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MAJOR ARTICLE

Fishing for a Diagnosis, the Impact of Delayed Diagnosis on the Course of *Mycobacterium marinum* Infection: 21 Years of Experience at a Tertiary Care Hospital

Natalia E. Castillo, Pooja Gurram, M. Rizwan Sohail, Madiha Fida, and Omar Abu Saleh

Division of Infectious Diseases, Mayo Clinic College of Medicine and Science, Rochester, Minnesota, USA

Background. *Mycobacterium marinum* is a common but underreported mycobacterial infection. We conducted a large retrospective study to determine risk factors and describe the therapeutic interventions and outcomes in patients with uncomplicated and complicated *M. marinum* infection.

Methods. Culture-confirmed *M. marinum* infection cases were identified from the Mayo Clinic Clinical Mycology Laboratory from January 1998 to December 2018. Complicated *M. marinum* infection was defined as the presence of tenosynovitis, septic arthritis, or osteomyelitis. Differences in complicated vs uncomplicated *M. marinum* infections were analyzed using statistical comparisons.

Results. Twelve cases had a complicated *M. marinum* infection. Patients with a complicated infection were older (64.3 ± 11.1 vs 55.8 ± 14.5; $P = .03$), had longer duration of symptoms (5 vs 3 months; $P = .011$), and had more surgical debridements (1 vs 0; $P < .001$). Length of treatment and number of drugs used were not statistically significant. Complicated *M. marinum* cases received more medications (2 vs 1; $P = .263$) and were treated longer (5.7 vs 3.5 months; $P = .067$). Antibiotic susceptibilities were performed in 59% of the patients. All isolates were susceptible to clarithromycin. From the tetracyclines, doxycycline had a better susceptibility pattern.

Conclusions. *M. marinum* infection is an important cause of skin and soft tissue infection. Poor water exposure documentation, unusual clinical presentation, and empiric antibiotic treatment before definitive *M. marinum* diagnosis often contribute to a delayed diagnosis. Complicated *M. marinum* cases had longer duration of symptoms and more surgical debridements. No difference in the number of drugs used or clinical outcome was observed.

Keywords. clarithromycin; complicated infection; *Mycobacterium marinum*; skin and soft tissue infection.

Mycobacterium marinum or "fish tank granuloma" is a pathogenic, nontuberculous mycobacterium (NTM) that has been associated with skin, soft tissue, joint, bone, and disseminated infections [1]. It is an endemic fish pathogen widely distributed in aquatic environments such as fish tanks, swimming pools, and natural bodies of water [2]. Despite increasing numbers of cases reported in recent years, the diagnosis of *M. marinum* is often missed or delayed.

M. marinum infections are typically a subject of case reports or small case series, with great variation in diagnostic approach and therapeutic interventions [3]. By conducting this study in a large cohort of patients with biopsy-proven *M. marinum* infection, we sought to determine risk factors and describe and compare the therapeutic interventions and outcomes in patients with uncomplicated and complicated *M. marinum* infection.

METHODS

We retrospectively reviewed computer-generated records from the Mayo Clinic Clinical Mycology Laboratory from January 1998 to December 2018 using the laboratory information management system. From January 1998 to July 2014, all cases of culture-confirmed infection with *M. marinum* were identified using 16S/D2 Fast Sequencing [4]. From July 7, 2014, to December, 2018, most of the cases of culture-confirmed infection with *M. marinum* were identified using matrix-assisted laser desorption/ionization–time of flight (MALDI-TOF) [5].

Electronic medical records of all patients who had provided research use authorization during the study period were reviewed to identify demographic, clinical, microbiologic, treatment, and outcome data. Underlying comorbidities, immune status, clinical presentation, laboratory findings, and susceptibility patterns were tabulated. We collected and managed study

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Correspondence: O. Abu Saleh, MD, Division of Infectious Diseases, Department of Medicine, 200 First Street SW, Rochester, MN 55905 (abusaleh.omar@mayo.edu).

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data using Research Electronic Data Capture (REDCap) electronic data capture tools, hosted at the Mayo Clinic [6].

