Expert Opinion

Treatment of *Mycobacterium marinum* cutaneous infections

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Mycobacterium marinum is a non-tuberculous Mycobacterium found in non-chlorinated water, with worldwide prevalence. It is the most common atypical Mycobacterium that causes opportunistic infection in humans. It presents as a solitary, red-to-violaceous plaque or nodule with an overlying crust or verrucous surface, or as inflammatory nodules or abscesses, usually in a sporotrichotic type of distribution. Deep infections may also occur. Although diagnosis is confirmed by isolation and identification of the organism in practice diagnosis remains largely presumptive based on clinicohistological features and the response to treatment. Polymerase chain reaction allows the routine early detection of the organism from a biopsy specimen. In the near future, it seems possible that histopathological examination might be greatly assisted by the rapidly improving possibilities with *in vivo* imaging. There have been many therapeutic modalities used effectively in the treatment of *M. marinum* infections. Spontaneous remission has also been reported in untreated infections and in immunocompetent hosts. However, there is no proven treatment of choice because *M. marinum* is naturally multi-drug resistant species and treatment is based primarily on the personal experience and preference of individual investigators, without the benefit of large studies. In superficial cutaneous infections minocycline, clarithromycin, doxycycline and trimethoprim-sulfamethoxazole as monotherapy are effective treatment options, but drug resistance varies and thereby combination therapy usually of two drugs may be required. Ciprofloxacin has shown considerable effectiveness. In cases of severe infections, including those with a sporotrichoid distribution pattern, a combination of rifampicin and ethambutol seems to be the recommended regimen. The use of isoniazid, streptomycin and pyrazinamide as empirical treatment options should be avoided. Surgical treatment is not usually recommended and must be cautiously applied. Cryotherapy, X-ray therapy, electrodesiccation, photodynamic therapy and local hyperthermic therapy have been reported as effective therapeutic alternatives. *M. marinum* infection should always be included in the differential diagnosis of all cases with poor-healing wounds in upper extremities and a history of exposure to aquariums.

Keywords: fish tank granuloma, *Mycobacterium marinum*, skin infection, treatment

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1. Introduction

Mycobacterium marinum is an aerobic, environmental, waterborne Mycobacterium that belongs to Runyon's classification Group I photochromogenic non-tuberculous Mycobacteria. It is usually found in non-chlorinated water occupying many aquatic environments, commonly infecting fish and amphibians in a worldwide distribution [1]. It is also the most common atypical Mycobacterium that causes infection to humans [101].

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M. marinum infection is also called 'fish tank granuloma' or 'aquarium granuloma' or 'swimming pool granuloma'. However, infections related to swimming pool bathing has substantially fallen due to construction improvements and the chlorination of water. *M. marinum* infection is opportunistic and occurs ~ 2 weeks after direct inoculation of the organism either from fish fins and bites or from the handling of aquariums. In 90% of cases, this takes place via trauma to the upper extremity and is not transmittable from person to person [102].

2. Clinical picture

M. marinum infections may have several clinical presentations, but none of these are considered pathognomonic. It is usually presents in immunocompetent patients as a solitary, red-to-violaceous plaque or nodule with an overlying crust or verrucous surface (**Figure 1**) that may ulcerate. Inflammatory nodules or abscesses can develop in severely immunosuppressed patient, usually in a sporotrichotic type of distribution [2]. This 'sporotrichoid' disease begins with distal inoculation and may lead to the development of nodular lymphangitis. Over a period of months, localised cutaneous disease can spread to deeper soft tissues, causing tenosynovitis, arthritis, bursitis and/or osteomyelitis of the underlying bone; it can also be life-threatening [3,102], and lesions may or may not be painful.

Infections with *M. marinum* can be theoretically classified into four different clinical categories to help in guide treatment options [4]:

- Type I: single or limited (1 – 3 lesions) superficial cutaneous infections (ulcerated, crusted or verrucous plaques or nodules).
- Type II: numerous (> 3) lesions in a sporotrichoid distribution pattern or with inflammatory nodules, abscesses and granulomas.
- Type III: deep infections with or without skin involvement, including tenosynovitis, arthritis, bursitis and/or osteomyelitis.
- Type IV: disseminated infection, lung involvement and other systemic manifestations. Bacteraemia is usually seen in immonocompromised patients, but is considered very rare [4,5,102].

3. Diagnosis

Diagnosis is usually delayed, suggesting that most physicians are not familiar with the disease. This is probably because of the rareness of the infection and a failure to establish a history of exposure to aquatic environments or to tropical fish [4]. Therefore, key diagnostic elements for *M. marinum* infections are a high index of suspicion raised by negative bacterial tissue cultures, poor response to conventional antibiotic treatments and a history of aquatic exposure [6].

