2–4 g of probenecid by mouth/day in divided doses; doxycycline, 100 mg two to three times a day; trimethoprim/sulfamethoxazole (TMP/SMZ), two tablets (160/800 mg) three times a day, or equivalent doses of SMZ or sulfisoxazole alone. Any antituberculosis agents were discontinued. Aggressive surgical debridement was encouraged, especially in patients with deeply invasive or extensive disease. Patients were followed up with repeat cultures and assessment of peak serum-drug levels and serum inhibitory levels. All patients have completed their chemotherapy at the time of writing.

For most of these cases clinical disease has been reported by us and others [1, 6, 11, 18–21]. Eighteen individual cases are referenced since results of therapy have been presented [6, 11, 18–21].

Treatment definitions. Therapeutic agents were evaluated only if the patient received a minimum of one month of treatment and if an isolate of the infecting organism was susceptible in vitro. A "microbiological failure" was a patient with a positive culture after eight weeks of therapy for nonsternal disease or after 16 weeks of therapy for sternal disease. A "clinical failure" was a patient who died with active disease or whose clinical disease worsened or failed to improve after eight weeks of therapy.

Organisms. Organisms were identified according to standard methods [22] except for the currently unnamed third biovariant of *M. fortuitum*. Previous classification of this group included only isolates that were positive for mannitol and inositol and negative for citrate [22]. We grouped *M. fortuitum* positive for any two or all three of the carbohydrates as the "third biovariant complex."

Susceptibility testing. Isolates were initially tested by using a disk-diffusion method with Mueller-Hinton agar enriched with Middlebrooke OADC (oleic acid, albumin, dextrose, and catalase) [23]. (OADC or ADC supplements are required for growth of *M. chelonei* on this medium [11].) Agents tested and their respective susceptible-zone diameters were as follows: amikacin and kanamycin (>9 mm), cefoxitin (any zone), sulfisoxazole (≥20 mm), doxycycline (≥25 mm), minocycline (≥30 mm), and erythromycin (≥30 mm). A fine haze of growth inside the zone was ignored for cefoxitin, sulfisoxazole, and erythromycin.

MICs were also determined with either macrotubes and non-cation-supplemented Mueller-Hinton broth (MHB) or by agar-disk elution [17] (sulfonamides could not be tested with macrotubes or erythromycin on agar because of a trailing endpoint with these methods). All isolates were also sent to the Centers for Disease Control for MIC determinations with a broth-microdilution method with cation-supplemented MHB [12]. Susceptibility was defined according to recommendations of the National Committee for Clinical Laboratory Standards [24] except for SMZ and cefoxitin, for which susceptibility was defined as an MIC ≤32 μg/ml.

Serum inhibitory concentrations (SICs). Serum samples were obtained at or near peak and trough concentrations of amikacin (when the patient was being treated with amikacin plus cefoxitin) or cefoxitin (when the patient was being treated with cefoxitin alone). Since both *M. fortuitum* and *M. chelonei* grow poorly in 50% serum (R. J. W., unpublished observations), serum samples were diluted with cation-supplemented MHB. The organism isolated from the patient was added to produce a final concentration of 10^4–10^5 cfu/ml. A positive control in 50% serum and another in broth was important to evaluate the expected growth. The SIC was defined as the highest dilution with no visible growth after incubation for 72 hr. SICs, rather than serum bactericidal concentrations, were determined since the purpose of the studies was to provide a confirmatory test of the MICs, and preliminary studies [21] had shown that some isolates of both species are inhibited, but not killed, by these drugs (R. J. W., unpublished observation).

Results

Clinical cases. A total of 136 patients with nonsputum isolates of rapidly growing mycobacteria referred for susceptibility testing had evidence of clinical disease. In 123 cases the patient was found to be infected with *M. fortuitum* or *M. chelonei*, the primary physician was contacted, and therapy on the basis of clinical status and susceptibility results was completed. Subsequent results relate to these 123 cases.

Organisms. Seventy-six (63%) of the 123 isolates were *M. fortuitum:* 60 (79%) were biovariant *fortuitum*, 3 (4%) were biovariant *peregrinum*, and 13 (17%) belonged to the third biovariant complex. Of the 47 isolates of *M. chelonei*, 32 (68%) were ssp. *abscessus* and 15 (32%) were ssp. *chelonei.*

Susceptibilities. The isolates of *M. fortuitum* were relatively drug susceptible. All were susceptible to ≤16 μg/ml of SMZ. Of the 57 isolates of biovariant *fortuitum*, all had MICs of 16–32 μg/ml for cefoxitin and ≤2 μg/ml for amikacin, and ~50% had MICs ≤1 μg/ml for doxycycline. The 13 isolates of the third biovariant complex were more drug resistant. Four (31%) were resistant to cefoxitin, seven (54%) had high MICs for amikacin (4–8 μg/ml), and all were doxycycline resistant. All but one isolate of *M. fortuitum* were resistant to erythromycin.

The 47 isolates of *M. chelonei* were amikacin and kanamycin susceptible (modal MICs, 8 and 4 μg/ml, respectively). Isolates of ssp. *abscessus* had modal MICs for cefoxitin of 32 μg/ml, and ~33% were erythromycin susceptible. None were doxycycline susceptible. Of the 15 isolates of ssp. *chelonei*, all were cefoxitin resistant (MICs ≥128 μg/ml). However, these isolates were more susceptible to oral antimicrobial agents. Five isolates (33%) were doxycycline susceptible and all MICs were ≤4 μg/ml for erythromycin. Neither subspecies was sulfonamide susceptible.

1. *Mycobacterium fortuitum.* Clinical diseases and results of therapy are listed in table 1. We saw comparable numbers of infections following accidental penetrating trauma (38) and as a complication of surgery (32). The nosocomial infections usually followed augmentation mammaplasty, insertion of a vascular access device (venous or peritoneal catheters), or median sternotomy. Osteomyelitis was clinically evident in six cases of posttraumatic infection and in eight of nine of the cases of sternal-wound infection (14 cases in all). Of these, all had positive wound cultures and all but two had positive bone biopsy cultures and (when examined) a compatible histopathologic picture. One patient, for

Table 1. Clinical diseases and results of therapy in 123 patients infected with *M. fortuitum* and *M. chelonei.*

Disease	No. successfully treated/ total no. of cases	
	M. fortuitum	*M. chelonei*
Primary infections (posttraumatic)		
Cellulitis	32/32	12/15 (1)
Osteomyelitis	6/6	2/2
Keratitis	–	4/5
Surgical infections		
Sternal (osteomyelitis)	7/9 (2)	4/5
Mammaplasty	8/8	1/1
Wound infections	4/7	4/5
Catheter related	6/7	1/2
Prosthetic valve endocarditis	0/1 (1)	0/2 (2)
Disseminated disease	2/2	5/9 (2)
Meningitis	1/2	–
Occult bacteremia	2/2	–
Miscellaneous	–	1/1
Totals	68/76 (3)	34/47 (5)

NOTE. Patients who were well or improved but lost to long-term follow-up therapy were considered treatment successes. The nos. in parentheses are deaths directly related to infection with *M. fortuitum* or *M. chelonei.*

Table 2. Drug regimens in patients infected with *M. fortuitum* or *M. chelonei*.

