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Review Article

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Treatment of Extrapulmonary Nontuberculous Mycobacterial Diseases

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ABSTRACT

Nontuberculous mycobacteria (NTM) diseases mainly manifest as pulmonary illnesses, but 20 - 30% of NTM isolates originate from extrapulmonary diseases. These diseases cause a variety of clinical syndromes, including skin and soft-tissue infections, musculoskeletal infections, lymphadenitis, and disseminated disease. In skin and soft-tissue infections, musculoskeletal infections, prolonged treatment with combinations of antibiotics is effective in the treatment of NTM diseases, with surgery as an important complementary tool. The recommended duration of therapy for skin and soft-tissue infection is usually 2 – 4 months for mild disease and 6 months for severe disease, while treatment of musculoskeletal NTM disease usually requires at least 6 - 12 months. Management options of NTM lymphadenitis include surgical intervention, medical therapy, or observation. Treatment of disseminated NTM disease generally requires 6 to 12 months after immune restoration. However, despite a considerable increase in knowledge about NTM diseases, determining optimal treatment approaches remains a complex and challenging task.

Keywords: Nontuberculous mycobacteria; Extrapulmonary; Skin and soft-tissue infections; Musculoskeletal infections

INTRODUCTION

Nontuberculous mycobacteria (NTM) are facultative pathogens that are widely distributed in the environment with high isolation rates worldwide, and are not known to spread via human-to-human transmission [1]. Currently, >125 NTM species have been classified (a full list can be found at http://www.bacterio.net/mycobacterium.html) and the number of new species is constantly increasing.

The incidence of NTM disease is increasing worldwide [2, 3]. The most common clinical syndrome is pulmonary disease, but recent retrospective studies of laboratory records have revealed that 20 - 30% of NTM isolates are of extrapulmonary origin [4-8]. Extrapulmonary NTM diseases include skin and soft-tissue infections, musculoskeletal infections, lymphadenitis, and disseminated disease [9-11]. Ocular NTM infection is rare but potentially devastating. Recently, outbreaks of skin and soft-tissue infections after invasive procedures,

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mostly caused by rapidly growing mycobacteria (RGM), reported increasingly [12]. In addition, international outbreak of invasive cardiovascular infections with *Mycobacterium chimaera* occurred due to contaminated water tanks of heater–cooler units used during open-chest heart and vascular surgery [13, 14]. Individuals susceptible to extrapulmonary NTM diseases differ greatly from those with pulmonary disease in terms of both prevalence and associated risk factors [8]. In one Korean study, species commonly isolated from pulmonary specimens were *Mycobacterium intracellulare* (38.9%), *M. avium* (23.1%), *M. abscessus* (8.4%), and *M. kansasii* (7.7%); while common extrapulmonary specimens were *M. avium* (25.0%), *M. fortuitum* complex (20.9%), and *M. intracellulare* (16.6%) [15].

Due to a lack of systematic epidemiologic studies, the optimal treatment regimens and durations remain undefined for most NTM species, as do the roles of surgery. Therefore, despite a considerable increase in knowledge about NTM diseases, their treatment is still a therapeutic challenge, and the outcomes can be disappointing. The purpose of this review is to summarize the current knowledge concerning the treatment of extrapulmonary diseases associated with NTM.

SKIN AND SOFT TISSUE INFECTIONS

The most common manifestation of extrapulmonary NTM disease is skin or soft-tissue infection. These infections usually develop after traumatic injury, cosmetic procedures, or surgery, which can expose wounds to soil, water, or medical devices contaminated with environmental mycobacteria [16-22]. Previous report has suggested that incidence of cutaneous NTM infection has increased nearly 3-fold during the past 30 years [12]. RGM associated more with cosmetic and surgical procedures, whereas slow glowing mycobacteria (SGM) infections were limited to patients with traumatic injuries [12]. RGM often present with single-site than multisite infections [12].