Definitions

Cases were classified as uncomplicated if *M. marinum* infection was limited to cutaneous or subcutaneous tissue. Complicated *M. marinum* infection was defined if tenosynovitis, septic arthritis, or osteomyelitis was present radiographically or noted during surgical exploration. Cases with positive blood cultures for *M. marinum* were also classified as complicated.

An immunocompromised state was defined as immunosuppression due to the presence of any autoimmune condition, solid organ/bone marrow transplant, chronic corticosteroid use (prednisone equivalent of ≥5 mg/d for at least 1 month), or other immune-suppressive medication use. Patients were classified as having active malignancy if they had advanced metastatic disease or were undergoing chemotherapy or radiation therapy at the time of the occurrence of *M. marinum* infection.

Water exposure was defined as any documented contact to lake water, salt water, fish tank, or aquarium. Fever, tachycardia, hypotension, weight loss, night sweats, and lymphadenopathy were recorded as systemic symptoms. Time to diagnosis was defined as the time from symptom onset to culture-confirmed *M. marinum* infection. Time to culture positivity was defined as the time from sample collection to culture-confirmed *M. marinum* infection. Surgical debridement was defined as bedside incision and drainage, and/or irrigation and debridement done in the operating room (OR). Punch biopsy was considered part of a diagnostic procedure.

An *M. marinum* antimicrobial regimen was defined as a pathogen-directed therapy regimen used for >50% of the total duration of therapy. Treatment duration was defined as the total number of months of pathogen-directed therapy for *M. marinum*. Treatment outcomes were defined as cure if there was no evidence of disease after cessation of therapy or if subsequent documentation after the diagnosis of *M. marinum* did not mention persistence or recurrence of disease. *M. marinum* infection was defined as recurrent if there were new clinical findings on physical exam and/or imaging and microbiologic or histopathologic evidence of disease after cessation of therapy. *M. marinum* cases who were lost to follow-up or had no documentation of outcome in any subsequent medical records were excluded from outcome analysis.

Statistical Analysis

Statistical analysis was performed using JMP, version 14.1.0 (SAS Institute Inc., Cary, NC, USA). Descriptive information about patients with *M. marinum* infection was reported as frequencies and proportions for categorical variables and mean ± SD or median (interquartile range [IQR]) for continuous variables. Time differences for categorical variables among groups (complicated vs uncomplicated *M. marinum* infection) were tested using the chi-square test or Fisher exact test, as appropriate. Differences between continuous variables in the 2 study groups were tested using a 2-sample *t* test and Wilcoxon–Mann-Whitney test, after assessing variables for normality with the Shapiro-Wilk normality test. A *P* value <.05 was considered statistically significant.

Ethics

This study was reviewed and approved by the Institutional Review Board at the Mayo Clinic.

RESULTS

General Characteristics of the Patients

Forty-six cases of culture-confirmed infection with *M. marinum* were included (Table 1). Twelve cases (26%) presented with a complicated *M. marinum* infection. The median time to diagnosis (IQR) was 3.6 (2.3–6.1) months. Only 15 cases (33%) had documented water exposure during the initial evaluation, compared with 33 cases (73%) after microbiology diagnosis was confirmed ($P < .001$). Most of the patients were immunocompetent, and only 2 patients had a solid organ transplant (kidney and kidney/pancreas transplant) (Table 1).

The median symptom duration when patients sought medical attention (IQR) was 24 (9–246) days. Most of the *M. marinum* infections were localized in the upper extremity. Two-thirds of the patients presented with superficial skin nodules, papules, and erythematous plaques (Table 2). Only 4 patients had systemic symptoms: 2 patients had fever, 2 patients had night sweats, and 1 patient presented with hypotension and weight loss in the clinical context of active malignancy.

Laboratory findings are summarized in Table 2. All patients in whom sporotrichosis serology was ordered (39%) had a negative result. Eight patients (17.3%) had a tuberculin skin test (TST) and/or QuantiFERON–TB Gold test (QFT) performed. Only 1 patient had a positive TST with a positive QFT and was treated for latent tuberculosis after completing therapy for *M. marinum* infection. Two out of the 3 patients had a false-positive QFT (weakly positive tuberculosis Ag minus nil), and the third case had a history of latent tuberculosis as a child.