Therapy	*M. fortuitum* (no. of cases)	*M. chelonei* (no. of cases)
Sulfonamide alone or TMP/SMZ	23	0
Doxycycline	5	3
Erythromycin	0	6
Amikacin	2	10
Cefoxitin	0	1
Multiple agents (including amikacin + cefoxitin)	33	21
Surgery only	13	3
No therapy	0	3
Totals	76	47

whom bone biopsy was not performed until after four weeks of chemotherapy, had a positive result by histopathology but the cultures were negative.

Therapy. Therapy for these 76 patients is listed in table 2. Thirteen patients were cultured with or without surgical debridement, but by the time the pathogen was identified and drug susceptibilities were determined, the patients were already essentially well. Two of these patients received amikacin for two weeks, but the remainder did not receive any appropriate chemotherapy. These patients primarily had infections of puncture wounds (five) or of iv-catheter sites (four).

The remaining 63 patients with continued active disease received chemotherapy. Twenty-nine patients with no systemic signs or symptoms and localized disease (often following a puncture wound) received single-drug therapy with an oral agent as outpatient treatment. Most (23 [79%]) of these patients were treated with sulfisoxazole, SMZ, or TMP/SMZ. Twenty of the 29 patients with cellulitis or abscess were treated for four to 16 weeks (mean, 10.6 weeks). Of these, <50% received surgical debridement. Four patients received long-term therapy (six months or longer). Four patients with posttraumatic osteomyelitis of the extremities and one with sternal osteomyelitis received single-drug outpatient therapy for a mean period of 6.8 months.

The remaining 34 patients had extensive disease that required treatment in the hospital. All but two patients (both with occult bacteremic disease) had surgical debridement, and all but one received combination-drug therapy. Of the 33 patients who received combination chemotherapy, 31 (94%) received amikacin, and an equal number also received a sulfonamide or TMP/SMZ. Cefoxitin was administered to 52% of the patients, all but once in combination with amikacin. Nine (27%) patients also received doxycycline.

The duration of therapy for the 34 patients with extensive disease (including 10 cases of osteomyelitis) was much longer than that for the first group. Patients received amikacin alone (two received kanamycin) or amikacin plus cefoxitin for one to six weeks (mean, 4.0 and 3.8 weeks, respectively) followed by oral therapy for an additional one to 12 months (mean, 6.5 and 4.4 months, respectively). There was no difference in therapy for patients with or without osteomyelitis. Details of the therapy for patients with sternal-wound disease are listed in table 3.

SICs and serum drug levels. Serum drug levels or SICs were measured in thirty-six (57%) of 63 patients receiving chemotherapy. Of the 28 patients whose specific drug levels (usually amikacin or sulfonamide) were determined, all but one had levels within the therapeutic range. SICs were determined at 20 different intervals for eight patients (table 4). For the five patients with isolates of *M. fortuitum* for which the MICs for amikacin were ≤1.0 μg/ml and the MICs for cefoxitin were 16–32 μg/ml, peak SICs of amikacin plus cefoxitin were all 1:8–1:32. Peak SICs of cefoxitin alone in two patients were 1:2–1:4. In the one patient with an isolate of the unnamed third biovariant complex with an MIC for amikacin of 4–8 μg/ml and an MIC for cefoxitin and moxalactam of 64–128 μg/ml, SICs of amikacin plus either of the other drugs ranged from 1:4 at the peak (amikacin) to <1:2 at the trough.

Results of therapy. The success rate for treatment of patients infected with *M. fortuitum* was 90%. Patients with localized cellulitis or abscesses usually cleared their infection within a month. Patients with extensive disease with surgical debridement responded more slowly, with definite responses being measured in weeks rather than in days. In patients with extensive disease most cultures became negative within four weeks; only six patients were culture positive for more than six weeks (figure 1). Of the 72 patients who survived, 96% were cured of their disease, including several of the patients who were initially classified as therapeutic failures. Acquired drug resistance was not observed in any case.

Follow-up. Sixty (83%) of 72 patients have been followed up for a mean period of 12 months (range, 1–32 months) after healing of their wound and dis-

Table 3. Results of surgery and chemotherapy in 14 patients with sternal-wound infections.

Case no.	Age/sex, state	Organism	Surgical treatment	Drugs	Duration	Outcome
1	55/F, Texas	*M. fortuitum*	None	Doxycycline	6 months	Well, 6 months
2	72/M, Texas	*M. fortuitum*	Debridement	Amikacin, doxycycline	4 weeks	Died, multiple medical complications [6]
3	Adult/F, Georgia	*M. fortuitum*	Debridement, sternectomy	Amikacin, sulfisoxazole	10 months	Well, 18 months
4	67/M, Oregon	*M. fortuitum*	Debridement	Amikacin TMP/SMZ	4 weeks 12 months	Well, 2 years
5	53/M, Texas	*M. fortuitum*	Sinus tract excision	Doxycycline, TMP/SMZ	11 months	Well, 3 months
6	67/M, Texas	*M. fortuitum*	None	Minocycline TMP/SMZ	2 weeks 6 months	Well, 2 years
7	2/M, Nebraska	*M. fortuitum*	Debridement	Amikacin TMP/SMZ	6 weeks 16 months	Well, 1 year
8	51/M, Indiana	*M. fortuitum*	Sternectomy	Amikacin Isoniazid, ethambutol, rifampin	3 weeks 8 months	Well, 2 years
9	56/M, Illinois	*M. fortuitum*	Debridement	Amikacin, cefoxitin, sulfisoxazole	3 months	Died, multiple medical complications
10	49/M, Texas	*M. chelonei*	Debridement	Amikacin, cefoxitin	6 months	Well, 6 months [6]
11	76/M, Texas	*M. chelonei*	Debridement	Amikacin, cefoxitin	6 months	Well, except small sinus tract, 16 months [6]
12	53/M, Texas	*M. chelonei*	Debridement	Amikacin	7 months	Well, 10 months
13	57/M, Maryland	*M. chelonei*	Debridement	Kanamycin, cefoxitin	14 weeks	Well, 1 year
14	40/F, Texas	*M. chelonei*	None	Amikacin, cefoxitin	5 months	Stormy course; well, 18 months

continuation of chemotherapy. All but two patients (97%) have been followed up for a minimum of three months and most for at least six months. Twelve patients were lost to follow-up: three improved while still receiving chemotherapy and nine were well after their therapy was discontinued.

