Sixty-three Cases of Mycobacterium marinum Infection

Clinical Features, Treatment, and Antibiotic Susceptibility of Causative Isolates

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Background: Mycobacterium marinum is a nontuberculous mycobacterium responsible for skin infections. Although cases have been seldom reported, no series of M. marinum infection has been recently reported and the treatment is not standardized.

Methods: A national survey was conducted on culture-confirmed M. marinum infections that occurred in France from January 1, 1996, to December 31, 1998. Clinical characteristics and therapeutic data were analyzed, and the minimum inhibitory concentrations of 11 antibiotics were determined against the causative isolates.

Results: Sixty-three cases of M. marinum infection were studied. In 53 (84%) of the patients, inoculation was related to fish tank exposure. The site of infection was mainly the upper limb (in 60 [95%] of the 63 patients), and infection was spread to deeper structures in 18 (29%) of the patients. All patients were treated with antibiotics (median time, 3½ months), and 30 (48%) underwent surgery. Various antibiotic regimens were prescribed, and the initial regimen was modified in 22 (35%) of the patients. Clarithromycin, cyclines, and rifampin were the most commonly prescribed antibiotics. Cure was observed for 55 (87%) of the patients. Failure was related to deep structure involvement (3 of 45 vs 5 of 18 patients; P=.04) but not to any antibiotic regimen. All strains showed the same susceptibility pattern without acquired resistance. The 90% minimum inhibitory concentrations of rifampin and rifabutin were far lower (0.5 and 0.06 µg/mL, respectively) than the 90% minimum inhibitory concentrations of clarithromycin (2 µg/mL) and the cyclines (minocycline, 4 µg/mL; and doxycycline, 8 µg/mL).

Conclusions: Mycobacterium marinum infections are emerging infections related to fish tank hobby. Because of the severity of the cases with spread of infection, clinical awareness of M. marinum infection and its associated risk factors is important so that the diagnosis can be made and therapy can be initiated promptly.

Arch Intern Med. 2002;162:1746-1752

Mycobacterium marinum is a nontuberculous photochromogenic mycobacterium (group I of the Runyon classification). Mycobacterium marinum causes disease in many fish species from cold or warm, fresh or salted water, and human infection follows contact with fishes or contaminated water. First described as “swimming-pool granuloma,” M. marinum skin infection is often acquired from aquarium maintenance and called “fish tank granuloma.” The infection is commonly limited to a skin disease on the limbs but can spread to deeper structures, resulting in tenosynovitis, arthritis, and osteomyelitis. Disseminated infections are exceptional. The incidence of M. marinum infection in humans is underestimated, but rates of up to 0.27 case per 100,000 inhabitants have been observed. Surgery, antimicrobial therapy, and cryotherapy have been recommended for the treatment of M. marinum infections, but none of these treatments has proved to be superior to another. Antibiotic efficacy and its correlation to in vitro susceptibility are unknown because cases were reported separately in the literature, no therapeutic trial has been done, and data on M. marinum susceptibility are scarce (limited number of strains and antibiotics).

The aim of the present survey, organized by the National Reference Center for Mycobacterial Disease and Drug Resistance (NRC), was to draw recommendations for the treatment of M. marinum infection from the data collected on the culture-positive M. marinum infections that occurred in France. From clinical records, special attention was given to the outcome with regard to the spread of infection to deeper structures, the antibiotics given, and additional surgery.
**PATIENTS AND METHODS**

**PATIENTS**

Anonymous standardized forms were sent at the end of 1996 by the NRC to dermatologists, infectious disease specialists, and microbiologists (Azay-Mycobacterium group) of university hospitals all over France. A case patient was defined as a patient with a culture-positive infection with *M. marinum*. All cases diagnosed and treated between January 1, 1996, and December 31, 1998, were reported, and the corresponding strain was sent to the NRC laboratory (Laboratory of Bacteriology, Groupe Hospitalier Pitié-Salpêtrière, Paris, France).