A punch biopsy was performed in 33 patients (71.3%). Eighty-five percent of uncomplicated *M. marinum* cases had a punch biopsy compared with 33.3% of complicated *M. marinum* cases ($P = .001$). Bedside incision and drainage were performed in 9 patients (18.5%). No statistically significant differences were observed between complicated and uncomplicated *M. marinum* groups for bedside incision and drainage (23.5% vs 8.3%; $P = .409$). Nineteen patients (41.3%) were taken to the OR for irrigation and debridement. Patients with complicated *M. marinum* infection required significantly more procedures in the OR (91.7% vs 23.5%; $P < .001$) compared with uncomplicated *M. marinum* cases (Table 3). Only 9 cases had >1 surgical

Table 1. Baseline Characteristics

Patient Demographics	n = 46
Age, mean ± SD, y	58 ± 14.05
Female, No. (%)	18 (39)
Male, No. (%)	28 (60.9)
White, No. (%)	41 (89.1)
Comorbidities, No. (%)	
Obesity	5/30 (16.7)
Diabetes	5 (10.8)
CKD stage 3	8/27 (29.6)
Autoimmune disordera	5 (10.8)
Active malignancy	1 (2.2)
Immunosuppression	8 (17.4)
Transplant	2 (4.3)

Abbreviation: CKD, chronic kidney disease.

[a]Autoimmune disorder: Crohn's disease, diabetes mellitus type 1, rheumatoid arthritis, ulcerative colitis, and polymyalgia rheumatica.

debridement performed in the OR, with a median (IQR) of 2 (2–5) surgical procedures.

The median time to culture positivity (IQR) was 3.5 (2.8–4.8) weeks. From all 46 cases, histopathologic examination was positive for granulomas in 74% of the cases. Seven cases (15.2%) had a positive auramine-rhodamine stain, and 3 cases (6.5%) had a positive Ziehl-Neelsen stain during histopathologic evaluation. Six cases of culture-confirmed infections with *M. marinum* were polymicrobial and were deemed not clinically significant. The most common organisms in these cases were *Corynebacterium species* (1 colony), *Cutibacterium acnes* (from broth only), coagulase-negative staphylococci, *Brevundimonas diminuta,* and *Penicillium* species. Most of these organisms are nonpathogenic and/or part of the skin flora.

Table 2. Clinical Presentation and Laboratory Findings at Initial Presentation

Clinical Presentation	n = 46
Upper extremity lesions, No. (%)	43 (93.5)
Redness, No. (%)	28 (61)
Pain, No. (%)	25 (54.3)
Abscess, No. (%)	9 (19.6)
Skin manifestations,a No. (%)	34 (74)
Lymphangitis, No. (%)	12 (26.1)
Constitutional symptoms, No. (%)	4 (8.7)
Symptom duration, median (IQR), d	24 (9–246)
Laboratory findings	
WBC, mean ± SD, ×10(9)/L	6.2 ± 2.2
Platelets, median (IQR), ×10(9)/L	243 (197–281)
Creatinine, mean ± SD, mg/dL	1.08 ± 0.2
ESR, median (IQR), mm/h	5 (1.5–13.5)
CRP, median (IQR), mg/L	3 (0.6–8.35)
Time of positive culture, median (IQR), wk	3.5 (2.8–4.8)

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IQR, interquartile range; WBC, white blood cell count.

[a]Skin manifestations include nodules, papules, and plaques.

Treatment

Sixty-five percent of the patients (28/43) received antibiotics alone for suspected bacterial skin and soft tissue infection (SSTI) before *M. marinum* diagnosis. The 2 most commonly prescribed classes of antibiotics were cephalosporins (46%) and penicillins (29%). Twenty-one percent (6/28) of the patients received antifungal medication, and 5 out of these 6 patients (83%) received itraconazole.

An *M. marinum*–directed antibiotic regimen was prescribed to 43 patients (93%). Three cases (7%) did not receive treatment. One patient expired due to malignancy before diagnosis was established, the second was lost to follow-up (before antibiotic initiation), and the third patient was cured only with excision. Monotherapy was prescribed in 52.1% of the patients, with trimethoprim and sulfamethoxazole (TMP/SMX) being the most common monotherapies (38%), followed by tetracyclines (33%) and clarithromycin (17%). Eleven cases (25%) received a 2-antibiotic regimen that included macrolides in 91% of the cases, in addition to tetracycline (n = 4), TMP/SMX (n = 3), rifampin (n = 2), rifabutin (n = 1), and ethambutol (n = 1). About one-third of the patients (12/43) who started therapy were lost to follow up.