Three patients had relapses of their disease. One was a nurse with occult bacteremia [1] who developed several additional culture-positive episodes. The other two patients had disseminated disease and developed subsequent infections within two months at sites other than that of the original infection. No patient whose infection healed while receiving chemotherapy subsequently relapsed with disease at the same site. Surgical excision or drainage of diseased sites in several patients in the absence of drug therapy was followed by healing, but the healed areas then broke down and drained within four to six weeks of the surgery.

Therapeutic failures. The eight therapeutic failures (table 5) included three fatal and five nonfatal cases. The fatal cases were two patients with sternal-wound infections and one with prosthetic valve endocarditis. All had multiple complications, either medical or surgical or both, and died with active disease.

Five nonfatal cases were also therapeutic failures (table 5). One patient refused surgical debridement. Although he improved clinically while receiving therapy, cultures were positive for 14 weeks. The patient recovered when his drug therapy (TMP/SMZ) was continued. A second patient had cellulitis that drained for >18 months before a correct diagnosis was made. Culture-positive drainage persisted despite more than four months of appropriate chemotherapy. Surgical debridement combined with combination chemotherapy eventually resulted in a cure. Two patients had prosthetic devices (peritoneal catheter

Table 4. Serum inhibitory levels in patients receiving amikacin or cefoxitin or both.

Case no., species*	Disease	Drug	Dose†	MIC (μg/ml)	Level	Inhibitory titer
1, Mf	Cellulitis	Amikacin	400 mg, im	2	Peak	1:4
2, Mf	Occult bacteremia	Amikacin	500 mg	1	Peak	1:32
		Cefoxitin	3 g	16	Trough	1:4
3, Mf	Occult bacteremia (child)	Amikacin	7.5 mg/kg	1	Trough	1:8
		Cefoxitin	33 mg/kg	16	Random	1:8
					Random	1:8
4, Mf	Abdominal wound infection	Amikacin	500 mg	0.5	Peak	1:16
		Cefoxitin	2 g	32		
5, Mf	Cellulitis, osteomyelitis (hand)	Amikacin	500 mg	1.0	Peak	1:16
		Cefoxitin	3 g	32	Trough	1:4
6, Mf	Cellulitis (foot)	Amikacin	500 mg	4	Peak	1:4
		Cefoxitin	3 g	128	Trough	1:4
					Trough	<1:2
		Amikacin	500 mg	4	Peak	1:2
		Moxalactam	3 g	64	Trough	1:2
7, Mf	Sternal infection (renal failure)	Cefoxitin	1 g	32	Peak	<1:2
			1.5 g		Peak	1:4
						1:4
8, Mf	Prosthetic valve endocarditis	Amikacin	500 mg		Peak	1:16
		Cefoxitin	2 g		Trough	1:16
9, Mc	Cellulitis, osteomyelitis (ankle)	Amikacin	500 mg	8	Peak	1:4
		Cefoxitin	3 g	32	Trough	1:2
10, Mc	Cellulitis, osteomyelitis (arm)	Amikacin	500 mg	4	Peak	1:4
		Cefoxitin	4 g	16		
11, Mc	Prosthetic infection (hip)	Amikacin	500 mg	8	Peak	1:4
		Cefoxitin	2 g	32	Trough	1:2
12, Mc	Disseminated disease [21]	Amikacin	500 mg	8	Peak	1:4
		Cefoxitin	2 g	32	Trough	<1:2
		Cefoxitin (probenecid)	6 g	32	Peak	<1:2
13, Mc	Perirectal abscess	Cefoxitin (probenecid)	2 g	16	Peak	1:4
14, Mc	Disseminated disease, osteomyelitis	Amikacin	500 mg	8	Peak	1:2
		Cefoxitin	2 g	32		
15, Mc	Septic arthritic infection (ankle)	Amikacin	500 mg	8	Peak	1:4
		Cefoxitin	4 g	32		
16, Mc	Multiple abscesses (breast)	Amikacin	400 mg	8	Peak	1:4
		Cefoxitin	4 g	32	Trough	<1:2
		Cefoxitin (probenecid)	4 g		Peak	1:2
					Trough	<1:2

NOTE. Probenecid was given as a 1.0-g dose by mouth. Unless otherwise stated, other drug doses were given iv and patients were adult.

* Mf, *M. fortuitum;* Mc, *M. chelonei.*

† Dose given is per infusion or injection, not daily dose.

and Marlex® mesh; Davol, Cranston, RI). The patient with the peritoneal catheter was cured with continued chemotherapy after removal of the device, whereas the other patient remains culture positive with the Marlex mesh in place.

2. *Mycobacterium chelonei.* The clinical diseases encountered that were caused by this species (table 1) were similar to those caused by *M. fortuitum* except that *M. chelonei* was responsible for more cases of disseminated disease and keratitis and fewer

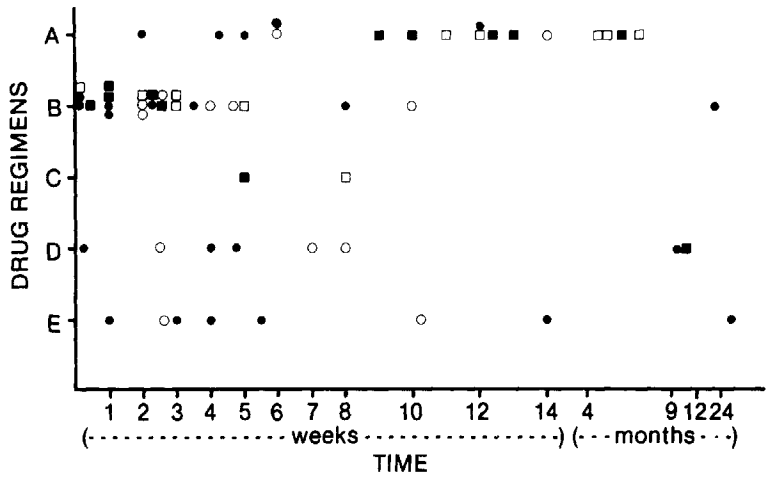

Figure 1. Results of follow-up cultures obtained following initiation of drug therapy. Each symbol represents the time of the last positive or first negative (or both) culture from one patient. These cultures were usually obtained only for patients with more serious infections, especially those with persistent open wounds. Wounds that improved quickly or closed up had no follow-up cultures. With the exception of sternal infections due to *M. chelonei*, almost all wounds were culture negative within six weeks. Treatment groups (drug regimens) were as follows: *A*, combination therapy (sternal-wound infections); *B*, combination therapy (nonsternal infections); *C*, cefoxitin only; *D*, doxycycline only; *E*, sulfonamide or TMP/SMZ only. Circles represent infections with *M. fortuitum:* ○, culture negative; ●, culture positive. Squares represent infections with *M. chelonei:* □, culture negative; ■, culture positive.

cases of augmentation mammaplasty infections and posttraumatic cellulitis.