Routine culture techniques do not allow *M. marinum* to grow and the diagnosis is easily missed, resulting in inappropriate treatments, Tissue biopsy is required for culture and histological examination. The organism is isolated from the lesion, as well as from the patient's aquarium and infected fish. The required temperature for optimal growth is 30 – 32°C, and this explains why it almost exclusively infects the cooler extremities and is confined to superficial structures, rarely achieving systemic distribution. Colonies are smooth, shiny and creamy coloured, turning yellow under exposure to light (photochromogenic). More rapid identification may be achieved by polymerase chain reaction.

Histopathological examination usually reveals a nonspecific inflammatory infiltration consisting of lymphocytes, epithelioid cells and Langhan's giant cells, usually without caseation. Histologically, the early lesion usually reveals a collection of polymorphonuclear cells surrounded by histiocytes.

Although a definite diagnosis is confirmed by isolation and identification of the organism, in practice it remains largely presumptive, based on clinico-histological features and the response to appropriate antimicrobial treatment, regardless of culture results [7]. Additionally, as with other Mycobacteria, *in vitro* results do not necessarily correlate with *in vivo* success; therefore, routine susceptibility testing of *M. marinum* is not recommended [8].

In the near future, it is possible that histopathological examination might be greatly assisted by the rapidly improving possibilities with *in vivo* imaging, such as magnetic resonance spectroscopic/microscopic techniques or even two-photon microscopy/tomography and high-resolution ultrasound.

4. Therapy

M. marinum is a rare cause of skin infections. Although spontaneous resolution has been reported, the aim of treatment is for a rapid recovery from the infection and the prevention of progression to deeper structures. Monotherapy is usually applied for skin and soft tissue infection, but this is ineffective for deeper structure infections [9]. Moreover, the duration of treatment is longer in patients with deeper structure infections. Acquired resistance has not yet been reported for *M. marinum* [9].

There is no established treatment of choice for *M. marinum* infection because it is a naturally multi-drug resistant species and its treatment is based primarily on the personal experience and preference of individual investigators, without the benefit of large studies [10]. Both effective curing and treatment failures have been reported with all 'recommended' drugs. In the English literature, very few case series of *M. marinum* infections have been reported; thus, comparison of different treatment regimens is difficult [11]. There are no large series of *M. marinum*

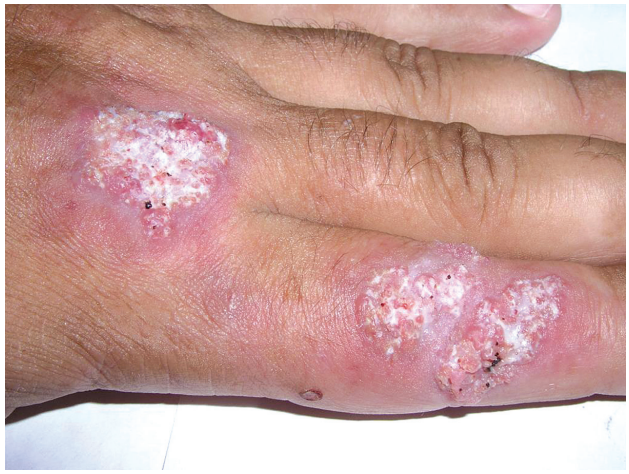

Figure 1. Verrucous plaques on the dorsa of the left hand.

infection recently reported (no controlled studies, and none are likely to be performed because of the sparcity of cases [11]).

In a thorough search of all relevant articles and/or abstracts since 1986 (**Table 1**), regarding the treatment of *M. marinum* skin infections, the present authors tried to record, where possible, all cured or significantly improved patients. All treatment failures and patients who were lost to follow-up were excluded. A significant number of different treatments have been recorded (**Box 1**), and attempts were made to classify them in categories of antibiotic monotherapy, antimycobacterial monotherapy, surgical therapy and combination treatment.

4.1 Tetracyclines

Tetracyclines (primarily minocycline and, secondly, doxycycline) have been widely used to treat *M. marinum* infections either as monotherapy or in combination with other medication (**Table 1**). According to Kim [12], minocycline became more commonly used for systemic chemotherapy than antituberculosis drugs.

In the first review of aquarium-borne *M. marinum* skin infections by Huminer *et al.* [13], two patients (100%) responded to minocycline, and none of three patients to tetracycline. Iredell *et al.* [14] reported that 7 out of 9 (77.7%) patients responded to tetracyclines and Edelstein reported [10] 10 responders out of 14 (71,42%) who were treated with minocycline. In a retrospective study, Ang *et al.* [7] recorded three (100%) responding patients who received minocycline, and five (100%) who were given minocycline and trimethoprim-sulfamethoxazole (TMS).

Wu *et al.* [3] described a response in one patient (100%) who was treated with doxycycline, one (100%) with doxycycline and TMS, and one (100%) with a combination of doxycycline, rifampicin, clarithromycin and ciprofloxacin. Kullavanijaya *et al.* [15] reported positive results in one patient (100%) who was treated with minocycline, and in one (100%) treated with tetracycline. In addition, Leuenberger *et al.* [16] reported the successful treatment of 12 patients with tetracyclines and trimethoprim.