Twenty-five percent of the patients (11/43) reported adverse effects from antibiotics. Nausea was the most common side effect (45%), followed by hepatitis (18%), hyperkalemia (9%), rash (9%), and optic neuropathy (9%). Rifampin and ethambutol were discontinued due to hepatitis. TMP/SMX, doxycycline, and ethambutol were identified as the culprit for hyperkalemia, rash, and optic neuropathy, respectively.

The median duration of antibiotic therapy (IQR) was 4.5 (3–6.4) months. Overall, treatment duration was longer in patients with complicated *M. marinum* infection compared with patients with uncomplicated infection; however, this difference was not statistically significant (Table 3). Patients with complicated *M. marinum* infection were older and had more surgeries per case. A delay in diagnosis was more common in patients with complicated *M. marinum* infection (Table 3).

Antibiotic Susceptibilities

Twenty-seven patients (59%) had susceptibilities performed; minimum inhibitory concentrations were not documented in all isolates. All isolates were susceptible to clarithromycin, rifabutin, and rifampin (except for 1 isolate that was resistant to rifampin). The majority of the isolates (88%) were susceptible to TMP/SMX. All isolates that were tested (n = 9) were susceptible to linezolid (Table 4). Based on susceptibilities, antibiotic therapy was modified in 17.4% of cases (Table 5). No differences in cure rates between *M. marinum* infection groups (uncomplicated vs complicated) were observed.

Table 3. Uncomplicated vs Complicated *M. marinum* Infection

	Uncomplicated (n = 34)	Complicated (n = 12)	*P* Value[a]
Female, No. (%)	15 (45.7)	3 (25)	0.315
Male, No. (%)	19 (52.3)	9 (81.8)	
Age, mean ± SD, y	55.8 ± 14.5	64.3 ± 11.1	**0.030**[c]
Immunosuppression, No. (%)	6 (17.7)	2 (16.7)	1.000
DM, No. (%)	4 (11.8)	1 (8.3)	1.000
WBC, mean ± SD, ×10(9)/L	5.9 ± 2.0	6.8 ± 2.4	0.299
Platelets, median (IQR), ×10(9)/L	243 (197–273)	237 (176–297)	0.741
Creatinine, mean ± SD, mg/dL	1.1 ± 0.3	1.1 ± 0.2	1.000
ESR, median (IQR), mm/h	5 (2–12)	9.5 (1.3–14.3)	0.642
CRP, median (IQR), mm/h	1.8 (0.4–3)	3 (0.6–48)	0.138
Duration of symptoms before diagnosis, median (IQR), d	21.5 (9–201.5)	36 (15.3–101.5)	0.298
Time to diagnosis, median (IQR), mo	3 (2–6)	5 (4–15)	**0.011**[c]
No. of surgical debridements,[b] median (IQR)	0 (0–0.25)	1 (1–2)	**<.001**[c]
No. of drugs used, median (IQR)	1 (1–2)	2 (1–2.75)	0.263
Length of treatment, median (IQR), mo	3.5 (2–6.2)	5.7 (4–8.3)	0.067

Abbreviations: CRP, C-reactive protein; DM, diabetes mellitus; ESR, erythrocyte sedimentation rate; IQR, interquartile range; WBC, white blood cell count.

[a]The 2-sample Wilcoxon test was used to calculate *P* values for continuous nonparametric variables. The 2-sample *t* test was used to calculate *P* values for continuous parametric variables. The Pearson chi-square test was used to calculate *P* values for categorical variables.

[b]Surgical debridement in the operating room.

[c]Indicates significant value.

Outcomes

The median follow-up time (IQR) was 2.8 (0.3–12) years. The most common clinical presentation of a complicated *M. marinum* infection was tenosynovitis (75%), followed by septic arthritis (8.3%), olecranon bursitis (8.3%), and bloodstream infection (8.3%). No cases of osteomyelitis were documented.