Therapy. Therapy for the 47 cases is listed in table 2. Unlike *M. fortuitum*, isolates of *M. chelonei* ssp. *abscessus* are usually resistant in vitro to all potentially useful oral antimicrobial agents (doxycycline, erythromycin, and SMZ) and susceptible only to cefoxitin, amikacin, and kanamycin. Hence therapy in some situations depended not only on the extent of clinical disease but also on the decision whether available parenteral therapy would cause more problems than the disease.

Six patients received no chemotherapy. Two patients were cured by surgical resection alone. One patient with disseminated disease who was receiving high-dose corticosteroids for Felty's syndrome was not treated, but had complete resolution of her disease following local incision and drainage and discontinuation of the steroids. Two patients with localized disease remain culture positive after 12 months and three years.

The remaining 41 patients with active disease received chemotherapy. Twenty patients received single-drug therapy. Patients treated with doxycycline (three) or erythromycin (six) received chemotherapy for three to nine months. Ten patients were treated with amikacin alone (mean, five weeks) and one with cefoxitin alone.

Twenty-one patients received combination chemotherapy. All received an aminoglycoside (20 received amikacin and one also received kanamycin), and all but one received cefoxitin. Most patients received the combination for four to six weeks followed by cefoxitin alone for an additional six to eight weeks. For 17 cases the total duration of therapy ranged from six to 14 weeks. Three patients with extensive sternal-wound disease received intermittent therapy with amikacin or cefoxitin or both for five to seven months. Almost all isolates were resistant to all oral agents, so only four patients received subsequent therapy with oral drugs such as erythromycin.

SICs and serum drug levels. We determined the serum drug levels of 27 (82%) of 33 patients who received systemic therapy; all were within the therapeutic range. SICs were determined 11 times on six patients (table 4). Of the four patients receiving amikacin (MICs, 4–8 μg/ml) and cefoxitin (MICs, 32 μg/ml), all had peak SICs of 1:4 and trough levels of ≤1:2. Peak SICs of patients receiving cefoxitin alone ranged from <1:2 to 1:4.

Results of therapy. The success rate for treatment of infections with *M. chelonei* was only 75%. As with infections with *M. fortuitum*, most wounds closed within four weeks of the onset of chemotherapy. Cultures of nonsternal infections were negative within six weeks (figure 1). The sternal-wound infections

Table 5. Patients infected with *M. fortuitum* who were therapeutic failures.

Case	Disease	Therapy	Clinical course	Probable reason for failure
1	Prosthetic valve endocarditis	Amikacin, cefoxitin (6 weeks)	Clinically responded, died at surgery	Surgical complications
2	Infected Tinkoff catheter (chronic ambulatory peritoneal dialysis)	Doxycycline (9 months)	Remained culture positive for 8 months until catheter removed, then healed quickly	Persistent prosthetic device (organism still susceptible)
3	Infected Marlex mesh (abdomen)	TMP/SMZ (3 months)	No improvement; disease still active 2 years later	Unable to remove Marlex mesh (organism still susceptible)
4	Sternal-wound infection	Amikacin; cefoxitin, SMZ (3 months)	Improved; multiple medical complications; died; large retrosternal abscess at autopsy	Low serum inhibitory levels; medical complications; inadequate surgical drainage (abscess)
5	Cervical laminectomy-wound infection	TMP/SMZ (8 months)	Clinically improved, ultimately cured, but culture positive for 14 weeks	Unknown (isolate still susceptible)
6	Ankle bursectomy-wound infection	Amikacin, sulfisoxazole, minocycline, ethambutol (4 months)	Persistent drainage for 12 months; ultimately cured with combination of surgery and drug therapy	Chronicity of disease (18 months) with severe local scarring; isolate still susceptible
7	Sternal-wound infection [6]	Amikacin, cefoxitin, doxycycline (4 weeks)	Cardiac and renal failure; died	Medical complications, treated only 4 weeks
8	Meningitis, dural abscess (gunshot wound)	Amikacin, cefoxitin, TMP/SMZ, moxalactam (12 months)	Stormy course; fever for 10 months despite negative cultures; multiple surgeries	? Poor CSF circulation (subarachnoid block)

NOTE. Therapeutic failures are defined as follows: (*1*) patients who died with active disease regardless of duration of therapy; (*2*) patients whose wounds were still culture positive after eight weeks of chemotherapy for patients with nonsternal infections and after 16 weeks for patients with sternal-wound infections; (*3*) patients who failed to respond clinically after eight weeks of chemotherapy.

(all with osteomyelitis) remained culture positive for 8–13 weeks; one patient had a positive culture as late as six months. Twelve (28%) of 47 patients were considered therapeutic failures. The major problem and cause for treatment failure was the absence of an oral drug that was active against *M. chelonei* ssp. *abscessus*.

The therapeutic margin for the erythromycin- and doxycycline-susceptible isolates treated with these agents was good, as eight of the nine strains had MICs for these agents of ≤ 1.0 μg/ml and serum levels of three to five times the MICs were anticipated or documented. Seven of these patients did well, with total resolution of their disease within three months.

One patient was treated with cefoxitin alone. This was an elderly man with a large perirectal abscess with fistulae formation, which could not be adequately debrided because of its proximity to the anus. Because the patient was partially deaf, he was treated with cefoxitin alone plus probenecid. We documented cefoxitin serum levels of 142 μg/ml and SICs of 1:4. The patient responded well to 12 weeks of therapy (mostly at home with a Hickman catheter), and is well one year posttherapy.

Only one isolate developed drug resistance. This was from a patient with prosthetic valve endocarditis who was treated with amikacin alone. The initial isolate had an MIC of amikacin of 8 μg/ml, whereas the relapse isolate had an MIC >1,024 μg/ml.

Follow-up. Follow-up was obtained in 33 (79%) of the 42 nonfatal cases. Of the 10 patients lost to follow-up, five were asymptomatic and five were improved at the time contact was lost. The remaining 32 patients have been followed up for a mean of 11.2 months (range, 0–30 months). All but one patient (97%) have been followed up for three months and all but eight (76%) for at least six months. Relapses occurred in four patients after chemotherapy ceased;

Table 6. Patients infected with *M. chelonei* who were therapeutic failures.