1. Rapidly growing mycobacteria

Rapidly growing mycobacteria (RGM), including *M. abscessus* complex, *M. chelonae*, and *M. fortuitum*, are increasingly encountered species causing skin and soft tissue infections. Acupuncture, contaminated ultrasound gel, mesotherapy, and injection of dermal fillers have been reported as the causes of large outbreaks in the last 2 decades [16-22]. *M. abscessus* complex and *M. chelonae* are frequently related to long-term steroid treatment, immunosuppression, or concurrent illnesses [21]. Cutaneous and soft tissue *M. fortuitum* infections occur in immunocompetent people, usually after penetrating trauma or invasive surgery at the infection site. The recommended duration of therapy for cutaneous RGM infection is usually 4 months for mild disease and 6 months for severe disease. Medical therapy including at least 2 antibiotics is recommended to mitigate the risk of emergent antibiotic resistance. Surgery can be an important complementary approach to treat these diseases, depending on the severity and location [9-11].

M. abscessus complex (*M. abscessus*, *M. bolletii,* and *M. massiliense*) is usually susceptible to amikacin and imipenem/cefoxitin [23]. Clofazimine is highly efficacious against *M. abscessus* complex *in vitro* and exhibits synergy with amikacin [24, 25]; it also appears to have some synergy with macrolides [26]. Macrolides are considered a standard tool in the treatment of NTM infections. However, the erythromycin ribosomal methylase (*erm*) gene, which is associated with inducible resistance to macrolide antibiotics, has been identified in

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several clinically relevant RGM, including the *erm*(41) gene in the *M. abscessus* complex [27]. Because of the presence of functional *erm*(41) genes in *M. abscessus* and *M. bolletii*, which confer inducible macrolide resistance, macrolides should not be used as active *M. abscessus* complex antibiotics, unless the organism is known to be macrolide-susceptible [23]. In contrast, *M. massiliense* have nonfunctional *erm*(41) genes [28]. When the *M. abscessus* complex is susceptible to macrolide, azithromycin should be considered the macrolide of choice, because it has the added benefits of fewer drug–drug interactions and daily dosing rather than the twice-daily dosing required with clarithromycin [29]. Recent data has demonstrated that azithromycin is also more active, easier to tolerate, and causes somewhat less activation of the inducible macrolide resistance mechanism [30]. *M. massiliense* isolates in the largest surgical-site infection epidemic were generally susceptible to amikacin and clarithromycin, but resistant to cefoxitin, ciprofloxacin, and doxycycline [31]. In addition, they were reproducibly tolerant to 2% glutaraldehyde solution for disinfecting surgical devices [31].

M. chelonae is distinguished from the *M. abscessus* complex by its macrolide susceptibility and cefoxitin resistance [9]. In one study of outbreaks of cutaneous infection associated with tattooing, most patients were successfully treated with clarithromycin, both alone and in combination with tobramycin [32]. In another study, most patients exhibited clinical improvement after treatment with a macrolide antibiotic and/or doxycycline [33].

M. fortuitum strains are usually susceptible to multiple oral antibiotics [9]. This isolate was generally susceptible to amikacin, cefoxitin, ciprofloxacin, doxycycline, gentamicin, and minocycline, and resistant to sulfa, clarithromycin, azithromycin, and amoxicillin/clavulanate [34]. One study investigated 61 patients and reported no difference in outcome between 15 patients receiving monotherapy (usually doxycycline or minocycline) and 33 patients receiving dual drug therapy (usually ciprofloxacin in combination with clarithromycin, doxycycline, or minocycline) for a median duration of 4 months [34].