Ninety percent of the cases (28/31) were cured, and the median time of follow-up (IQR) was 7.5 (2–13.5) years. Two cases (4.3%) had a recurrence at 5 and 4 months, respectively. The first patient had a new nodule after completing a 6-month course of empiric antibiotic treatment with minocycline. Based on susceptibilities, the patient received a second course of clarithromycin and rifampin for 6 months, with complete resolution of the skin nodules. The second case presented with new nodules near the original lesions after completing a 6-month course of ethambutol, azithromycin, and rifampin in the setting of immunosuppression (poorly controlled diabetes type 1). The patient underwent a new excisional biopsy and restarted on treatment with ethambutol, azithromycin, and rifampin for 1 year. Six months after completing treatment, the patient underwent a successful pancreas transplant operation without recurrence of *M. marinum* infection.

The 1 patient who expired had multiple comorbidities, including a renal transplant on immunosuppression and active malignancy. *M. marinum* in the blood was detected postmortem, and the patient did not receive appropriate treatment. The initial source of bloodstream infection was unknown.

Table 4. Susceptibilities Patterns of *Mycobacterium marinum*

Drug	No.[a]	Susceptible, No. (%)	Intermediate, No. (%)	Resistant, No. (%)
Ciprofloxacin	25	1 (4)	2 (8)	22 (88)
Clarithromycin	25	25 (100)	–	–
Amikacin	17	17 (100)	–	–
TMP/SMX	25	22 (88)	–	3 (12)
Ethambutol	26	23 (88)	1 (4)	2 (8)
Rifabutin	25	25 (100)	–	–
Moxifloxacin	23	10 (43)	5 (22)	8 (35)
Doxycycline	10	8 (80)	–	2 (20)
Rifampin	24	23 (96)	–	1 (4)
Minocycline	15	2 (13)	12 (80)	1 (7)
Linezolid	9	9 (100)	–	–

Abbreviations: MIC, minimum inhibitory concentration; TMP/SMX, trimethoprim and sulfamethoxazole.

[a]Number tested.

Table 5. Antibiotic Therapy Modifications Based on Susceptibility Testing

Age,[a] y/Gender	Initial Antibiotic Treatment	Modified Antibiotic Treatment[b]	Reason
57/M	Clarithromycin + rifampin + ethambutol	Clarithromycin + rifampin + doxycycline	Ethambutol resistant
72/M	Clarithromycin + TMP/SMX + ciprofloxacin	Clarithromycin + TMP/SMX + doxycycline	Fluoroquinolone resistant
86/F	Clarithromycin + levofloxacin	Clarithromycin + rifampin	Fluoroquinolone resistant
77/M	TMP/SMX + levofloxacin	Clarithromycin	Fluoroquinolone resistant, rash with TMP/SMX
74/F	TMP/SMX	Clarithromycin	Better MICs for clarithromycin
43/M	Clarithromycin + moxifloxacin	Clarithromycin + minocycline	Susceptible to moxifloxacin and minocycline, unknown reason
42/M	TMP/SMX + clarithromycin	TMP/SMX	Susceptible to TMP/SMX and clarithromycin, switch to monotherapy, adverse effect with clarithromycin
63/M	Clarithromycin + levofloxacin	Clarithromycin + TMP/SMX	Fluoroquinolone resistant

Abbreviations: LFTs, liver function tests; TMP/SMX, trimethoprim and sulfamethoxazole.

[a]Age at diagnosis.

[b]Based on susceptibility testing performed using Clinical and Laboratory Standards Institute criteria.

DISCUSSION

Several small retrospective studies have described the overall clinical presentation and purported risk factors of *M. marinum* infection. However, there are no large studies from the United States that have analyzed the impact of management interventions based on complexity or severity of infection (Table 6). Our study compares management strategies (both medical and surgical) in uncomplicated vs complicated *M. marinum* infections and describes the outcomes in each group of patients. We highlight the role of alternative monotherapy options for *M. marinum*, including doxycycline, TMP/SMX, and linezolid. Moreover, we analyze the effect of uncomplicated vs complicated *M. marinum* infection on treatment duration and the need for further surgical debridement.