The following information was collected: patient characteristics (sex and age), immune and human immunodeficiency virus status, fish tank and swimming hobbies, injury and contact with fishes, infection history, site and clinical type of the lesions, spread of infection to deeper structures (tendon, joint, or bone), antimicrobial therapy (name of the antibiotic and date of start and discontinuation), surgery, and clinical outcome. Forms were filled in by the clinicians and microbiologists in charge of the patient. Additional data were collected, when needed, by telephone or written correspondence between the NRC and the clinician or microbiologist. An antibiotic regimen was eligible for efficacy evaluation if it had been given for at least 15 days. Outcome was defined as cure when no sign of infection was observed at the end of treatment or significant improvement was noticed at the end of the follow-up, and as failure when no improvement, after effects, or relapse was observed.

**STRAINS**

The strains of *M. marinum* were grown on Lowenstein-Jensen medium on arrival at the NRC laboratory. They were identified based on the phenotypic characteristics, as previously described, and then stored at -80°C in Youmans broth, supplemented with 20% fetal bovine serum. The minimum inhibitory concentrations (MICs) of 11 antibiotics (rifampin, rifabutin, ethambutol hydrochloride, amikacin, doxycycline, minocycline, clarithromycin, ofloxacin, levofloxacin, ciprofloxacin, and sparfloxacin) were determined by the agar dilution method in Mueller-Hinton agar supplemented with 5% Middlebrook OADC (oleic acid, albumin, dextrose, and catalase) (Fisher Scientific International, Elancourt, France), as previously described.

**ANALYSES**

Data were computerized and analyzed using computer software (Epi Info 6.1; Centers for Disease Control and Prevention, Atlanta, Ga). When appropriate, differences between categories were analyzed using the χ² test for quantitative values and the t test for qualitative values.

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**RESULTS**

**GENERAL CHARACTERISTICS OF THE PATIENTS**

Culture-confirmed infection with *M. marinum* was reported for 66 patients from 1996 to 1998 in France. The incidence of *M. marinum* infection in France was, therefore, about 0.04 case per 100 000 inhabitants per year. Three cases were excluded because of insufficient information on patient outcome. The 63 cases included in the study distributed as 10 cases in 1996, 28 in 1997, and 25 in 1998. The patients included 37 males and 26 females, and their median age was 46 years (range, 4-77 years). A total of 31 hospitals, distributed in all areas of France, reported cases. Exposure to a fish tank in a household with indoor or outdoor aquariums was reported for 53 patients (84%), and death of the tank fishes was reported in 15 of the 23 informed cases. Injury or contact with a fish spine or oysters was reported for 5 patients, and swimming pool hobby was reported for 1. The source of infection was unknown for 4 patients. Four patients had the human immunodeficiency virus, including 2 who had the acquired immunodeficiency syndrome.

**CLINICAL CHARACTERISTICS**

Clinical characteristics by treatment outcome are presented in Table 1. Among the 27 patients with a recorded history of infection, the median time between...
inoculation and the appearance of lesions was 16 days (range, 0-292 days). The site of the skin lesions was the upper limb in 60 (95%) of the 63 patients. Only 3 patients had skin lesions on the lower limb: a hospitalized child, an old woman who owns a fish tank but did not do its maintenance herself, and a child who went to a swimming pool. More than 1 skin lesion was observed in 32 (67%) of 48 patients informed about this item. The clinical description of the skin lesions was reported for 61 patients. Nodules were observed in 41 (67%) of the patients, including a sporotrichoid aspect in 16 (39% of the nodules). The other skin lesions were ulcers, abscesses, and pustules. Adenitis was observed in 10 patients. Deep structure infection (tendon, joint, or bone) was reported in addition to skin lesions for 18 patients: tenosynovitis in 15, arthritis in 7, and osteitis in 3 (arthritis being combined with osteitis in 3 patients and with tenosynovitis in 4) (Figure). Deep structure infection was more common in females than in males (11 of 26 females vs 7 of 37 males; P=.04) but was not related with other characteristics.