Case	Disease	Therapy	Clinical course	Probable reason for failure
1	Cellulitis (hand)	Amikacin (6 weeks; outpatient)	Improved, but lesions persisted	High MIC (16 μg/ml), difficulty with outpatient therapy
2	Infected foot (multiple cactus thorns)	Doxycycline (9 months)	Improved; two remaining nodules excised after 9 months. Culture positive, but still doxycycline susceptible	Residual foreign body (isolate still susceptible)
3	Disseminated disease [21]	Amikacin, cefoxitin (12 weeks)	Improved, cultures of blood negative. Died of lymphoma while infection still active	Inadequate therapy, fatal underlying disease
4	Prosthetic valve endocarditis	Amikacin, cefoxitin (3 months)	Cultures of blood negative only with valve resection (done twice); died with active disease	No bactericidal activity
5	Prosthetic valve endocarditis [6]	Amikacin (6 weeks)	Initially responded, relapsed, and died	? Absence of bactericidal activity (not tested); organism developed amikacin resistance; refused surgery
6	Sternal-wound infection [6]	Amikacin, cefoxitin	Improved clinically, but positive culture at 6 months; subsequent cultures negative	Unknown (isolate not tested for susceptibility)
7	Disseminated disease	Amikacin, cefoxitin	Improved clinically, cultures of blood became negative, but had multiple recurring skin lesions over the next 12 months	Underlying leukemia; isolate still susceptible; problem of long-term parenteral therapy
8	Ulcerative keratitis	Topical amikacin (4 weeks)	Improved, then developed deep stromal abscess that required keratoplasty	? Failure of drug penetration (isolate still susceptible)
9	Infected caesarian section incision	Surgery	Multiple attempts at surgical debridement (no chemotherapy); disease still active at 3 years	No chemotherapy
10	Infected catheter site (groin)	None	Wound still draining at 1 year; not extensive enough to warrant parenteral chemotherapy or surgical debridement	No therapy
11	Disseminated disease	Amikacin, cefoxitin, sulfisoxazole	Leukemia in relapse, died	Immediately fatal disease
12	Disseminated disease	Amikacin, cefoxitin	Improved clinically, then relapsed; successfully re-treated with same drugs	Immunosuppressed
13	Septic arthritis, osteomyelitis (ankle)	Amikacin, cefoxitin (7 weeks)	Healed, then relapsed 8 weeks later (culture negative)	Treated for only 7 weeks

three of whom had disseminated disease. Three patients were successfully re-treated, and one remains a treatment failure.

Therapeutic failures. Twelve (25%) of 47 patients were clinical or microbiological failures or both (table 6). One patient with prosthetic valve endocarditis had no negative cultures of blood during administration of chemotherapy except briefly after removal of his infected valve (replaced twice), and he died when the disease recurred a third time. The other patient with prosthetic valve endocarditis initially responded, then relapsed and died when the infecting organism developed resistance to amikacin [6]. One patient with ulcerative keratitis seemed to re-

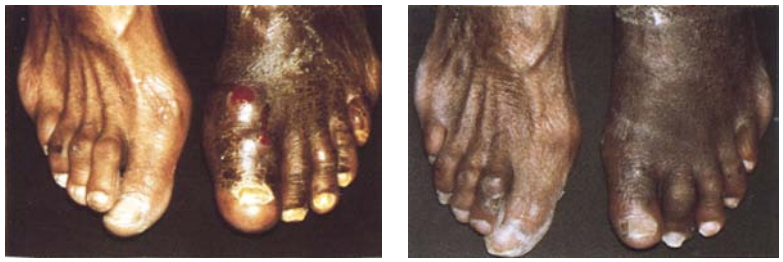

Figure 2. *Left.* Man with chronic osteomyelitis caused by *M. fortuitum* in his left first toe, with two draining sinuses. The wound healed after less than three months of treatment with doxycycline. *Right.* Follow-up picture two years later. A bone biopsy at this time showed only fibrosis.

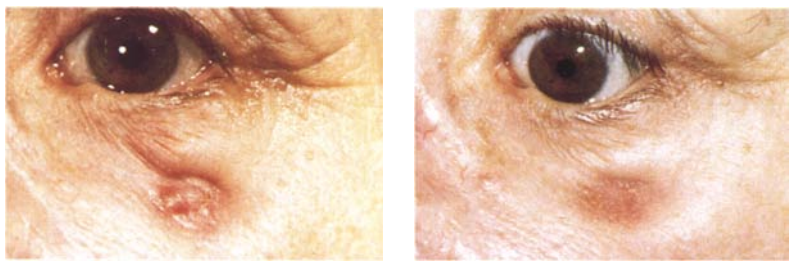

Figure 3. *Left.* Patient with a traumatic fracture of the floor of the orbit. Following insertion of a bone prosthesis, the patient developed a localized infection with *M. fortuitum*. Excision of the nodular lesion at a previous surgery had been unsuccessful. *Right.* The same lesion after six weeks of treatment with oral sulfisoxazole.

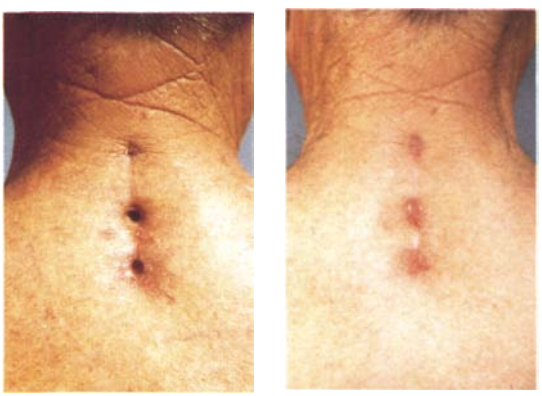

Figure 4. *Left.* Patient with infected cervical laminectomy incision with development of multiple sinus tracts, two of which had been surgically manipulated. *Right.* Appearance of the wound after six months of chemotherapy.

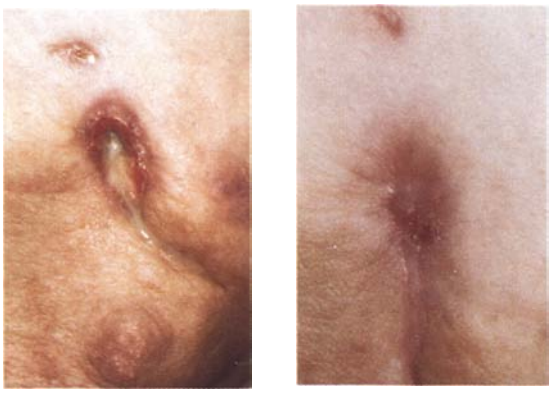

Figure 5. *Left.* Posttraumatic cellulitis of the breast with a draining sinus (*M. chelonei* infection). Note the watery mucoid drainage from the edge of the wound. *Right.* Close-up of the same lesion after three weeks of iv therapy with cefoxitin and amikacin and nine weeks of cefoxitin alone. The patient was well and asymptomatic one year later.