The clinical spectrum of disease associated with *M. marinum* infection depends on the host and route of the exposure. Sources of contamination in cases of cutaneous *M. marinum* infection are not always identified, and *M. marinum* infection continues to be underestimated. As shown in our study, most of the individuals were initially treated for a bacterial SSTI, presumably due to poor water exposure documentation. In our cohort, water exposure was only documented in one-third of the cases. This is consistent with prior reports where a probable source of contamination was identified in only 28% of the cases [7].

M. marinum–related SSTI is the most common clinical presentation. In our cohort, 74% of the cases presented with nodules, papules, and plaques. Similar to prior reports, the vast majority of cases occurred in the upper extremity [8–10]. Lymphangitis may be present, but it is clinically indistinguishable from other

Table 6. Published Studies on *Mycobacterium marinum* Infection[a]

Ref.	Country	Year(s)	No.[b]	Complicated *M. marinum* Infection, No.[b] (%)	Upper Limb, No.[b] (%)	Aquatic Exposure, No.[b] (%)	Diagnosis, Mean/Median, mo	Treatment Duration, Mean/Median,[b] mo	Surgery Performed, No.[b] (%)	Cure, No.[b] (%)	Isolate (S), No.[b]
[20]	Hong Kong	1981–2009	166	166 (100)	166 (100)	131 (79)	4.9/–	7.2/–	166 (100)	–	–
[13]	USA	1985–1992	31	0 (0)	28 (90)	16 (52)	–	4.3/4	1 (3)	22 (81)	–
[18]	Israel	1991–2005	16	1 (6)	–	12 (75)	7.1/5.9	2.7/3	0 (0)	15 (94)	15
[21]	Hong Kong	1993–2002	17	0 (0)	16 (94)	4 (24)	–	4.6/–	0 (0)	16 (94)	–
[22]	France	1994–2007	35	10 (29)	35 (100)	–	–	2.9/–	0 (0)	34 (97)	–
[23]	Singapore	1995–1997	38	0 (0)	28 (74)	22 (58)	–	3.7/–	1 (3)	27 (68)	
[24]	France	1996–1998	63	18 (29)	60 (95)	59 (94)	–	–/3.5	30 (48)	55 (87)	61
[25]	USA	1996–2014	28	19 (68)	26 (93)	20 (87)	–/3.5	–/5	22 (79)	21 (75)	–
[9]	Taiwan	1997–2008	25	9 (36)	24 (96)	–	2.4/–	8.3/–	22 (88)	24 (96)	–
[26]	Taiwan	1999–2010	27	3 (11)	22 (81)	15 (56)	–/3	–	10 (37)	18 (67)	30
[27]	Lebanon	2005–2008	14	0 (0)	8 (57)	5 (36)	5.8/4	4.6/–	0 (0)	–	–
[14]	China	2008	18	0 (0)	18 (100)	–	13.2/–	–	–	83	–
[11]	USA	2013–2014	29	14 (49)	29 (100)	29 (100)	–/3	–	16 (55)	29 (100)	–

Abbreviation: S, susceptibilities reported.

[a]Studies published in the last 10 years.

[b]Number of cases.

nonmycobacterial infections, nocardiosis, or sporotrichosis. Sporotrichosis serologies were performed in almost 40% of our cases. Before *M. marinum* diagnosis, 5 patients received empiric treatment with itraconazole, with no clinical improvement. Spontaneous resolution of infection may also occur, and 1 of the cases was cured after surgical resection without antimycobacterial therapy.

Complicated *M. marinum* cases have been more commonly reported in immunosuppressed patients [11]. In our study, 26% (12/46) of the cases were classified as complicated *M. marinum* infection. Only 2 patients (2/12) were immunosuppressed (1 patient had a kidney transplant, and the second patient had rheumatoid arthritis), suggesting that both immunocompetent and immunosuppressed patients are equally at risk of developing complications associated with *M. marinum* infection. Age was also a statistically significant factor in patients with complicated *M. marinum* infection. Immunosenescence is a physiological part of aging linked to higher rates of infection that may have significant implications for the type of *M. marinum* infection.