A histologic examination was done in 51 (81%) of the 63 patients. Pathologic typical findings of mycobacterial infection were reported for 29 (81%) of the 36 written results that were transmitted.

**TREATMENT**

All 63 patients received antibiotics. The median duration of antibiotic therapy was 3½ months (range, 1-25 months). The duration was significantly longer for patients with deeper structure infections than for patients with infections limited to the skin and soft tissue (median duration, 7½ vs 4 months; P=.004).

One single antibiotic regimen was prescribed for 41 patients, 2 successive regimens were prescribed for 15 patients, and 3 successive regimens were prescribed for 7 patients. The number of successive regimens was not related to general or clinical characteristics (data not shown).

A total of 132 antibiotic prescriptions were given to the 63 patients, ie, a mean of 2 antibiotic prescriptions per patient. The most frequently prescribed antibiotics were clarithromycin, cyclines, including minocycline and doxycycline, rifampin, and ethambutol. All patients received at least 1 of these antibiotics. The antibiotics administered and the number of their courses are listed in **Table 2** by treatment outcome and the severity of the infection (spread to deeper structures).

Antibiotic therapy was given as a monotherapy in 23 patients (37%) and as a combination of at least 2 drugs in 40 patients (63%). Antibiotics prescribed as a monotherapy were cyclines for 19 patients (minocycline for 14 and doxycycline for 5) and clarithromycin for 4 patients. Monotherapy was significantly associated with infection limited to skin and soft tissue (20 of 45 vs 3 of 18 patients; P=.04). Frequent drug combinations were clarithromycin plus rifampin (n=20), cyclines plus clarithromycin (n=11 [n=4 with doxycycline and n=7 with minocycline]), rifampin plus ethambutol (n=8), and cyclines plus rifampin (n=6 [n=3 with doxycycline and n=3 with minocycline]).

Cyclines were prescribed more for infection limited to skin and soft tissue than for infection spread to deeper structures. In contrast, rifamycins (rifampin and rifabutin) and ethambutol were prescribed more for infection spread to deeper structures than infection limited to skin and soft tissue; clarithromycin was equally prescribed in both cases (Table 2).

In addition to antibiotics, 30 patients underwent surgery for excision or debridement, including 17 with infection limited to skin and soft tissue and 13 with infection spread to deeper structures. Conversely, no surgery was performed for 5 patients with deep structure infection (2 with arthritis, 1 with tenosynovitis, 1 with tenosynovitis and arthritis, and 1 with osteitis, tenosynovitis, and arthritis) and for 28 with infection limited to the skin and soft tissue. Surgery was indeed associated with deep structure infection (13 of 18 vs 17 of 45 patients; P=.01) but not with other characteristics (sex, age, aspect and site of the lesion, and outcome).

**OUTCOME**

The outcome was evaluated for the 63 patients: 55 (87%) were cured and 8 (13%) experienced treatment failure. The patients in whom treatment failed are described in **Table 3**. Failure was significantly related to infection spread to deeper structures (3 of 45 vs 5 of 18 patients; P=.04) and to the skin lesion aspect of the ulcer (4 of 6 vs 4 of 49 patients; P=.02). Infections in human immunodeficiency virus–positive patients (n=4) were not different from those in human immunodeficiency virus–negative patients with regard to the source of infection, clinical characteristics, and outcome.

The efficacy of antibiotic therapy was evaluated by the number of failures according to the number of prescriptions and the severity of the infection (spread to deeper structures). Failure was not related to the prescription of one specific antibiotic or regimen or to the duration of the treatment (median, 6 vs 5 months; P=.13).