Casal and Casal [17], in a multicentre study, reported 12 (100%) responding patients who were administered minocycline; Ryan and Bryant [18] 5 patients (100%) who were treated with minocycline; and Ho *et al.* [19], in the most recent retrospective study, reported 11 (100%) who responded to minocycline, 1 (100%) to a combination of minocycline, rifampicin, isoniazid and pyraminazide, and 4 (100%) to doxycycline.

Aubry *et al.* [9], in the largest reported series of 63 *M. marinum* infections, referred to the successful courses of the drugs that were given and not to the successful therapeutic regimens that were administered to every patient separately. According to this information, it was reported that 22 out of 24 patients (91.6%) responded to courses of minocycline, and 11 (100%) to courses of doxycycline, either as monotherapy or in combination.

Minocycline, alone or with hyperthermic treatment [20-24], or in combination with levofloxacin and clarithromycin [25], or with rifampicin, ethambutol and surgery [26], has also been reported to act effectively against *M. marinum*. Likewise, doxycycline alone [27] or in combination with ciprofloxacin [4], with clarithromycin [28], or with clarithromycin and ethambutol [29] has been reported as successful therapeutic alternatives for *M. marinum* infections, in case reports or small series.

In conclusion, minocycline 100 mg b.i.d. and doxycycline 100 mg b.i.d. have been the most commonly recommended medications; however, treatment failures have been also reported [9,23,30,31].

4.2 Trimethoprim-sulfamethoxazole

TMS has been successfully used in the treatment of *M. marinum* infections, and some authors have reported it as the drug of choice for the disease because it is safe, inexpensive and efficacious [15]. However, treatment failures have been described with TMS [9,10,13].

In 1986, Huminer *et al.* [13] reported 13 out of 17 (76.5%) patients who responded to TMS. Iredell *et al.* [14] reported a response in seven out of nine patients (77.7%), and Kullavanijaya *et al.* [15] nine (100%) patients. In other studies, Joe *et al.* [32] reported successful treatment with TMS, Wu *et al.* [3] reported one patient (100%) treated effectively with doxycycline and TMS, and Leuenberger and Bodmer [16] reported successful treatment with tetracyclines and TMS.

Ang *et al.*, in a retrospective study [7], described 13 out of 14 (92.8%) patients who were successfully treated with TMS (in one patient no improvement was seen), and successful treatment in 5 (100%) administered minocycline in combination with TMS. Ho *et al.* [19], in another retrospective study, recorded one patient (100%) who responded to TMS.

Table 1. All studies since 1986 on the treatment of *Mycobacterium marinum* skin infections.

Ref.	N	Antimicrobial agents		Combination therapy		Surgical therapy	Other
		Antibiotic agents	Antimycobacterial agents	Surgical + antimicrobials	Antibiotic + antimycobacterial		
Tsai [6]	3			+			
Rajesh [68]	3			+			
Belic [42]	1				(RIF-EMB-CLR)		
Wiegell [72]	1						Photodynamic therapy
Helgason [69]	1			+			
Ho [19]	17	11 (MIN), 4 (DOX), 1 (TMS)			1 (MIN-RIF-INH-PZA)		
Streit [29]	1				(CLR-EMB-DOX)		
Janik [23]	1	(MIN)					
Noguchi [63]	3			(EMB-RIF-INH)			
Contios [43]	2				(RIF-CLR)		
Cummins [24]	1	(MIN, DOX-R)					
Hess [70]	26			+			
Bormann [25]	3	(LFX-CLR-MIN)					
Brans [44]	3				(RIF-CLR)		
Lewis [45]	6				(RIF-EMB-CLR)		
Hisamichi [22]	1	(MIN)					Hyperthermic treatment
Trampuz [67]	1					+	
Aubry [9]	55	30		25			
Wu [3]	9	1 (CLR), 1 (DOX), 1 (DOX-TMS)	1 (INH-RIF-EMB)		1 (CLR-EMB), 1 (DOX-CLR-RIF-CIP), 1 (CLR-RIF-EMB), 2 (INH-RIF-EMB-CLR)		
Ena [83]	2	+					
Ho [71]	1			+			
Torres [53]	1			(EMB-AZC)			
Casal [17]	27	12 (MIN)	8 (RIF)		7 (CLR-EMB)		

AMC: Amikacin; AZC: Azithromycin; CIP: Ciprofloxacin; CLR: Clarithromycin; DOX: Doxycycline; EMB: Ethambutol; ERC: Erythromycin; INH: Isoniazid; LFX: Levofloxacin; M: Monotherapy; MIN: Minocycline; PRN: Protionamid; PZA: Pyrazinamide; R: Resistant; RIF: Rifampicin; RIFB: Rifabutin; STR: Streptomycin; TMS: Sulfamethoxazole-trimethoprim; TRC: Tetracycline.

Table 1. All studies since 1986 on the treatment of *Mycobacterium marinum* skin infections (continued).