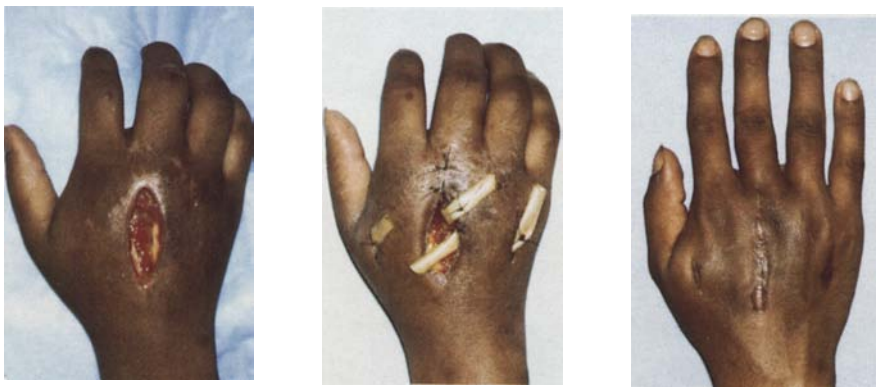

Figure 6. *Left*. Posttraumatic cellulitis and osteomyelitis of the right hand due to *M. fortuitum* following a gunshot wound. A single surgical incision has been made. *Center*. The hand following additional incision and debridement. *Right*. Clinical results after three months of therapy (amikacin plus cefoxitin followed by oral TMP/SMZ). The patient remains well and asymptomatic at six months follow-up after therapy had ceased.

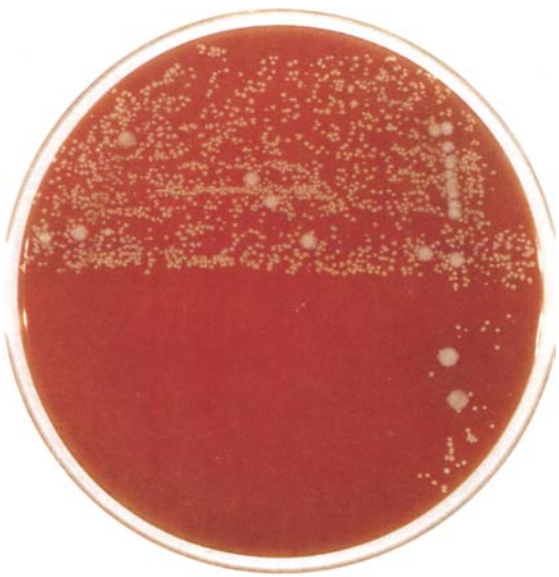

Figure 7. Culture on a blood-agar plate of the wound of a patient infected with *M. fortuitum* before therapy. The small colonies are *M. fortuitum* and the 15–20 large colonies are *Staphylococcus epidermidis*.

spond to topical amikacin with healing of the epithelium, but disease then progressed and keratoplasty was required (cultures were still positive at the time of surgery). As previously noted, two patients treated with surgery alone or receiving no treatment had persistent disease for one and three years, respectively. One patient with localized cellulitis in the hand failed to respond to surgical excision and drainage plus a six-week course of amikacin. After six months the lesions gradually cleared spontaneously. Five (10.6%) of the 47 patients died with active disease.

Five patients were therapeutic failures, including four immunosuppressed patients with disseminated disease. Three responded to combination therapy but relapsed each time therapy was stopped.

Graphic examples of wound infections due to *M. fortuitum* and *M. chelonei* before and after therapy are shown in figures 2–6. Figure 7 shows the primary isolation plate with numerous colonies of *M. fortuitum* obtained from the patient shown in figure 4.

Discussion

Unlike infections of the lung, in which disease due to acid-fast organisms is frequently considered, infections of the skin and soft tissue are seldom considered as primarily due to acid-fast organisms, and hence a delay in diagnosis is the rule rather than the exception. Some of these infections may have a benign course and resolve spontaneously, with no etiologic diagnosis being made. When one evaluates cutaneous disease due to *M. fortuitum* or *M. chelonei* (usually of more than two-months duration), as defined by a positive culture, however, the current study suggests that only 10%–20% of these infections will rapidly resolve without intervention. In a recent outbreak of postinjection abscesses in a group of 13 student nurses, the average time to spontaneous resolution was 8.8 months [7]. The period to resolution was similar in an outbreak following diphtheria-pertussis-tetanus injections in schoolchildren [25]. In a review of 17 infections following augmentation mammaplasty, >80% of infections persisted at least three months and >33% persisted more than six months [3].

In the outbreak of sternal-wound infections due to *M. chelonei* in Charlotte, North Carolina, in 1976 [5], 26% of the patients died, and only patients who had a total sternectomy had a reasonably good outcome. The possible role of chemotherapy with antibacterial agents was unknown at that time, and it was really this outbreak that prompted susceptibility studies of these organisms. Thus, although some infections due to these species are self-limited, others may persist for months to years, and serious disease can result in death.

Previous reports of the successful use of antibacterial agents in the therapy of infections due to *M. fortuitum* and *M. chelonei* on the basis of in vitro susceptibilities are very limited. This reflects the lack of knowledge of the activity of traditional antibacterial agents against these mycobacterial species, the unavailability of susceptibility testing, the absence of standardized methods of susceptibility testing, and the failure of clinicians and bacteriologists to recognize the organism as a pathogen and to know when and where to suspect it. Most of these problems have been resolved in part, but only in the last few years. There are, however, case reports of the successful use of erythromycin [26–28], doxycycline [3, 18], sulfonamides [29, 30], and amikacin [3, 18] on the basis of in vitro susceptibilities, the isolates of which were not included in the current study.

Although this is not a controlled study, we believe the response rate in the current series, when compared with the prior historical controls, provides unequivocal evidence of the benefit to patients (especially with serious infections) of chemotherapy combined with surgical debridement. These measures shorten the duration of disease and may be lifesaving in the occasional patient with life-threatening disease. In our study, 11 of 14 patients with sternal-wound disease were cured, and deaths occurred only in patients with renal failure and multiple medical complications. Of the eight patients with infected mammaplasty incision sites, six were asymptomatic within six weeks of removal of the prosthesis and initiation of specific chemotherapy, and all were successfully treated. Six patients had successful reimplantations, one patient refused reimplantation, and one patient did not have the original prosthesis removed.

On the basis of the results of susceptibility studies in almost 250 isolates of the *M. fortuitum* complex [31] and the results of the current studies, reasonable suggestions for the management of infections due to these organisms can be made. All patients with abscess formation or significant deep infections require surgical incision and drainage with the wound packed open. Persistent drainage occurs for weeks, even in patients with adequate chemotherapy, and

rapid healing of the overlying skin may allow development of subcutaneous abscesses or sinus tracts in the area of the incision (cultures of which are usually negative). Catheters and prosthetic devices should be removed. In infections of sites of augmentation mammaplasty, Toranto [32] has successfully treated these infections by injection of amikacin locally and im, then removing the original prosthesis, debriding the area, and implanting a second prosthesis at the same surgery. Removal of the implants, followed by chemotherapy and subsequent reimplantation appears to work as well. Removal of infected peritoneal dialysis catheters is not always required, but one of the patients infected with *M. fortuitum* failed to respond therapeutically until the catheter was removed, as did one-third of those during two epidemics in patients receiving peritoneal dialysis [3].