For infections limited to skin and soft tissue, cure was observed in 42 (93%) of 45 patients, including 20 undergoing monotherapy (16 received cyclines and 4 received clarithromycin). The 3 patients in whom treat-
For infections spread to deeper structures, treatment with a combination of 2 antibiotics, among cyclines, clarithromycin, and rifampin, resulted in cure of most (13 of 18 patients). However, 4 of the 5 patients in whom treatment failed (patients 4, 5, 6 and 8, detailed in Table 3) were also treated with a combination of clarithromycin with rifampin, rifabutin, or cyclines for a minimum of 2 months. Of these 4 patients, 3 had received corticosteroids before the diagnosis. Unfortunately, because we did not record the information on corticosteroid therapy for all the patients, we could not evaluate it as a risk factor.

### Table 2. Antibiotic Courses Given to Patients With a *Mycobacterium marinum* Infection With Regard to the Spread of Infection and the Outcome*

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Total Courses</th>
<th>SSTIs</th>
<th>DSIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Claritythromycin</td>
<td>39</td>
<td>24</td>
<td>15</td>
</tr>
<tr>
<td>Minocycline</td>
<td>24</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>11</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Rifampin</td>
<td>21</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>4</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Ethambutol hydrochloride</td>
<td>13</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Sparfloxacin</td>
<td>3</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Amikacin</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pristinamycin</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Amoxicillin plus clavulanate potassium</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sulfamethoxazole plus trimethoprim</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

*SSTI indicates infection limited to skin and soft tissue; and DSI, infection spread to deeper structures.

### Table 3. Characteristics of Patients With *Mycobacterium marinum* Infection in Whom Treatment Failed*

<table>
<thead>
<tr>
<th>Patient No./ Sex/ Age, y</th>
<th>Exposure</th>
<th>Type of Skin Lesion</th>
<th>Site</th>
<th>DSI</th>
<th>Antibiotic (MIC)</th>
<th>Duration</th>
<th>Surgery</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/F/47</td>
<td>Fish tank</td>
<td>Sporotrichoid</td>
<td>Hand</td>
<td>No</td>
<td>Clarithromycin (0.5) and minocycline (2)</td>
<td>8 mo</td>
<td>Yes</td>
<td>No improvement</td>
</tr>
<tr>
<td>2/M/49</td>
<td>Fish tank</td>
<td>Ulcer</td>
<td>Hand and arm</td>
<td>No</td>
<td>Minocycline (4)</td>
<td>15 d</td>
<td>Yes</td>
<td>Relapse</td>
</tr>
<tr>
<td>3/M/40</td>
<td>Fish tank</td>
<td>Papule</td>
<td>Arm</td>
<td>No</td>
<td>Ethambutol hydrochloride (2)</td>
<td>5 mo</td>
<td>No</td>
<td>Relapse</td>
</tr>
<tr>
<td>4/M/47</td>
<td>Fish tank</td>
<td>Nodule</td>
<td>Hand</td>
<td>No</td>
<td>Clarithromycin (1) and rifampin (0.5)</td>
<td>6 mo</td>
<td>Yes</td>
<td>Relapse</td>
</tr>
<tr>
<td>5/F/39</td>
<td>Oyster contact</td>
<td>Ulcer</td>
<td>Hand</td>
<td>Yes</td>
<td>Rifampin (0.06), ethambutol (2), and clarithromycin (0.25)</td>
<td>2 mo</td>
<td>Yes</td>
<td>Aftereffects</td>
</tr>
<tr>
<td>6/F/49</td>
<td>Fish contact</td>
<td>Abscess</td>
<td>Hand</td>
<td>No</td>
<td>Ethambutol (0.06) and ethambutol (2)</td>
<td>2 mo</td>
<td>Yes</td>
<td>Aftereffects</td>
</tr>
<tr>
<td>7/F/57</td>
<td>Fish tank</td>
<td>Ulcer</td>
<td>Arm</td>
<td>Yes</td>
<td>Clarithromycin (4) and ciprofloxacin (8)</td>
<td>3 wk</td>
<td>No</td>
<td>No improvement</td>
</tr>
<tr>
<td>8/F/24</td>
<td>Unknown</td>
<td>Ulcer</td>
<td>Leg</td>
<td>Yes</td>
<td>Isoniazid (ND), rifampin (0.5), ethambutol (4), and pyrazinamide (ND)</td>
<td>15 d</td>
<td>No</td>
<td>No improvement</td>
</tr>
</tbody>
</table>

*DSI indicates infection spread to deeper structures; MIC, minimum inhibitory concentration in micrograms per milliliter; and ND, not determined.