Ref.	N	Antimicrobial agents		Combination therapy		Surgical therapy	Other
		Antibiotic agents	Antimycobacterial agents	Surgical + antimicrobials	Antibiotic + antimycobacterial		
Witthaut [49]	1			(RIF-EMB-CLR)			
Lim [50]	1			(RIF-EMB-CLR)			
Bhatty [4]	3	1 (CIP), 1 (CIP-DOX)		1 (CIP-RIF)			
Hofbauer [21]	1	(MIN)					
Ang [7]	26	13 (TMS), 3 (MIN), 5 (MIN+TMS)			4	1	
Tan [36]	1 HIV+	(TMS)					
Leuenberger [16]	12	(TRC/TMS)	(RIF-EMB)				
Farooqui [54]	1				(EMB-CIP)		
Laing [51]	1				(CLR-RIFB)		
Saadatmand [20]	1	(MIN)					
Gimenez Garcia [41]	1	(CLR)					
Lee [37]	3				(RIF-TMS)		
Papanaoum [38]	1				(RIF-TMS)		
Ryan [18]	5	(MIN)					
Shih [46]	1				(CLR-EMB)		
Byg [28]	1	(CLR-DOX)					
Iijima [55]	1	(LFX)					
Speight [62]	1		(RIF)				
Dorronsoro [35]	2	(TMS)	(RIF-EMB)				
Laing [47]	3	(CIP-CLR)			(CLR-EMB), (RIF-CIP)		
Brady [40]	1	(CLR)					
Flisch [84]	1				+		
Feddersen [48]	1				(CLR-RIF-PRN)		
Joe [32]	41	(TMS)	(RIF-EMB)				
Parent [5]	1		+				

AMC: Amikacin; AZC: Azithromycin; CIP: Ciprofloxacin; CLR: Clarithromycin; DOX: Doxycycline; EMB: Ethambutol; ERC: Erythromycin; INH: Isoniazid; LFX: Levofloxacin; M: Monotherapy; MIN: Minocycline; PRN: Protionamid; PZA: Pyrazinamide; R: Resistant; RIF: Rifampicin; RIFB: Rifabutin; STR: Streptomycin; TMS: Sulfamethoxazole-trimethoprim; TRC: Tetracycline.

Table 1. All studies since 1986 on the treatment of *Mycobacterium marinum* skin infections (continued).

Ref.	N	Antimicrobial agents		Combination therapy		Surgical therapy	Other
		Antibiotic agents	Antimycobacterial agents	Surgical + antimicrobials	Antibiotic + antimycobacterial		
Kuhn [39]	1	(CLR)					
Edelstein [10]	15	10 (MIN)	5 (RIF-EMB)				
Kullavanijaya [15]	15	9 (TMS), 1 (TRC), 1 (MIN)	3 (STR-INH-EMB), 1 (RIF-EMB)				
Alinovi [34]	1	(TMS)					
Iredell [14]		7 (TMS), 7 (TRC)	6 (RIF-EMB)			+3	
Guarda [33]	1	(TMS)					
Clark [26]	1			(MIN-RIF-EMB)			
Kern [27]	8	(DOX-M)			(RIF-antimicrobial)		
Lacy [64]	4			(RIF-EMB)			
Chow [61]	24		14 (RIF-EMB)	10 (RIF-EMB)			
Ljungberg [31]	2	(TMS, DOX-R)		(RIF-EMB)			
Arai [60]	1	(AMC)					
Wendt [65]	1			(RIF-EMB-INH)			
Huminer [13]	39	14 (TMS), 1 (ERC), 2 (MIN)	8 (RIF-EMB) 2 (INH-STR), 3	2		7	Oral prednisolone, spontaneous resolution
Donta [30]	2		1 (RIF), 1 (RIF-EMB)				
Harth [74]	1			(CLR-RIFB-EMB)			
Chopra [75]	1			(CLR)			
Lam [76]	1				(CLR-EMB-RIF)		

AMC: Amikacin; AZC: Azithromycin; CIP: Ciprofloxacin; CLR: Clarithromycin; DOX: Doxycycline; EMB: Ethambutol; ERC: Erythromycin; INH: Isoniazid; LFX: Levofloxacin; M: Monotherapy; MIN: Minocycline; PRN: Protionamid; PZA: Pyrazinamide; R: Resistant; RIF: Rifampicin; RIFB: Rifabutin; STR: Streptomycin; TMS: Sulfamethoxazole-trimethoprim; TRC: Tetracycline.

Box 1. Effective therapeutic options for *Mycobacterium marinum* infections.

Spontaneous resolution
Oral medications
– Minocycline
– Doxycycline
– Trimethoprim-sulfamethoxazole
– Clarithromycin
– Azithromycin
– Ciprofloxacin
– Amikacin
– Rifampicin
– Rifabutin
– Ethambutol
Surgical treatment
Cryotherapy
X-ray therapy
Electrodesiccation
Photodynamic therapy
Local hyperthermic therapy
Combination treatments

Aubry *et al.* [9] reported one (50%) successful course of TMS, given to the patients either as monotherapy or in combination.