2. *Mycobacterium marinum*

M. marinum is a slowly growing, waterborne mycobacterium. Infection is rare and is caused by direct injury from fish fins, or after cutaneous trauma and subsequent exposure to contaminated water or infected animals. Susceptible individuals include those with aquatic-based occupations and interests, including fishers, fishery workers, seafood handlers, and water-related recreational enthusiasts [35, 36]. Infection results in localized cutaneous disease in immunocompetent individuals. Less commonly, deeper tissues may be involved, causing tenosynovitis, arthritis, and osteomyelitis. *M. marinum* is susceptible to clarithromycin, rifampin, ethambutol, amikacin, linezolid, and trimethoprim/sulfamethoxazole [35]. Routine susceptibility testing of *M. marinum* isolates is not recommended, because the species does not exhibit variability in susceptibility to clinical useful antibiotic agents nor significant risk of acquired mutational resistance [37]. Although successful treatment of *M. marinum* infection has been reported with single drug therapies, these should be limited to patients with mild disease. Treatment with at least 2 active agents is recommended for at least 1 – 2 months after resolution of skin lesions. Combinations including clarithromycin, rifampin, and/or ethambutol are likely best [35, 36]. The addition of amikacin has been used to successfully treat refractory disease [38]. Surgical treatment may be required for deep tissue infections [9]. Local heat application may be a useful adjuvant therapy, because of the low temperatures required for optimal *M. marinum* growth [39].

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3. *Mycobacterium ulcerans*

M. ulcerans, the causative agent of Buruli ulcer, is found mainly in tropical and subtropical regions [40]. Potential reservoirs include water, fish and shellfish, animals, and insects, including mosquitoes [40]. A combination of rifampin and streptomycin for 8 weeks was introduced as a first line therapy for patients with Buruli ulcer in 2004 [41]. Australian study group evaluated the efficacy of rifampin-based oral medical therapy combined with either clarithromycin or a fluoroquinolone for 8 weeks [42], and showed an excellent rate of cure and an acceptable toxicity profile. Currently, the World Health Organization recommends 8 weeks of rifampicin with either streptomycin or clarithromycin as a treatment for Buruli ulcer [43, 44]. As an adjunctive treatment, surgery plays an important role in the management of Buruli ulcer for patients with large, severe ulcers.

4. *Mycobacterium avium* complex

M. avium complex (MAC) was considered to consist of only *M. intracellulare* and *M. avium*. MAC now comprises more than 10 species or subspecies [45]. Cutaneous MAC disease is caused by direct inoculation via trauma, injection, or surgery. Typical skin lesions include ulcerations, erythematous plaques, and abscesses, and a combination of debridement and chemotherapy is usually recommended. Treatment with at least 3 drugs (usually clarithromycin, rifampin, and ethambutol) for 6–12 months is required. For severe cases, amikacin is recommended for the first 6 weeks [45, 46].

MUSCULOSKELETAL INFECTIONS

NTM diseases involving the musculoskeletal system are rare and their clinical presentations differ with the immune status of the patient. Immunocompetent patients usually present with focal infections in tendon sheaths, bursa, joints, and bones, which are caused by direct inoculation of the organisms through trauma, penetrating injury, needle injection, or contamination during surgical procedures [47, 48]. Immunocompromised patients often present with vertebral involvement, usually as a component of disseminated disease.

Several case studies of NTM musculoskeletal infections have been performed [48, 49]. In a study of 29 cases over 13 years in Korea, all patients required surgical intervention in addition to antibiotics, and the isolates were *M. intracellulare* in 6 patients, *M. fortuitum* in 3, *M. abscessus* in 2, and *M. marinum* in 1. Involved sites included the hand/wrist (n = 9), knee (n = 5), spine (n = 4), foot (n = 2), elbow (n = 2), shoulder (n = 1), ankle (n = 2), leg (n = 3), and in 1 patient, multiple sites. The mean duration of antibiotics was 13.5 months (0.5–60 months) [49]. In a series of 14 cases of nonspinal NTM musculoskeletal infection over 6 years in the USA, all but 1 patient were ultimately cured by combined medical and surgical treatment [48]. Prosthetic joint infection (PJI) (n = 6), septic arthritis (n = 5), osteomyelitis (n = 3), tendon sheath infection (n = 2), skin abscess (n = 2), cellulitis (n = 2), and surgical wound infection (n = 1) were observed. The median duration of antibiotics was 14 months (2–39 months). The median duration for the 7 patients with RGM was 6 months, but was longer for patients with slow-growing NTM (14 months).