### ANTIBIOTIC MICs

The MICs were determined for the 11 antibiotics that were given to the patients (rifampin, rifabutin, ethambutol, amikacin, doxycycline, minocycline, clarithromycin, and fluoroquinolones [including ofloxacin, levofloxacin, ciprofloxacin, and sparfloxacin]) against all the strains isolated from the 63 patients but 2 (because of insufficient growth). For each antibiotic, the MICs were distributed in a narrow range, and the modal MIC was close to the 50% MIC and to the geometric mean MIC (Table 4). The MICs of rifampin and rifabutin were lower than the MICs of the other antibiotics (90% MIC of 0.5 and 0.06 µg/mL, respectively). The MICs of the cyclines, clarithromycin, clarithromycin, and rifampin, resulted in cure of most (13 of 18 patients). However, 4 of the 5 patients in whom treatment failed (patients 4, 5, 6 and 8, detailed in Table 3) were also treated with a combination of clarithromycin with rifampin, rifabutin, or cyclines for a minimum of 2 months. Of these 4 patients, 3 had received corticosteroids before the diagnosis. Unfortunately, because we did not record the information on corticosteroid therapy for all the patients, we could not evaluate it as a risk factor.
and Farr18 (21 days). From the literature, only half of the report is not different from that reported by Jernigan. Cleaning of swimming pool water associated cases are rare because of the implementation of disinfecting practices.22

There was no difference between the geometric mean MICs for strains isolated from patients who were cured and the geometric mean MICs for strains isolated from patients in whom treatment had failed (data not shown). Acquired resistance to an antibiotic was not observed in strains isolated from either cured patients or patients in whom treatment had failed.

We reported 63 cases of culture-confirmed M. marinum infection during a 3-year period. It is, to our knowledge, the largest series reported in the literature.19,20 Infectious diseases caused by nontuberculous mycobacteria, including M. marinum and Mycobacterium ulcerans, that cause skin infections have increased in healthy and in immunocompromised patients in the past decade and may be considered as emerging infections.17 Infection with M. marinum follows contact with a fish tank or shellfish and results in skin infections because the M. marinum optimal growth temperature is 30°C.2 The incubation period is difficult to evaluate because patients with a fish tank in the household might be contaminated at each cleaning. The median incubation time of 16 days that we report is not different from that reported by Jernigan and Farr18 (21 days). From the literature, only half of the M. marinum cases reported were associated with aquarium exposure,18 in contrast to 53 (84%) of the cases associated with a fish tank in the present study. Fish tank hobby is obviously the main risk factor for M. marinum infection, although the prevalence of infection among fish tank owners is not known. However, M. marinum is rarely isolated from dead fishes or tank water.19-21 As confirmed by the report of only 1 case in our study, swimming pool-associated cases are rare because of the implementation of swimming pool water-disinfecting practices.22

Infection was more frequent in males than in females, as reported in other studies,23 but in contrast with the study by Edelstein.3 The clinical presentation in our patients was relatively similar to that from other studies for the site and the aspect of the lesions. In most cases, the upper limb was affected, which is related to fish tank exposure. The most common clinical appearance was a cutaneous nodule with a frequent sporotrichoid aspect, as reported in other studies.24 In our survey, the spread of infection to deeper structures concerned one third of the patients, contrary to other studies, in which it was rare.3 Because our study was restricted to culture-confirmed M. marinum cases of infection, it is probable that severe cases, which are more frequently investigated, were reported preferentially. These severe cases justify the search for the most effective therapy. Spread to deeper structures (arthritis, tenosynovitis, and osteitis) was more frequent in females than in males. This might be explained by the prescription of corticosteroids before the diagnosis, which is common in the case of female rheumatic disease and might have facilitated the spread of infection.25