The drug has also been reported administered either alone [33-35]: in HIV+ patients as monotherapy [36] or in combination with antimycobacterials agents [37,38], in isolated cases.

4.3 Macrolides

Macrolides (especially clarithromycin) have been established in the treatment of some atypical mycobacterial infections, including *M. marinum.*

Wu *et al.* [3], in a retrospective study, reported one patient (100%) who responded to clarithromycin alone; one (100%) to a combination of clarithromycin and ethambutol; one (100%) to clarithromycin, ethambutol and rifampicin; one (100%) to doxycycline, clarithromycin, ciprofloxacin and rifampicin; and two (100%) who were administered a combination of isoniazid, rifampicin ethambutol and clarithromycin. Casal and Casal [17] reported seven patients (100%) who were effectively treated with clarithomycin and ethambutol.

Clarithromycin has also been used effectively as monotherapy [39-41], with antimycobacterials [42-48], or in combination with other antimicrobials [25,28,47], with both drug categories [29] and with surgical treatment [49-51] in isolated case reports.

Aubry *et al.* [9] reported 32 out of 39 (82.05%) successful courses with clarithromycin, either as monotherapy or in combination. Laing *et al.* [47] reported one (100%) patient who responded to clarithromycin combined with ciprofloxacin, and one (100%) to clarithromycin and ethambutol. In another study, Laing *et al.* [51] reported the replacement of clarithromycin with rifabutin because of nausea, despite the clinical improvement that was achieved by clarithromycin. It is preferable not to administer these two drugs together because interactions between clarithromycin and rifabutin may alter the efficacy of the macrolide and enhance the toxicity of rifabutin.

Erythromycin has not proven to be effective in the treatment of *M. marinum* infections: Huminer *et al.* [13] reported only one out of six patients (16.7%) who responded well to erythromycin.

Pristinamycin has been reported to effectively treat *M. marinum* infection in one case [9].

Azithromycin, although inactive against strains of *Mycobacterium tuberculosis*, performs well against other Mycobacteria [52]. There is only one report [53] of the successful treatment of *M. marinum* infection in a lung transplant recipient with surgical excision of the lesions and treatment with ethambutol and azithromycin for 12 months, and in practice further clinical trials will clarify the place of azithromycin [52].

4.4 Quinolones

Ciprofloxacin 500 mg b.i.d. is the most commonly used quinolone against *M. Marinum*, and has shown considerable effectiveness as a different therapeutic alternative. However, treatment failures have been observed with this agent [9].

Wu *et al.* [3] reported one patient (100%) who responded to ciprofloxacin in combination with doxycycline, clarithromycin and rifampicin. Bhatty *et al.* [4] described one patient (100%) who was successfully treated with ciprofloxacin alone, one (100%) with ciprofloxacin and doxycycline, and one (100%) with ciprofloxacin and rifampicin combined with surgical excision of the granulomatous lesion. Aubry *et al.* [9] reported two out of four (50%) successful courses of ciprofloxacin, one out of three (33.3%) courses of ofloxacin, and two out of three (66.6%) of sparfloxacin, either as monotherapy or in combination. Laing *et al.* [47] reported one patient (100%) who responded to ciprofloxacin and clarithromycin, and one (100%) to ciprofloxacin and rifampicin.

Farooqui *et al.* [54] described a case of *M. marinum* infection successfully treated with ciprofloxacin and ethambutol in an isolated case. Levofloxacin was reported to act effectively as monotherapy against *M. marinum* by Iijima *et al.* [55], as well as in combination with clarithromycin and minocycline [25].

New fluoroquinolones, such as gatifloxacin, levofloxacin, moxifloxacin and sparfloxacin, and the newer oxazolidinones, have shown potential against *M. marinum* strains [9,24,56-59]. Clinical experience of these agents is limited, and their activity has still to be demonstrated and further investigated through more case studies; however, at present, they are considered promising therapeutic alternatives.

4.5 Aminoglycosides

Amikacin is the most characteristic representative of the aminoglycoside type. The agent was first administered successfully in 1986, by Arai *et al.* [60]. The authors of the present review were able to find one more case of the successful treatment of *M. marinum* infection using amikacin, by Aubry *et al.* [9]. Nonetheless, the drug has not been widely used, probably because it can only be administered by injection and is not available for topical or oral administration.

4.6 Antimycobacterial agents

Antimycobacterial agents have been extensively used in the treatment of *M. marinum* infections. The combination of rifampicin 600 mg/day and ethambutol 15 – 25 mg/kg/day has been used effective, and are considered probably the 'standard' for severe disease or in patients with impaired immune systems [11,30]. However, treatment failures or recurrences have been noted with this regimen [9,13].

