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

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Summary: *M. marinum* is an important cause of skin and soft tissue infection. Delay in diagnosis may lead to complicated *M. marinum* infection. Treatment should be tailored to host and type of *M. marinum* infection.

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ABSTRACT

Background: *Mycobacterium marinum* (*M. 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 versus 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 versus 55.8 ± 14.5, p=0.03), had longer duration of symptoms (5 versus 3 months, p=.011), and had more surgical debridements (1 versus 0, p<.001). Length of treatment and number of drugs used were not statistically significant. Complicated *M. marinum* cases received more medications (2 versus 1, p=0.263) and were treated longer (5.7 versus 3.5 months, p=0.067). 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 prior to 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 and clinical outcome was observed.
INTRODUCTION

*M. marinum* or “fish tank granuloma” is a pathogenic, non-tuberculous 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 number 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 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 $\geq 5$ mg/day for at least one 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 as part of a diagnostic procedure.

*M. marinum* antimicrobial regimen was defined as pathogen-directed therapy regimen which was used for more than 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 subsequent documentation after the diagnosis of *M. marinum* does not mention persistence or recurrence of disease. *M. marinum* infection was defined as recurrent if there was new clinical findings on physical exam and/or imaging, and microbiologic or histopathologic evidence of disease after cessation of therapy. *M. marinum* cases that were lost to follow-up or had no documentation of outcome in any subsequent medical records were excluded from outcome analysis.

**Statistical analysis**

The statistical analysis was performed using JMP®, Version 14.1.0. SAS Institute Inc., Cary, NC, 1989 – 2019. Descriptive information about patients with *M. marinum* infection was reported as frequencies and proportions for categorical variables, and mean ± standard deviation (SD) or median (interquartile range – IQR) for continuous variables. Time differences for categorical variables among groups (complicated versus uncomplicated *M. marinum* infection) were tested using chi square test or Fisher’s exact test as appropriate. Differences between continuous variables in the two study groups were tested using 2 sample *t*-test and Wilcoxon-Mann Whitney test, after assessing variables for normality with the Shapiro-Wilk normality test. 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 was 3.6 months (IQR 2.3 – 6.1 months). Only 15 cases (33%) had a documented water exposure during initial evaluation compared to 33 cases (73%) after microbiology diagnosis was confirmed (p<.001). Most of the patients were immunocompetent and only two patients had a solid organ transplant (kidney, and kidney/pancreas transplant) (Table 1).

The median symptoms duration when patients sought medical attention was 24 days (IQR, 9 - 246 days). Most of 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 four patients had systemic symptoms: two patients had fever, two patients had night sweats, and one 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 one 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 three 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 to 33.3% complicated M. marinum cases (p=.001). Bedside incision and drainage was 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% versus 8.3%, p=0.409). 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% versus 23.5%, p<.001) compared to uncomplicated M. marinum cases (Table 3).
Only nine cases had more than one surgical debridement performed in the OR with a median of two OR procedures (IQR, 2 – 5 surgical procedures).

The median time to culture positivity was 3.5 weeks (IQR, 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 three 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* (one colony), *Cutibacterium acnes* (from broth only), coagulase-negative staphylococci, *Brevundimonas diminuta*, and *Penicillium* species. Most of these organisms are non-pathogenic and/or part of the skin flora.

**Treatment**

Sixty-five percent of the patients (28/43) received antibiotics alone for suspected bacterial skin and soft tissue infection (SSTI) prior to *M. marinum* diagnosis. The two most common prescribed classes of antibiotics were cephalosporins (46%) followed by penicillins (29%). Twenty-one percent (6/28) of the patients received anti-fungal medication and five out of these six patients (83%) received itraconazole.

*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 (prior to 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 monotherapy (38%), followed by tetracyclines (33%), and clarithromycin (17%). Eleven cases (25%) received a two 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) that 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 was 4.5 months (IQR, 3 – 6.4 months).

Overall, treatment duration was longer in patients with complicated *M. marinum* infection compared to 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 one 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 the cases (Table 5). No differences in cure rates between *M. marinum* infection groups (uncomplicated versus complicated) were observed.
Outcomes

The median follow up time was 2.8 years (IQR 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 was 7.5 years (IQR 2–13.5 years). Two cases (4.3%) had a recurrence at five and four 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 one year. Six months after completing treatment, the patient underwent a successful pancreas transplant operation without recurrence of *M. marinum* infection.

