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,
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 growing 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/cefotaxin [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...
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].
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
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 PJI 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
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/mm³ [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/mm³ 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].

| Species | Suggested antibiotic regimens for patients with extrapulmonary nontuberculous mycobacterial disease |
|---------|--------------------------------------------------------------------------------------------------|
| **Mycobacterium abscessus complex** |  |
| Macrolide-resistant *M. abscessus* | **Severe (initial):** amikacin + cefoxitin/imipenem + tigecycline  |
|  | **Severe (continued) or mild:** 3–5 of the following antibiotics: cl dofazimine, 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: cl dofazimine, 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:** rifampicin + ethambutol + azithromycin/clarithromycin |

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

REFERENCES

1. Falkinham JO 3rd. Nontuberculous mycobacteria in the environment. Clin Chest Med 2002;23:529-51.
2. Simons S, van Ingen J, Hsueh PR, Van Hung N, Dekhuijzen PN, Boeree MJ, van Soolingen D. Nontuberculous mycobacteria in respiratory tract infections, eastern Asia. Emerg Infect Dis 2011;17:343-9.
3. Prevots DR, Marras TK. Epidemiology of human pulmonary infection with nontuberculous mycobacteria: a review. Clin Chest Med 2015;36:13-34.
4. Hermansen TS, Ravn P, Svensson E, Lillevang T. Nontuberculous mycobacteria in Denmark, incidence and clinical importance during the last quarter-century. Sci Rep 2017;7:6696.
5. Smith GS, Ghio AJ, Stout JE, Messier KP, Hudgens EE, Murphy MS, Pfaffer SL, Maillard JM, Hilborn ED. Epidemiology of nontuberculous mycobacteria isolations among central North Carolina residents, 2006-2010. J Infect 2016;72:678-86.
6. Henkle E, Hedberg K, Schafer SD, Winthrop KL. Surveillance of extrapulmonary nontuberculous mycobacteria infections, Oregon, USA, 2007-2012. Emerg Infect Dis 2013;19:2627-30.
7. Blanc P, Dutronc H, Peuchant O, Dauchy FA, Cazanave C, Neau D, Wirth G, Pellegrin JL, Morlat P, Mercie P, Tunon-de-Lara JM, Doutre MS, Pelissier P, Dupon M. Nontuberculous mycobacterial infections in a French hospital: a 12-year retrospective study. PLoS One 2016;11:e0168290.
8. Brode SK, Marchand-Austin A, Jamieson FB, Marras TK. Pulmonary versus nonpulmonary nontuberculous mycobacteria, Ontario, Canada. Emerg Infect Dis 2017;23:1898-901.
9. Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitz G, Iademarco MF, Isman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K; ATS Mycobacterial Diseases Subcommittee. American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial disease. Am J Respir Crit Care Med 2007;175:367-416.
10. Holt MR, Kasperbauer S. Management of extrapulmonary nontuberculous mycobacterial infections. Semin Respir Crit Care Med 2018;39:399-410.
11. Piersimoni C, Scarparo C. Extrapulmonary infections associated with nontuberculous mycobacteria in immunocompetent persons. Emerg Infect Dis 2009;15:1351-8; quiz 1544.
12. Wentworth AB, Drage LA, Wengenack NL, Wilson JW, Lohse CM. Increased incidence of cutaneous nontuberculous mycobacterial infection, 1980 to 2009: a population-based study. Mayo Clin Proc 2013;88:38-45.
13. Allen KB, Yuh DD, Schwartz SB, Lange RA, Hopkins R, Bauer K, Marders JA, Delgado Donayre J, Milligan N, Wentz C. Nontuberculous mycobacterium infections associated with heater-cooler devices. Ann Thorac Surg 2017;104:1237-42.
14. Chand M, Lamagni T, Kranzer K, Hedge J, Moore G, Parks S, Collins S, Del Ojo Elias C, Ahmed N, Brown T, Smith EG, Hoffman P, Kirwan P, Mason B, Smith-Palmer A, Veal P, Lalor MK, Bennett A, Walker J, Yeap
A, Isidro Carrion Martin A, Dolan G, Bhatt S, Skingsley A, Charlett A, Pearce D, Russell K, Kendall S, Klein AA, Robins S, Schelzen S, Newsholme W, Thomas S, Collyns T, Davies E, McMenamin J, Doherty L, Peto TE, Crook D, Zambon M, Phin N. Insidious risk of severe Mycobacterium chimaera infection in cardiac surgery patients. Clin Infect Dis 2017;64:335-42.

15. Kim N, Yi J, Chang CL. Recovery rates of non-tuberculous mycobacteria from clinical specimens are increasing in Korean tertiary-care hospitals. J Korean Med Sci 2017;32:1263-7.

16. Cheng A, Sheng WH, Huang YC, Sun HY, Tsai YT, Chen ML, Liu YC, Chuang YC, Huang SC, Chang CI, Chang LY, Huang WC, Hsueh PR, Hung CC, Chen YC, Chang SC. Prolonged postprocedural outbreak of Mycobacterium massiliense infections associated with ultrasound transmission gel. Clin Microbiol Infect 2016;22:382.e1-11.