Rifamycins, rifampicin and rifamputin are the most common therapeutic choices of antimycobacterials. Huminer *et al.* [13] reported eight out of nine patients (88.9%) who responded to rifampicin plus ethambutol, and Iredell *et al.* [14] six (100%) to the same combination therapy. Chow *et al.* [61] described 14 out of 24 patients (58.33%) who were treated successfully with rifampicin plus ethambutol, and the other patients (41,66%) required additional surgical debridement to control the infection. Kullavanijaya *et al.* [15], reported one individual (100%) who was cured with rifampicin plus ethambutol, and three (100%) with a combination of streptomycin, ethambutol and isoniazid, and Kern *et al.* [27] noted successful treatment with rifampicin plus antimicrobials. Joe *et al.* [32] reported successful treatment with rifampicin plus ethambutol, and Leuenberger and Bodmer [16] with the same regimen in 12 patients. Wu *et al.* [3] described one patient (100%) who responded to rifampicin, ethambutol plus isoniazid, and five (100%) who responded to various combinations of rifampicin, antibiotics and antimycobacterials. Edelstein [10] reported 5 patients (100%) who were treated with rifampicin plus ethambutol; Casal and Casal [17], 8 patients (100%) with rifampicin alone; and Aubry *et al.* [9], 16 out of 21 (76.1%) successful courses of rifampicin, 2 (50%) with rifabutin, 10 out of 13 (76.9%) with ethambutol, 1 (33.3%) with isoniazid, and 1 (50%) with pyrazinamide.

Rifampicin has been also used effectively in isolated cases, either alone [30,62] or in combination with other antibiotics [37,38,43,44,51], antimycobacterials [30,35], antibiotics plus antimycobacterials [19,42,45,48], and with antimicrobials plus surgery [30,31,49,50,63-65]. Rifabutin has been administered successfully with clarithromycin [51].

Ethambutol is the second most frequent antimycobacterial used in the treatment of *M. marinum* infections. It has rarely been used as monotherapy, but in combination with rifampicin or with other antimycobacterials [3,15], with antibiotics [17,46,47,53,54] or a combination of antibiotics and antimycobacterials [29,42,45] and with surgery plus antimicrobacterials [26,49,50,63].

Although isoniazid and streptomycin have been successfully administered together [13], or in combination with ethambutol [15] or other combination regimens, treatment failures are very common. Most cases are intrinsically resistant to isoniazid and streptomycin [13,19,50], and pyrazinamide is generally not recommended because *M. marinum* produces pyrazinamidase [66].

4.7 Surgical treatment

Surgical procedures such as excision of the lesion, incision and drainage, debridement and curettage have been reported for the treatment of *M. marinum* infections. They have been used with various results, either as the sole therapy [7,13,14,67] or in combination with antimicrobials [6,9,13,26,30,31,49,50,61,63-65,68-71], before or after surgical treatment.

In most patients, it seems that surgery is unnecessary and may be contra-indicated [13]. Due care is required in the decision of surgical treatment and timing [11], as surgical intervention may not be associated with improvement, and may even worsen the infection [13].

Limited infections, including one or few small superficial lesions that do not respond to systemic therapy, can be treated with surgical excision [4,11]. In cases of deeper infections with extensive damage of the underlying tissues, aggressive surgical debridement of the necrotic tissues, such as synovectomies and tenosynovectomies, may be required with adjunctive, appropriate drug therapy [4,11,61].

In severe cases, repeated surgery [13], or a ray amputation, may be more effective [65] in controlling the infection than antimicrobial therapy and repeated debridements.

4.8 Other therapeutic modalities

A variety of different therapeutic modalities have been used to treat *M. marinum* infections, as optimal therapy has not been established. Cryotherapy, X-ray therapy, electrodesiccation and photodynamic therapy have been reported as effective therapeutic alternatives [10,72]. Additionally, different antibiotic regimens [10] (e.g., amoxicillin plus clavulanate potassium [9], and ampicillin sodium plus cloxacillin sodium [13]) have been prescribed with various results.

Topical medications are of limited use. The application of clotrimazole cream and 0.025% fluocinolone acetonide cream [13] has not been proved to be helpful. According to the present authors' personal experience, antibiotic creams such as fucidic acid and mupirocin are ineffective, but after 1 month of topical tacrolimus 0.1% b.i.d., lesions deteriorate.

Huminer *et al.* [13] reported that *M. marinum* infection was exacerbated after intralesional injections

with corticosteroids. Chow *et al.* [61] confirmed this observation and also noted that prior to corticosteroid injections, persistent pain and a discharging sinus were unfavorable prognostic indicators of *M. marinum* infections. Nonetheless, a slight improvement has been noted in a patient receiving oral prednisolone (40 – 60 mg) [13], but the present authors believe this result to be questionable.

In a review of invasive *M. marinum* cases, 40% were worsened after the administration of corticosteroid injection at the site of infection, 26% while receiving systemic corticosteroids and 11% secondary to acquired immunodeficiency syndrome or chemotherapy. These findings suggest that immunological impairment is probably a significant factor in the pathogenesis of *M. marinum* infections [73]. In the same study, the average time to diagnosis from symptoms onset was 17 months, and surgical debridement was required in 69% of invasive infections.