Optimal treatment of M. marinum infection has not been established yet. The infection probably resolves spontaneously in some cases, although complete resolution may take up to 2 years.2,26 Surgery, cryotherapy, x-ray therapy, electrodesiccation, and different antibiotic regimens have been reported to cure the infected patients.3 The choice of the therapy seemed to be based more on personal experience and the preference of individual researchers than on the demonstrated efficacy of one or another therapy.3 Recent clinical reports27 suggest that antibiotic therapy alone is enough to cure most of the patients and that additional surgical debridement cures the remaining patients.

In our study, all patients were treated with antibiotics. To our knowledge, no study has compared different antibiotic regimens. In the literature, various antibiotics have been used, including cyclines, a combination of sulfamethoxazole and trimethoprim, rifampin plus ethambutol, and, more rarely, clarithromycin, levofloxacin, and amikacin.1,2,3,28,29 Cure and failure have been described with all of these drugs.23,29 The optimal duration of therapy also varied markedly in the literature, ranging from 6 weeks to 1 1/2 years.25 In our study, the duration of therapy ranged from 1 to 25 months (median, 3 1/2...
months). This duration was significantly longer for patients with infection spread to deeper structures, except for the patients in whom treatment failed. In these latter patients, the duration of treatment was too short.

To draw recommendations for a standardized treatment, we sought to evaluate the outcome by antibiotic regimens. Fifty-five (87%) of the patients were cured after therapy that included clarithromycin, rifampin, or cyclines. However, patients in whom treatment failed were observed among those treated with the same antibiotics. Consequently, a favorable treatment outcome could not be related to any specific antibiotic, consistent with the literature review.3,23,30

No treatment failure was related to a strain of *M. marinum* with acquired resistance to any antibiotic. Acquired resistance has been described in patients with mycobacterial infections only for drugs with a potent activity, such as streptomycin sulfate in patients with tuberculosis31 or clarithromycin in patients with *Mycobacterium avium* infection.32 Acquired resistance has not been described for *M. marinum* yet. This might indicate that none of the antibiotics given has a potent activity against *M. marinum*. This is confirmed by the in vitro susceptibility results of this study, which showed that *M. marinum* has a natural multidrug resistance pattern, as suspected by the results of other studies.12,13,14

Rifamycins, rifampin, and rifabutin are the only antibiotics that have low MICs and MICs close to those found for *Mycobacterium tuberculosis*. However, this was not fully correlated with the in vivo efficacy because 5 patients (who underwent a total of 5 courses of rifampin and 2 of rifabutin) in whom treatment failed had received rifamycins with a long duration of therapy (9, 7, 6, 4, and 4 months). The MICs of minocycline, doxycycline, clarithromycin, and amikacin were moderate values close to those reported for other atypical mycobacteria. Comparable values of MICs were observed for clarithromycin and amikacin against *M. avium* and for cyclines and amikacin against rapidly growing mycobacteria.34,35,36 Which have been correlated with in vivo efficacy.23,30 Only 2 treatment failures were observed with cyclines, but most of the patients treated by cyclines, and especially by cyclines alone, had infection limited to the skin and soft tissue. The MICs of ethambutol, ciprofloxacin, ofloxacin, and levofloxacin were far above the concentration break points and, consequently, in vivo efficacy was less probable. Failure was indeed observed in half of the patients treated with these antibiotics. The activity of the new fluoroquinolone, sparflloxacin (even its MICs were lower than those of the classic fluoroquinolones), has still to be demonstrated; in our study, 3 patients were treated with sparflloxacin, and treatment failed in 1.