For patients with serious infections, initial empirical therapy with amikacin (15 mg/kg per day) plus full-dose cefoxitin (200 mg/kg per day up to 12 g/day) combined with oral probenecid should be used. This will provide two-drug coverage for all isolates except for infrequent amikacin- or cefoxitin-resistant isolates and isolates of *M. chelonei* ssp. *chelonei*, which are all cefoxitin resistant (MICs, ≥128 μg/ml). This two-drug therapy essentially guarantees at least one active drug, and should reduce the risk of acquired drug resistance at a time when the number of organisms present is highest. Susceptibility studies should be performed on all clinically significant isolates. When these results are available, additional decisions can be made. If the isolate is of *M. chelonei* and not susceptible to any oral agent, therapy should be continued as long as possible (at least 12 weeks). If the isolate is cefoxitin susceptible, after four to eight weeks of amikacin the patient can be given cefoxitin only; often treatment can be given on an outpatient basis by using a central venous access device such as a Hickman catheter. We frequently gave these patients 4 g of cefoxitin iv three times per day with prior oral dosing with probenecid. If the isolate is of *M. fortuitum* the dose of amikacin can be lowered somewhat to reduce the risk of toxicity, as the MIC for this species is quite low (0.5–2.0 μg/ml). The risk of mutational resistance to cefoxitin is much less than for amikacin [32a] and for *M. chelonei* ssp. *abscessus* the therapeutic margin is comparable.

If the isolate is susceptible to an oral agent, attempts are still made to control the disease with amikacin and cefoxitin for a minimum of two to six weeks, depending on severity of the disease, then the patient's treatment is changed to the oral agents. The risk of mutational resistance to sulfonamide, minocycline, doxycycline, and erythromycin is low [32a] (no cases were observed in the current study), so that once the patient has had surgical debridement and several weeks of combination therapy, single-agent therapy can be employed with minimal risk of resistance.

For those isolates of *M. fortuitum* biovariant *fortuitum* susceptible to both sulfonamide and doxycycline (~50% of strains), an argument for using both drugs can be made; the response rate with these two drugs may be better than with either drug alone. That possibility is quite reasonable but could not be determined in the current study.

With less serious disease for which the patient is not admitted to the hospital, empirical therapy is much more difficult to choose given the variable susceptibility by subspecies and biovariants, as well as within these groups, to the oral agents. Again, susceptibility testing is essential for choice of the antimicrobal agent. If the time for testing to be done is short, one may wish to await results. If the interval is long, a sulfonamide or a sulfonamide plus erythromycin are the logical choices for treatment. If the isolate is an *M. chelonei* resistant to all oral agents, the decision should be made whether to treat the lesion symptomatically, to try to debride the lesion aggressively, or to admit the patient for therapy with amikacin plus cefoxitin. Patients with minor disease who are getting better spontaneously probably require no chemotherapy.

Recommendations for the duration of drug therapy are harder to make. Patients with minimal localized disease who respond well to chemotherapy appear to require only two to four months of therapy. Patients with extensive disease or osteomyelitis, such as sternal-wound infections, often have positive cultures for ≥12 weeks, so that a minimum of six months of therapy is necessary. In situations in which no oral agent is available, aggressive debridement with a minimum of three months of therapy may be the best that can be done. In general, continuation of therapy for four to six weeks after wound healing provides a good margin of safety and was the usual recommendation given to the patients' local physician in the current study.

Monitoring of therapy and therapeutic responses

in infections due to these mycobacteria is important, especially in serious or life-threatening disease. We found the use of the Schlicter test [33] (SICs) on patients receiving multidrug therapy to be a useful means of checking for adequate serum levels and susceptibility results in a single test. This test proved useful in a previous series of patients with sternal-wound infections due to *M. fortuitum* [34]. Follow-up wound cultures with some measure of the number of organisms is another means for monitoring therapeutic response.

Pulmonary disease was excluded from this series. The majority of patients with pulmonary disease are infected with *M. chelonei* ssp. *abscessus* [1], and oral therapy is not possible. The patients tend to be much older, their disease is often stable and of long duration, and there is less justification for aggressive chemotherapy. We have treated only a small number of these patients. They represent a very different and more difficult group to evaluate, and the success of chemotherapy has not been answered to our satisfaction. Some patients have been successfully treated on the basis of in vitro susceptibilities (once in combination with surgery) [18, 27, 35] and others have been therapeutic failures [36].

Successful chemotherapy is dependent on the availability of reliable susceptibility testing. At present this is available at only a small number of reference laboratories. The methodology is available [12, 17, 23], but few laboratories have used it, in part because of the infrequency of significant isolates. Most mycobacterial laboratories continue to test only against the antituberculous agents, a practice that we feel strongly is a waste of time and money and should no longer be continued. A similar recommendation has been made by the Scientific Assembly on Microbiology, Tuberculosis, and Pulmonary Infections of the American Thoracic Society and is under consideration as an official statement of that society. The relative slowness of major reference laboratories (identification of the organism is often performed before susceptibilities) can be a hindrance in treatment of patients with serious disease, something that results from the fact that these are reference laboratories and not primary clinical laboratories. The development of more readily available testing with good quality control remains a challenge to the microbiology community and is a necessity for optimal chemotherapy of infections due to *M. fortuitum* and *M. chelonei*.