The development of severe *M. marinum* infections has been described in patients receiving anti-TNF-α agents [74,75]; in both these cases, the drug used was etanercept. Recently, a patient with *M. marinum* arthritis that was thought to be rheumatoid arthritis was reported, and he was treated as such with corticosteroids, methotrexate and infliximab therapy, with a resultant worsening of the arthritis [76]. This patient was treated successfully after discontinuation of the immunosuppressive agents with a combination of rifampicin, clarythromycin and ethambutol.

Local hyperthermic treatment has been also reported [13,22], with some success. Irradiation therapy was proved to be ineffective in two patients [77,78].

5. A vision of the future

Infection with pathogenic Mycobacteria is followed by the recruitment of mononuclear cells that phagocytose bacteria and migrate deeper into tissues. Additional macrophages and other immune cells are recruited to form complex, tightly aggregated structures – the granulomas [80,81]. It is thought that granulomas are primarily protective host immune structures that provide a focused immune response to restrict Mycobacteria; however, the bacilli within granulomas are not always eradicated, being incompletely effective [80].

In recent studies where a zebrafish infection model was used, it was revealed that Mycobacterium expresses specific virulence factors that enhance macrophage aggregation into granulomas, starting very early after infection [81]. This information creates greater complexity regarding the role of granulomas in the pathogenesis of mycobacterial infections.

Pasnik and Smith [82] have also reported a DNA vaccine encoding the *M. marinum Ag85A* gene that was injected in juvenile hybrid striped bass *Morone saxatilis* × *Morone chrysops*. It was shown that this vaccine provided significant but limited duration of protection against an acute high-dose *M. marinum* challenge.

It seems that increasing insight into the mechanisms of infection and granuloma formation will gradually lead to improved and more effective pharmaceutical treatments.

6. Conclusion

M. marinum is a non-tuberculous mycobacterium living freely in an aquatic environment. It is responsible for the development of a distinctive cutaneous infection that may result through abraded skin, following contact with contaminated salt or fresh water or infected aquariums. Activities that bring people into contact with fish tanks – increasing in popularity – seem to represent the main risk factors for *M. marinum* infections [9]; thus, aquarium workers should use gloves when cleaning fish tanks [79].

M. marinum is an uncommon cause of skin infections. Therefore, substantial delay has been observed between the appearance of the lesions and the correct diagnosis. The delay is further enhanced by the technical difficulties raised during microbiological confirmation of the organism, by isolation and identification.

The disease usually presents as a solitary, red to violaceous papule and/or nodule evolving to a verrucous plaque that may ulcerate on areas of trauma. Inflammatory nodules or abscesses can develop in severely immunosuppressed patient, usual in a sporotrichoid distribution pattern. Systematic manifestations are rare. Deep infections including tenosynovitis, arthritis, bursitis and osteomyelitis may result, even without skin inolvement, from extension of the infection or from direct inoculation. Immunological impairment, resulting either from immunosuppressive agents (corticosteroids, methotrexate, TNF-α inhibitors, chemotherapy) or acquired immune deficiency syndrome, or other conditions, probably play a significant role in the establishment of *M. marinum* infections.

The diagnosis of a skin *M. marinum* infection requires a high index of suspicion, a detailed exposure history, as well as a knowledge of the laboratory growth characteristics of the organism [11]. Although diagnosis is confirmed by isolation and identification of the organism, in practice, diagnosis remains largely presumptive based on clinicohistological features and the response to treatment [7]. Tissue cultures and antimicrobial sensitivity testing can be performed on this organism; however, as with other Mycobacteria, *in vitro* results do not necessarily correlate with *in vivo* success [11]. Polymerase chain reaction allows the early detection of the organism from a biopsy specimen. This technique may prove to be helpful and supersede conventional methods in the rapid diagnosis and species identification of non-tuberculous infections, and become the test of choice in the future [24,83]. Nonetheless, polymerase chain reaction results should be interpreted with caution, as false-positives are possible [19].

There have been many therapeutic modalities used effectively in the treatment of *M. marinum* infections, such as topical treatment, systemic administration of antimicrobials and/or antimycobacterials, surgery, local thermotherapy and combined therapy. Spontaneous remission has also been reported in untreated infections and in immunocompetent hosts. A favourable treatment outcome cannot be related to any specific antibiotic, according to a review of the literature [9,13,30]. Because of the low incidence of this infection, a comparison of different treatment regimens is difficult and no controlled studies have been performed [11].

Monotherapy is usually, but not always, associated with infections limited to skin and soft tissues, and failures are related to deeper structure infections. Additionally, treatment duration appears to be longer in patient with deeper structure infections. However, there is no proven treatment of choice because *M. marinum* is a multi-drug resistant species, and treatment is based primarily on personal experience and the preference of individual investigators, without the benefit of large studies [10].