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

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 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 versus complicated *M. marinum* infections and describes 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 versus 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 as 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 is clinically indistinguishable from other non-mycobacterial infections, nocardiosis, or sporotrichosis. Sporotrichosis serologies were performed in almost 40% of our cases. Prior to *M. marinum* diagnosis, five patients received empiric treatment with itraconazole with no clinical improvement. Spontaneous resolution of infection may also occur and one of the cases was cured after surgical resection without anti-mycobacterial 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 two patients (2/12) were immunosuppressed (one 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 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 initiation symptoms onset [11]. In our cohort, 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 WBC, ESR, and CRP 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 since 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 the previous reports [13]. 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 a 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 four 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 (see 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 Disease Society of America (IDSA) statement recommend two active agents for 3 to 4 months along with surgical debridement for invasive infections [17]. In several studies, the most common monotherapy used is clarithromycin [9, 14, 18]. In our study, all of 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 (CLSI). 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 to 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 to 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 to uncomplicated cases. Thus, patients with a complicated *M. marinum* infection should be counseled regarding the possibility for multiple surgeries and 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 one 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 the 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 two 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.
REFERENCES

1. Aubry A, Mougari F, Reibel F, Cambau E. Mycobacterium marinum. Microbiology Spectrum 2017; 5(2): 04.

2. Sia TY, Taimur S, Blau DM, et al. Clinical and Pathological Evaluation of Mycobacterium marinum Group Skin Infections Associated with Fish Markets in New York City. Clinical Infectious Diseases 2016; 62(5): 590-5.

3. Rallis E, Koumantaki-Mathioudaki E. Treatment of Mycobacterium marinum cutaneous infections. Expert Opinion on Pharmacotherapy 2007; 8(17): 2965-78.

4. Hall L, Doerr KA, Wohlfel SL, Roberts GD. Evaluation of the MicroSeq system for identification of mycobacteria by 16S ribosomal DNA sequencing and its integration into a routine clinical mycobacteriology laboratory. J Clin Microbiol 2003; 41(4): 1447-53.

5. Patel R. MALDI-TOF MS for the diagnosis of infectious diseases. Clin Chem 2015; 61(1): 100-11.

6. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42(2): 377-81.

7. Jernigan JA, Farr BM. Incubation period and sources of exposure for cutaneous Mycobacterium marinum infection: case report and review of the literature. Clin Infect Dis 2000; 31(2): 439-43.

8. El Amrani MH, Adoui M, Patey O, Asselineau A. Upper extremity Mycobacterium marinum infection. Orthopaedics and Traumatology: Surgery and Research 2010; 96(6): 706-11.
9. Chen HY, Chen CY, Huang CT, et al. Skin and soft-tissue infection caused by nontuberculous mycobacteria in Taiwan, 1997-2008. Epidemiology and Infection 2011; 139(1): 121-9.

10. Bonamonte D, De Vito D, Vestita M, et al. Aquarium-borne Mycobacterium marinum skin infection. Report of 15 cases and review of the literature. European Journal of Dermatology 2013; 23(4): 510-6.

11. Johnson MG, Stout JE. Twenty-eight cases of Mycobacterium marinum infection: retrospective case series and literature review. Infection 2015; 43(6): 655-62.

12. Bishop GB, Born T, Kakar S, Jawa A. The diagnostic accuracy of inflammatory blood markers for purulent flexor tenosynovitis. J Hand Surg Am 2013; 38(11): 2208-11.

13. Edelstein H. Mycobacterium marinum skin infections. Report of 31 cases and review of the literature. Arch Intern Med 1994; 154(12): 1359-64.

14. Feng Y, Xu H, Wang H, Zhang C, Zong W, Wu Q. Outbreak of a cutaneous Mycobacterium marinum infection in Jiangsu Haian, China. Diagnostic Microbiology and Infectious Disease 2011; 71(3): 267-72.

15. Chazel M, Marchandin H, Keck N, et al. Evaluation of the SLOMYCO SENSITITRE<sup>sup></sup>/<sup>sup</sup> panel for testing the antimicrobial susceptibility of Mycobacterium marinum isolates. Annals of Clinical Microbiology and Antimicrobials 2016; 15 (1) (no pagination)(30).

16. Woods GL, Brown-Elliott BA, Conville PS, et al. In: nd. Susceptibility Testing of Mycobacteria, Nocardiae, and Other Aerobic Actinomycetes. Wayne (PA), 2011.

17. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007; 175(4): 367-416.
18. Dodiuk-Gad R, Dyachenko P, Ziv M, et al. Nontuberculous mycobacterial infections of the skin: A retrospective study of 25 cases. J Am Acad Dermatol 2007; 57(3): 413-20.

19. Osorio F, Magina S, Carvalho T, Goncalves MH, Azevedo F. Mycobacterium marinum skin infection with tenosynovitis successfully treated with doxycycline. Dermatology Online Journal 2010; 16(9): 7.

20. Cheung JP, Fung BK, Ip WY. Mycobacterium marinum infection of the deep structures of the hand and wrist: 25 years of experience. Hand surgery : an international journal devoted to hand and upper limb surgery and related research : journal of the Asia-Pacific Federation of Societies for Surgery of the Hand 2010; 15(3): 211-6.

21. Ho MH, Ho CK, Chong LY. Atypical mycobacterial cutaneous infections in Hong Kong: 10-year retrospective study. Hong Kong Med J 2006; 12(1): 21-6.

22. Eberst E, Dereure O, Guillot B, et al. Epidemiological, clinical, and therapeutic pattern of Mycobacterium marinum infection: a retrospective series of 35 cases from southern France. J Am Acad Dermatol 2012; 66(1): e15-6.

23. Ang P, Rattana-Apiromyakij N, Goh CL. Retrospective study of Mycobacterium marinum skin infections. Int J Dermatol 2000; 39(5): 343-7.

24. Aubry A, Chosidow O, Caumes E, Robert J, Cambau E. Sixty-three cases of Mycobacterium marinum infection: clinical features, treatment, and antibiotic susceptibility of causative isolates. Arch Intern Med 2002; 162(15): 1746-52.

25. Yacisin K, Hsieh JL, Weiss D, et al. Outbreak of non-tuberculuous mycobacteria skin or soft tissue infections associated with handling fish - New York City, 2013-2014. Epidemiology and Infection 2017; 145(11): 2269-79.
26. Wu TS, Chiu CH, Su LH, et al. Mycobacterium marinum infection in Taiwan. J Microbiol Immunol Infect 2002; 35(1): 42-6.

27. Abbas O, Marrouch N, Kattar MM, et al. Cutaneous non-tuberculous Mycobacterial infections: a clinical and histopathological study of 17 cases from Lebanon. J Eur Acad Dermatol Venereol 2011; 25(1): 33-42.
Table 1. Baseline characteristics

| Patient demographics | n= 46 |
|----------------------|-------|
| Age, mean ± SD       | 58 ± 14.05 |
| Female (%)           | 18 (39) |
| Male (%)             | 28 (60.9) |
| White (%)            | 41 (89.1) |

| Comorbidities        |       |
|----------------------|-------|
| Obesity (%)          | 5/30 (16.7) |
| Diabetes (%)         | 5 (10.8) |
| CKD stage 3 (%)      | 8/27 (29.6) |
| Autoimmune disorder* (%) | 5 (10.8) |
| Active malignancy (%)| 1 (2.2) |
| Immunosuppression (%)| 8 (17.4) |
| Transplant           | 2 (4.3) |

*Autoimmune disorder: Crohn’s disease, DM type 1, Rheumatoid arthritis, Ulcerative Colitis and Polymyalgia Rheumatica.
### Table 2. Clinical presentation and laboratory findings at initial presentation

| Clinical presentation              | n= 46 |
|-----------------------------------|-------|
| Upper extremity lesions           | 43 (93.5%) |
| Redness                           | 28 (61%) |
| Pain                              | 25 (54.3%) |
| Abscess                           | 9 (19.6%) |
| Skin manifestations a             | 34 (74%) |
| Lymphangitis                      | 12 (26.1%) |
| Constitutional symptoms           | 4 (8.7%) |
| Symptoms duration (days), median (IQR) | 24 (9-246) |

| Laboratory findings               |       |
|-----------------------------------|-------|
| WBC (x10(9)/L), mean ± SD         | 6.2 ± 2.2 |
| Platelets (x10(9)/L), median (IQR)| 243 (197-281) |
| Creatinine (mg/dL), mean ± SD     | 1.08 ± 0.2 |
| ESR (mm/h), median (IQR)          | 5 (1.5-13.5) |
| CRP (mg/L), median (IQR)          | 3 (0.6-8.35) |
| Time of positive culture (weeks), median (IQR) | 3.5 (2.8-4.8) |