NTM tenosynovitis occurs most frequently in the hand and wrist, because of the abundance of synovial fluid and tissue and a higher probability of penetrating injury. Usually, slowly growing species, especially *M. marinum*, are involved [50]. A study of 28 cases of musculoskeletal *M. marinum* infection found that 93% of cases involved the fingers or

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hands [51]. Although not pathognomonic, a radiographic or operative finding of "rice body" formation, white nodules consisting of acidophilic material surrounded by fibrin and collagen embedded within tendon sheaths or bursa, should raise suspicion for the diagnosis [52]. Most diseases were managed with triple-drug therapies and surgery, and the median treatment duration was 5 months (2–12 months) [51]. *M. terrae* complex can result in debilitating tenosynovitis of the upper extremities that complicates trauma [53].

NTM prosthetic joint infections can rarely occur. RGM are a more common cause of prosthetic joint infections than SGM [54]. A study of 8 cases of prosthetic joint infection caused by RGM over 4 decades at the Mayo Clinic required a combination of resection arthroplasty and antibiotic therapy [55]. After surgical debridement or resection arthroplasty, antimicrobial therapy was administered for a median duration of 31 weeks (2.5 – 54 weeks). *M. chelonae* (n = 3), *M. abscessus* (n = 2), *M. fortuitum* (n = 3), and *M. smegmatis* (n = 1) were isolated. A review article including 43 RGM PJIs in 41 patients showed that the majority of these infections were caused by *M. fortuitum* and *M. chelonae* and occurred in immunocompetent hosts [56]. Given the lack of a standard of care, a variety of treatment approaches were taken in 43 cases. Most patients were cured following two-stage exchanges and average length of 4 months (3 weeks – 6 months) antibiotic treatment following the removal of the infected joint and placement of a spacer. MAC complex also may be a rare cause of PJI, occurring almost exclusively in immunocompromised patients [54].

Vertebral osteomyelitis (VO) is also rare [57]. Literature review including a total of 69 cases of VO caused by NTM between 1961–2014 showed that MAC was the most common etiologic organism and a variety of immunosuppressive diseases were observed in 49.3% of the cases [57].

NTM musculoskeletal infections usually require combined medical and surgical management. A minimum of 6 months of multidrug antibiotic therapy, determined according to the antibiotic susceptibilities of the organism, is usually recommended but the optimal length of therapy is not known. Removal of all infected tissue is required, and repeated debridement and/or persistent drainage may be required [47]. Treatment durations of 12 months or longer may be warranted for severe infections or incomplete debridement [58].

LYMPHADENITIS

Cervical adenitis is the most common form of NTM disease in children [59]. Affected children are usually immunocompetent and aged <5 years [59]. In the absence of human immunodeficiency virus (HIV) infection, NTM lymphadenitis rarely affects adults, as *M. tuberculosis* accounts for > 90% of culture-proven mycobacterial lymphadenitis [60], while in children, approximately 80% of culture-proven NTM lymphadenitis is due to MAC [61]. RGM were common in a Taiwanese study reporting high recurrence rates after treatment [62]. In approximately 90% of cases, unilateral lymph nodes are involved, which are not tender. The nodes can rapidly enlarge and rupture, resulting in prolonged drainage [63].

Treatment of uncomplicated NTM lymphadenitis involves complete surgical resection of the involved lymph nodes. Randomized trials have demonstrated that surgical excision produces superior cure rates and esthetic outcomes to medical therapy [64, 65]. Antibiotic therapy or an observational approach may be considered for patients with incomplete excision of abnormal tissue or recurrent lymphadenitis after surgery. A recent systematic

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review of pediatric cervicofacial NTM lymphadenitis reported adjusted mean cure rates of 98.7%, 73.2%, and 70.4% for complete excision, antibiotic therapy, and conservative management, respectively. The optimal treatment regimen for MAC lymphadenitis remains undefined, but combination therapy including clarithromycin and rifampin and/or ethambutol may be beneficial.