References

1. Wallace RJ Jr, Swenson JM, Silcox VA, Good RC, Tschen JA, Stone MS. Spectrum of disease due to rapidly growing mycobacteria. Rev Infect Dis 1983;**5**:657–79
2. Nontuberculous mycobacterial infections in hemodialysis patients—Louisiana, 1982. MMWR 1983;**32**:244–6
3. Band JD, Ward JI, Fraser DW, Peterson NJ, Silcox VA, Good RC, Ostroy PR, Kennedy J. Peritonitis due to a *Mycobacterium chelonei*-like organism associated with intermittent chronic peritoneal dialysis. J Infect Dis 1982;**145**:9–17
4. Clegg HW, Foster MT, Sanders WE Jr, Baine WB. Infections due to organisms of the *Mycobacterium fortuitum* complex after augmentation mammaplasty: clinical and epidemiologic features. J Infect Dis 1983**147**:427–33
5. Hoffman PC, Fraser DW, Robicsek F, O'Bar PR, Mauney CU. Two outbreaks of sternal wound infections due to organisms of the *Mycobacterium fortuitum* complex. J Infect Dis 1981;**143**:533–42
6. Kuritsky JN, Bullen MG, Broome CV, Silcox VA, Good RC, Wallace RJ Jr. Sternal wound infections and endocarditis due to organisms of the *Mycobacterium fortuitum* complex. Ann Intern Med 1983;**98**:938–9
7. Gremillion DH, Mursch SB, Lerner CJ. Injection site abscesses caused by *Mycobacterium chelonei*. Infect Control 1983; **4**:25–8
8. Borghans JGA, Stanford JL. *Mycobacterium chelonei* in abscesses after injection of diphtheria-pertussis-tetanus-polio vaccine. Am Rev Respir Dis 1973;**107**:1–8
9. Bailey WC, Albert RK, Davidson PT, Farer LS, Glassroth, J, Kendig E Jr, Loudon RG, Inselman LS. Treatment of tuberculosis and other mycobacterial diseases. Am Rev Respir Dis 1983;**127**:790–6
10. Welch DF, Kelly MT. Antimicrobial susceptibility testing of *Mycobacterium fortuitum* complex. Antimicrob Agents Chemother 1979;**15**:754–7
11. Wallace RJ Jr, Jones DB, Wiss K. Sulfonamide activity against *Mycobacterium fortuitum* and *Mycobacterium chelonei*. Rev Infect Dis 1981;**3**:898–904
12. Swenson JM, Thornsberry C, Silcox VA. Rapidly growing mycobacteria: testing of susceptibility to 34 antimicrobial agents by broth microdilution. Antimicrob Agents Chemother 1982;**22**:186–92
13. Wallace RJ Jr, Dalovisio JR, Pankey GA. Disk diffusion testing of susceptibility of *Mycobacterium fortuitum* and *Mycobacterium chelonei* to antibacterial agents. Antimicrob Agents Chemother 1980;**16**:611–4
14. Cynamon MH, Patapow A. In vitro susceptibility of *Mycobacterium fortuitum* to cefoxitin. Antimicrob Agents Chemother 1981;**19**:205–7
15. Dalovisio JR, Pankey GA. In vitro susceptibility of *Mycobacterium fortuitum* and *Mycobacterium chelonei* to amikacin. J Infect Dis 1978;**137**:318–21
16. Casal M, Rodriguez F. In vitro susceptibility of *Mycobacterium fortuitum* and *Mycobacterium chelonei* to cefoxitin. Tubercle 1982;**63**:125–7
17. Stone MS, Wallace RJ Jr, Swenson JM, Thornsberry C, Christiensen L. Agar disk elution method for susceptibility testing of *Mycobacterium marinum* and *Mycobacterium fortuitum* complex to sulfonamides and antibiotics. Antimicrob Agents Chemother 1983;**24**:486–93

18. Dalovisio JR, Pankey GA, Wallace RJ Jr, Jones DB. Clinical usfulness of amikacin and doxycycline in the treatment of infection due to *Mycobacterium fortuitum* and *Mycobacterium chelonei*. Rev Infect Dis 1981; **3**:1068–74
19. Fojtasek MF, Kelly MT. Isolation of *Mycobacterium chelonei* with the lysis-centrifugation blood culture technique. J Clin Microbiol 1982;**16**:403–5
20. Horadam VW, Smilack JD, Smith EC. *Mycobacterium fortuitum* infection after total hip replacement. South Med J 1982;**75**:244–6
21. Carpenter JL, Troxell M, Wallace RJ Jr. Disseminated disease due to *Mycobacterium chelonei* treated with amikacin and cefoxitin: absence of killing with either agent and possible role of granulocytes in clinical response. Arch Intern Med 1984;**144**:2063–5
22. Silcox VA, Good RC, Floyd MM. Identification of clinically significant *Mycobacterium fortuitum* complex isolates. J Clin Microbiol 1981;**14**:686–91
23. Wallace RJ Jr, Swenson JM, Silcox VA, Good RC. Disk diffusion testing with polymyxin and amikacin for differentiation of *Mycobacterium fortuitum* and *Mycobacterium chelonei*. J Clin Microbiol 1982;**16**:1003–6
24. Tentative standard. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Philadelphia: National Committee for Clinical Laboratory Standards, 1983
25. Inman PM, Beck A, Brown AE, Stanford JL. Outbreak of injection abscesses due to *Mycobacterium abscessus*. Arch Dermatol 1969;**100**:141–7
26. Arroyo J, Medoff G. *Mycobacterium chelonei* infection: successful treatment based on a radiometric susceptibility test. Antimicrob Agents Chemother 1977;**11**:763–4
27. Irwin RS, Pratter MR, Corwin RW, Farrugia R, Teplitz C. Pulmonary infection with *Mycobacterium chelonei:* successful treatment with one drug based on disk diffusion susceptibility data. J Infect Dis 1982;**145**:772
28. Poisson M, Beroniade V, Falardeau P, Vega C, Morisset R. *Mycobacterium chelonei* peritonitis in a patient undergoing continuous ambulatory peritoneal dialysis (CAPD). Peritoneal Dialysis Bulletin 1983
29. Tice AD, Solomon RJ. Disseminated *Mycobacterium chelonei* infection: response to sulfonamides. Am Rev Respir Dis 1979;**120**:197–201
30. Santamaría-Jaúregui J, Sanz-Hospital J, Berenguer J, Munoz D, Gomez-Mampaso E, Bouza E. Meningitis caused by *Mycobacterium fortuitum*. Am Rev Respir Dis 1984; **130**:136–7
31. Swenson JM, Silcox V, Wallace RJ Jr, Thornsberry C. Antimicrobial susceptibility of 5 subspecies of rapidly growing mycobacteria [abstract no. 1053]. In: Proceedings of the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1983
32. Toranto IR. Atypical mycobacteria periprosthetic infections—diagnosis and treatment. Plast Reconstr Surg 1980;**66**:226–8

32a. Wallace RJ Jr, Hull SI, Bobey DG, Price KE, Swenson JM, Steele LC, Christensen L. Mutational resistance as the mechanism of acquired drug resistance to aminoglycosides and antibacterial agents in *Mycobacterium fortuitum* and *Mycobacterium chelonei*—evidence based on plasmid analysis, mutational frequencies, and aminoglycoside modifying enzyme assays. Am Rev Respir Dis, 1985 (in press)

33. Schlichter JG, MacLean H, Milzer A. Effective penicillin therapy in subacute bacterial endocarditis and other chronic infections. Am J Med Sci 1949;**217**:600–8
34. Preheim CC, Bittneu MJ, Giger DR, Sanders WE. *Mycobacterium fortuitum* sternotomy infections treated with amikacin, cefoxitin, and rifampin: serum state and killing titers [abstract no. 564]. In: Proceedings of the 22nd Interscience Conference on Antimicrobial Agents and Chemotherapy. Washington, DC: American Society for Microbiology, 1982
35. Wallace RJ Jr, Rosenbaum S. Vomiting and pneumonia: a fortuitous association? Journal of Respiratory Disease 1984:88–94
36. Bevelaqua FA, Kamelhar DA, Campion J, Christianson LC. *Mycobacterium fortuitum–chelonei*—two patients with fatal pulmonary infection. NY State J Med 1981;**81**:1621–4