Surgery seemed frequently inadequate to Chow et al.27 In our study, surgery was consistently done for most of the infections spread to deeper structures but also for 17 (38%) of the 45 patients with infections limited to skin and soft tissue, without clear benefit (surgery was performed in 5 of the 8 patients in whom treatment failed) and with unknown adverse effects. The place of surgery in the treatment of *M. marinum* infection needs to be evaluated with regard to the severity of the infection.

In upcoming years, the incidence of *M. marinum* infections might increase,17 as fish tank hobby and aquarium tourism increase in popularity. In addition to the treatment evaluation, preventative strategies should be developed for fish tank activity, such as wearing gloves when cleaning the tank.18

Accepted for publication November 15, 2001.

This study was supported by University of Paris VI (research group UPRES EA 1541), association Raoul Folliere, and association Claude Bernard, all located in Paris, France.

This study was presented in part at the 40th International Conference on Antimicrobial Agents and Chemotherapy, Toronto, Ontario, September 19, 2000.

This study was organized with the collaboration of the Groupe pour l’Étude et le Traitement des Infections à Mycobactéries and the Groupe Azay-Mycobactéries (groups of mycobacteriologists working in university hospitals) and with clinicians from the dermatology and infectious diseases departments of university hospitals. Vincent Jarlier, MD, PhD, and Jacques Grosset, MD, PhD, directors of the NRC, contributed to the design of the study and provided helpful discussion regarding the results. The following colleagues collected the data and sent the strains of *Mycobacterium marinum* and the information on patients included in the study: X. Gisconti, MD (Albi); Y. Douadi, MD, P. Esquenet, MD, H. Laurans, MD, C. Lok, MD, J.-L. Schmitt, MD (Amiens); E. Carpentier, MD, J.-L. Verret, MD (Angers); B. Hautefort, MD (Arles); C. Boval-Gallet, MD (Bligny); M.-S. Doutré, MD, B. Geniaux, MD, P. Mouton, MD, J. Texier-Mauguin, MD (Bordeaux); M.-L. Abalain, MD (Brest); A. Dompmartin, MD, M. Fines, MD, B. Malbruny, MD (Caen); M. Drochon, MD (Chateauroux); F. Gouadron, MD, J. Sirot, MD (Clermont Ferrand); E. Hachulla, MD, C. Savage, MD, J.-M. Bonnet-Blanc, MD (Lille); C. Martin, MD (Limoges); C. Grange-Blanquie, MD (Marseille); M.-J. Gevaudan, MD (Marseille); J.-F. Cuny, MD, A. Didion, MD (Metz); P. Cantot, MD, M. Dailloux, MD (Nancy); P. Bemer-Melchior, MD (Nantes); A. Le Coustumier, MD (Neuchâtel); F. Guillouët-Salvador, MD (Nice); A. Goubry, MD, B. Guillot, MD, J. Jourdan, MD (Nimes); B. Cadot, MD (Orsay); P. Di Maria, MD (Paris); G. Paul, MD, X. Puechal, MD, P. Robin, MD (Paris-Cochin); M. Bagot, MD, I. Bournerias, MD, L. Desforges, MD, H. Kanesi, MD, P. Wolkenstein, MD (Paris-Henri Mondor); X. Liote, MD, M.-J. Sanson Le Pors, MD (Paris-Lariboisière); C. Truffot-Pernot, MD (Paris-Pitié-Salpêtrière); F. Caux, MD, C. Dumontier, MD, V. Lalande, MD (Paris Saint-Antoine); O. Bajolet-Laudinat, MD, I. Beguinot, MD, P. Bernet, MD, L. Brasme, MD, A. Strady, MD (Reims); A. Carricajo, MD, H. Roussel, MD (Saint-Etienne); R. Bauriaud, MD, E. Bonnet, MD, J. Gallardo, MD, V. Marc, MD, S. Sicard, MD (Toulouse); E. Buy, MD, J. Unanue, MD (Villeneuve sur Lot).

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