DISSEMINATED DISEASE

Disseminated disease due to NTM predominantly occurs in patients with advanced HIV infection. Although incidence in these patients has declined since the introduction of highly active antiretroviral therapy [66], disseminated NTM disease is still observed in patients with HIV that have CD4 counts of <50 cells/mm^3 [6]. Generally, MAC causes disseminated disease during HIV. Initial treatment of disseminated MAC disease should include at least 2 drugs, because of the probability of emergent antimycobacterial resistance [67]. Macrolide antibiotics are the cornerstone of treatment. Ethambutol protects against macrolide resistance and is recommended as a second drug in the initial treatment of disseminated MAC disease [68]. Adding rifampin to the combination of clarithromycin and ethambutol may improve survival and reduce the emergence of drug resistance [69]. In patients with acquired immune deficiency syndrome, therapy can be discontinued after at least 12 months, once symptoms have resolved and their CD4 counts have exceeded 100 cells/mm^3 for 6 months [70].

Disseminated disease also has been reported in patients with immunosuppressive treatment and in stem cell and solid organ transplantation recipients [71]. Anti-tumor necrosis factor use is associated with increased risk of NTM disease; several other anti-rheumatic drugs such as high-dose oral corticosteroids, leflunomide, hydroxychloroquine, and drugs classed as highly immunosuppressive, are also associated with NTM disease [71]. Treatment of disseminated NTM disease generally requires 6 to 12 months after immune restoration (**Table 1**) [9].

Table 1. Suggested antibiotic regimens for patients with extrapulmonary nontuberculous mycobacterial disease

Species	Suggested regimens[a]
Mycobacterium abscessus complex	
Macrolide-resistant *M. abscessus*	**Severe (initial)**: amikacin + cefoxitin/imipenem + tigecycline **Severe (continued) or mild**: 3–5 of the following antibiotics: clofazimine, linezolid, minocycline, moxifloxacin, co-trimoxazole
Macrolide-susceptible *M. abscessus* and *M. massiliense*	**Severe initial**: amikacin + cefoxitin/imipenem + azithromycin/clarithromycin **Severe (continued) or mild**: azithromycin/clarithromycin + 2–4 of the following antibiotics: clofazimine, linezolid, minocycline, moxifloxacin, co-trimoxazole
Mycobacterium chelonae	**Severe (initial)**: azithromycin/clarithromycin + tobramycin ± imipenem **Severe (continued) or mild**: azithromycin/clarithromycin + doxycycline or clofazimine or linezolid
Mycobacterium fortuitum	**Severe (initial)**: amikacin + quinolone + minocycline **Severe (continued) or mild**: quinolone + minocycline
Mycobacterium marinum	**Severe (initial)**: amikacin + azithromycin/clarithromycin + rifampin + ethambutol **Severe (continued) or mild**: azithromycin/clarithromycin + rifampin + ethambutol
Mycobacterium ulcerans	**Severe (initial)**: rifampicin + streptomycin **Severe (continued) or mild**: rifampicin + clarithromycin or moxifloxacin
Mycobacterium avium complex	
Macrolide-susceptible	**Severe (initial)**: amikacin/streptomycin + rifampin + ethambutol + azithromycin/clarithromycin **Severe (continued) or mild**: rifampin + ethambutol + azithromycin/clarithromycin

[a]*In vitro* drug susceptibility tests should be performed as soon as possible after species identification.

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CONCLUSION

Management of extrapulmonary NTM diseases requires prolonged, targeted antibiotic therapy, but the current paucity of prospective, controlled, and randomized treatment studies makes the determination of optimal treatment regimens and durations difficult. Surgery also plays an important role in treating NTM infections. Further laboratory studies and multicenter controlled trials are needed to improve the diagnosis and treatment of these diseases.

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