Topical therapy as a sole treatment is completely ineffective and unnecessary. In superficial cutaneous infections, minocycline, clarithromycin [85], doxycycline and trimethoprim-sulfamethoxazole as monotherapy are effective treatment options. Ciprofloxacin has also shown considerable effectiveness as an alternative therapeutic option against *M. marinum*. In cases of severe infections, including a sporotrichoid distribution pattern, a combination of rifampicin and ethambutol seems to be the recommended regimen. The use of isoniazid, streptomycin and pyrazinamide should be avoided, as it is well documented that this organism is usually resistant to these agents [19,50]. New fluoroquinolones have shown efficient potency against *M. marinum* strains [9,24,56-59]. Clinical experience is still limited with these agents; however, they are promising potential therapeutic alternatives.

Surgical treatment is usually unnecessary and must be cautiously applied. Cryotherapy, X-ray therapy, electrodesiccation, photodynamic therapy and local hyperthermic therapy have also been reported as effective therapeutic alternatives.

7. Expert opinion

In a thorough search of the literature since 1986 (**Table 1**) regarding the treatment of *M. marinum* skin infections, we assessed only treated persons, with a variety of different treatments, and we concluded the following significant therapeutic quidelines:

- Activities bringing people into contact with fish tanks is the main risk factor for *M. marinum* infections, are increasing in popularity. Consequently, such people should use gloves when cleaning fish tanks or when in contact with tropical fish.
- Immunosuppresed patients or individuals with wounds or open skin lesions should avoid direct contact with aquariums or aquatic animals.
- Immunological impairment is probably a significant factor in the pathogenesis of the establishment of *M. marinum* infections.
- Routine susceptibility testing of *M. marinum* is not recommended.
- Topical therapy as a sole treatment is completely ineffective and unnecessary in *M. marinum* infections.
- In limited superficial cutaneous infections (Type I), the second-generation tetracycline minocycline (100 mg b.i.d.), clarithromycin 500 mg b.i.d. and the 'older', doxycycline (100 mg b.i.d.) and trimethoprim-sulfamethoxazole (800 mg b.i.d.), each as monotherapy, are considered effective treatment options.
- Drug resistance variants and combination therapy – usually of two drugs – may be required.
- In immunocompromised individuals or in cases of severe cutaneous infections (Type II or III) with nodules, abscesses and/or sporotrichoid distribution pattern, a combination of rifampicin 600 mg/day and ethambutol 15 – 25 mg/kg/day seems to be the most consistently recommended regimen.
- Ciprofloxacin 500 mg b.i.d. has shown considerable effectiveness as a therapeutic alternative against *M. marinum.*
- Azithromycin 500 mg/day possesses good activity against other Mycobacteria and may become a promising treatment in the future.
- In limited or severe cutaneous infections (Type I – III), surgical treatment may be required if the infection has not been controlled by chemotherapy.
- Deeper infections (Type III) may require prolonged systemic treatment and surgical debridement. However, the selection of cases and the time of surgical intervention require good judgment.
- In disseminated infection or bacteraemia (Type IV), combined (antimicrobial plus antimycobacterial) intravenous therapy of three drugs may be required. However, immunosuppressed patients respond poorly to the above therapy.
- According to the literature review, no favourable treatment outcome can be related to any specific antibiotic. Acquired resistance has not been reported for *M. marinum.*
- Treatment regimens vary in length, and are based on the resolution of each patient's lesions. There is no recommended duration of treatment; however 3 months of therapy is considered the average duration. It is recommended to continue therapy for 4 – 6 weeks after clinical resolution of lesions.
- The use of isoniazid, streptomycin and pyrazinamide as empirical treatment options should be avoided, as the resistance of the organism to these agents is well documented.
- Increased awareness and great emphasis is given in early diagnosis, as the disease is curable with appropriate treatment.

- Cryotherapy, X-ray therapy, electrodesiccation, photodynamic therapy and local hyperthermic therapy therapy have also been proposed as therapeutic alternatives.
- Molecular methods, such as polymerase chain reaction, will allow the early detection of the organism from a biopsy specimen. This technique may prove helpful and supersede conventional methods in the rapid diagnosis and species identification of non-tuberculous infections, and become the test of choice in the future. However, polymerase chain reaction should be interpreted with caution, as false-positives are possible.
- New fluoroquinolones such as gatifloxacin, levofloxacin, moxifloxacin and sparfloxacin and newer oxazolidinones have shown efficacy against *M. marinum* strains. Clinical experience with these agents is limited; however, they are promising therapeutic alternatives.
- Future technologies, aiming at the identification of specific antimicrobial-resistant genetic mutations in bacterial strains may lead to better antimicrobial treatment for affected individuals.
- In the future, it seems possible that histopathological examination might be greatly assisted by the rapidly improving possibilities with *in vivo* imaging.
- *M. marinum* infection should always be included in the differential diagnosis of all cases with poorly healing wounds in upper extremities, and in persons with a history of exposure to aquariums.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

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