Most of the cases of *M. marinum* infection are diagnosed weeks and months after symptom onset [11]. In our cohort, the median time from symptom onset to diagnosis was 3.6 months. Delay in diagnosis was reported more frequently in complicated cases. Elevation in inflammatory blood markers including white blood cell count, erythrocyte sedimentation rate, and C-reactive protein may be a clue for complicated infection such as purulent bacterial tenosynovitis [12]. However, as our results indicate, normal results (within reference range) for these inflammatory markers cannot rule out *M. marinum* infection.

Presence of granulomatous inflammation on histopathology is suggestive of NTM diagnosis. However, it has poor specificity, as several other infectious diseases can cause granulomatous inflammation. In our cohort, 74% of the cases had evidence of granulomatous infection, which is slightly higher than previous reports [13]. The auramine-rhodamine and Ziehl-Neelsen stains are used to identify acid-fast organisms (mainly mycobacteria) and were positive in 21.7% of the patients. A negative acid-fast stain does not rule out an NTM SSTI, and mycobacterial cultures are necessary to confirm or exclude the diagnosis. Interestingly, TST and QFT assay may be positive in some NTM infections, including *M. marinum*. In our study, TST and/or QFT were performed in 17.3% of the cases, and 4 cases were positive. In the literature, most of the positive tests are secondary to the known cross-reactivity between various mycobacteria and the low positive predictive value of the test [14].

The susceptibility pattern of *M. marinum* is well known, and acquired resistance is rare. Susceptibility testing is generally not recommended except in cases of treatment failure or relapse (Supplementary Table 1) [15, 16]. In our study, more than half of the cases had susceptibilities performed at the clinician's discretion. Routine susceptibility testing may be considered for all *M. marinum* isolates due to the potential resistance with tetracyclines (mainly minocycline) and fluoroquinolones. Fluoroquinolones should be avoided as part of any therapeutic regimen.

The most recent guidelines from the 2007 joint American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) statement recommended 2 active agents for 3 to 4 months, along with surgical debridement for invasive infections [17]. In several studies, the most common monotherapy used was clarithromycin [9, 14, 18]. In our study, all isolates were susceptible to clarithromycin, and monotherapy was effective in several cases of both uncomplicated and complicated *M. marinum* infections. Other potential alternatives include TMP/SMX and tetracyclines. Doxycycline should be the preferred tetracycline, as the majority of the isolates were minocycline intermediate, as per the Clinical and Laboratory Standards Institute. Some cases of complicated *M. marinum* infection have been successfully treated with doxycycline monotherapy, but nausea may be a barrier to adherence [19]. Susceptibilities to linezolid were not performed in all of our isolates, but the organism was susceptible when tested. If tolerated, linezolid may be an alternative regimen for treatment.

Some smaller case series have shown no differences in cure rates in patients treated with monotherapy with clarithromycin compared with the combination of clarithromycin plus rifampin and/or ethambutol [14]. Regardless of choice of antimicrobial therapy, longer treatment duration is usually prescribed for complicated cases. In our study, complicated *M. marinum* infection was treated for up to 6 months on average, compared with 3 months in uncomplicated cases.

Surgical debridement is also a key component of treatment of complicated *M. marinum* infections. In our cohort, patients with a complicated *M. marinum* infection underwent more procedures as compared with uncomplicated cases. Thus, patients with a complicated *M. marinum* infection should be counseled regarding the possibility of multiple surgeries and the need for longer treatment duration. At our institution, the majority of *M. marinum* cases had a diagnostic punch biopsy, and more than half of the cases had 1 surgical debridement performed. This is likely due to the fact that our population is more likely to be referred for a dermatology evaluation or surgical debridement.

Careful hand protection should be recommended to all individuals manipulating fish or fish tank water to prevent *M. marinum* infection. For individuals who develop chronic skin lesions after such exposure, prompt referral is recommended.

CONCLUSIONS

Diagnosis of *M. marinum* infection should be suspected based on patient history and physical examination and confirmed using histologic evaluation and mycobacterial cultures. Delay in diagnosis may lead to complicated *M. marinum* infection. Most experts recommend treatment with 2 active agents for

uncomplicated *M. marinum* cases. However, our study shows no difference in the number of drugs used and clinical outcome. Monotherapy combined with surgical debridement is usually sufficient to cure *M. marinum* infection. Complicated *M. marinum* infections are typically treated with longer antibiotic duration and require frequent surgical intervention.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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