*Skin manifestations include nodules, papules and plaques*
Table 3. Uncomplicated versus complicated *M. marinum* infection

|                         | Uncomplicated (n = 34) | Complicated (n = 12) | P value<sup>a</sup> |
|-------------------------|------------------------|----------------------|---------------------|
| Female                  | 15 (45.7%)             | 3 (25%)              | 0.315               |
| Male                    | 19 (52.3%)             | 9 (81.8%)            |                     |
| Age, mean ± SD          | 55.8 ± 14.5            | 64.3 ± 11.1          | 0.030<sup>c</sup>   |
| Immunosuppression       | 6 (17.7%)              | 2 (16.7%)            | 1.000               |
| DM                      | 4 (11.8%)              | 1 (8.3%)             | 1.000               |
| WBC (x10(9)/L), mean ± SD | 5.9 ± 2.0              | 6.8 ± 2.4            | 0.299               |
| Platelets (x10(9)/L), median (IQR) | 243 (197-273)         | 237 (176-297)        | 0.741               |
| Creatinine (mg/dL), mean ± SD | 1.1 ± 0.3              | 1.1 ± 0.2            | 1.000               |
| ESR (mm/h), median (IQR) | 5 (2-12)               | 9.5 (1.3-14.3)       | 0.642               |
| CRP (mm/h), median (IQR) | 1.8 (0.4 – 3)          | 3 (0.6-48)           | 0.138               |
| Duration of symptoms prior to diagnosis in days, median (IQR) | 21.5 (9-201.5) | 36 (15.3-101.5) | 0.298 |
| Time to diagnosis in months, median (IQR) | 3 (2-6)               | 5 (4-15)            | 0.011<sup>c</sup>  |
| Number of surgical debridements<sup>b</sup>, median (IQR) | 0 (0-0.25)            | 1 (1-2)              | <.001<sup>c</sup>   |
| Number of drugs used, median (IQR) | 1 (1-2)               | 2 (1-2.75)          | 0.263               |
| Length of treatment (months), median (IQR) | 3.5 (2-6.2)          | 5.7 (4-8.3)         | 0.067               |

Abbreviations: DM=diabetes, WBC = white blood cells, ESR=erythrocyte sedimentation rate, CRP= c-reactive protein

<sup>a</sup>The two-sample Wilcoxon test was used to calculate p values for continuous nonparametric variables. The two 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.

<sup>b</sup>Surgical debridement in the operating room

<sup>c</sup>Indicates significant value
### Table 4. Susceptibilities patterns of *Mycobacterium Marinum*

| Drug       | No. | Susceptible | Intermediate | Resistant |
|------------|-----|-------------|--------------|-----------|
| Ciprofloxacin | 25  | 1 (4%)      | 2 (8%)       | 22 (88%) |
| Clarithromycin | 25  | 25 (100%)   | -            | -         |
| Amikacin   | 17  | 17 (100%)   | -            | -         |
| TMX/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%)    | -            | -         |

Abbreviation: MIC=minimum inhibitory concentration

*a* No. Number tested.
Table 5. Antibiotic therapy modifications based on susceptibility testing

| Age (Years)\(^a\)/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: TMP/SMX= Trimethoprim/sulfamethoxazole, LFTs=liver function tests.

\(^a\)Age at diagnosis.

\(^b\)Based on susceptibility testing performed by CLSI criteria.
Table 6. Published studies on *Mycobacterium marinum* infection

| Ref  | Country   | Year (s)     | No.   | Complicated  | Upper | Aquatic  | Diagnosis, | Treatment | Surgery  | Cure  | Isolate |
|------|-----------|--------------|-------|--------------|-------|----------|------------|-----------|----------|-------|---------|
|      |           |              |       | *M. marinum* | limb, | exposure,| mean/median| duration, | performed,|        |         |
|      |           |              |       | infection, No.\(^b\)\(|%\) | No.\(^b\)\(|%\) | No.\(^b\)\(|%\) | (months)  | (months)  | No.\(^b\)\(|%\) |        |         |
| [20] | Hong Kong | 1981–2009    | 166   | 166 (100)    | 166   | 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       | 1996–2009    | 28    | 19 (68)      | 26 (93)| 20 (87)  | –/3.5     | –/5       | 22 (79)  | 21 (75) | –       |
|    | Country | Year          | 2014 | 2014 (100) | 2014 (100) | 2014 (100) | 2014 (100) | 2014 (100) | 2014 (100) |
|----|---------|---------------|------|------------|------------|------------|------------|------------|------------|
| [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)   | –          |

Abbreviations: S=susceptibilities reported

*Studies published in the last 10 years

*Number of cases