17. Rodriguez JM, Xie YL, Winthrop KL, Schafer S, Sehdev P, Solomon J, Jensen B, Toney NC, Lewis PF. Mycobacterium chelonae facial infections following injection of dermal filler. Aesthet Surg J 2013;33:265-9.

18. Ivan M, Dancer C, Koehler AP, Hobby M, Lease C. Mycobacterium chelonae abscesses associated with biomesotherapy, Australia, 2008. Emerg Infect Dis 2013;19:1493-5.

19. Galmés-Truyols A, Giménez-Duran J, Bosch-Isabel C, Nicolau-Riutort A, Vanrell-Berga J, Portell-Arbona M, Seguí-Prat B, Gumá-Torá M, Martí-Alomar I, Rojo-Arias MA, Ruiz-Veramendi M. An outbreak of cutaneous infection due to Mycobacterium abscessus associated to mesotherapy. Enferm Infecc Microbiol Clin 2011;29:510-4.

20. Koh SJ, Song T, Kang YA, Choi JW, Chang KJ, Chu CS, Jeong I, Song MK, Sung HY, Kang YH, Yim JJ. An outbreak of skin and soft tissue infection caused by Mycobacterium abscessus following acupuncture. Clin Microbiol Infect 2010;16:895-901.

21. Uslan DZ, Kowalski TJ, Wengenack LW, Virk A, Wilson JW. Skin and soft tissue infections due to rapidly growing mycobacteria. Arch Dermatol 2006;142:1287-92.

22. Winthrop KL, Abrams M, Yakrus M, Schwartz I, Ely J, Gillies D, Vugia DJ. An outbreak of mycobacterial furunculosis associated with footbaths at a nail salon. N Engl J Med 2002;346:1366-71.

23. Strnad L, Winthrop KL. Treatment of Mycobacterium abscessus complex. Semin Respir Crit Care Med 2018;39:362-76.

24. Shen GH, Wu BD, Hu ST, Lin CF, Wu KM, Chen JH. High efficacy of clofazimine and its synergistic effect with amikacin against rapidly growing mycobacteria. Int J Antimicrob Agents 2010;35:400-4.

25. van Ingen J, Totten SE, Helstrom NK, Heifts LB, Boeree MJ, Daley CL. In vitro synergy between clofazimine and amikacin in treatment of nontuberculous mycobacterial disease. Antimicrob Agents Chemother 2012;56:6324-7.

26. Ferro BE, Meletiadiis J, Wattenberg M, de Jong A, van Soolingen D, Mouton JW, van Ingen J. Clofazimine prevents the regrowth of Mycobacterium abscessus and Mycobacterium avium type strains exposed to amikacin and clarithromycin. Antimicrob Agents Chemother 2015;60:1097-105.

27. Esteban J, Martin-de-Hijas NZ, García-Almeida D, Bodas-Sánchez A, Gadea I, Fernández-Roblas R. Prevalence of emr methylase genes in clinical isolates of non-pigmented, rapidly growing mycobacteria. Clin Microbiol Infect 2009;15:919-23.

28. Koh WJ, Jeon K, Lee NY, Kim BJ, Kook YH, Lee SH, Park YK, Kim CK, Shin SJ, Huitr GA, Daley CL, Kwon OJ. Clinical significance of differentiation of Mycobacterium massiliense from Mycobacterium abscessus. Am J Respir Crit Care Med 2011;183:405-10.

29. Stout JE, Floto RA. Treatment of Mycobacterium abscessus: all macrolides are equal, but perhaps some are more equal than others. Am J Respir Crit Care Med 2012;186:822-3.
30. Choi GE, Shin SJ, Min KN, Oh T, Hahn MY, Lee K, Lee SH, Daley CL, Kim S, Jeong BH, Jeon K, Koh WJ. Macrolide treatment for Mycobacterium abscessus and Mycobacterium massiliense infection and inducible resistance. Am J Respir Crit Care Med 2012;186:917-25. 
PUBMED | CROSSREF

31. Duarte RS, Lourenço MC, Fonseca Lde S, Leão SC, Amorim Ade L, Rocha IL, Coelho FS, Viana-Niero C, Gomes KM, da Silva MG, Lorena NS, Pitombo MB, Ferreira RM, Garcia MH, de Oliveira GP, Lupi O, Vilaça BR, Serradas LR, Chebabo A, Marques EA, Teixeira LM, Dalcolmo M, Senna SG, Sampaio JL. Epidemic of postsurgical infections caused by Mycobacterium massiliense. J Clin Microbiol 2009;47:2149-55. 
PUBMED | CROSSREF

32. Goldman J, Caron F, de Quatrebarbes J, Pestel-Caron M, Courville P, Doré MX, Picard D, Duval-Modeste AB, Bravard P, Joly P. Infections from tattooing. Outbreak of Mycobacterium chelonae in France. BMJ 2010;341:c5483. 
PUBMED | CROSSREF

33. Kennedy BS, Bedard B, Younge M, Tuttle D, Ammerman E, Ricci J, Doniger AS, Escuyer VE, Mitchell K, Noble-Wang IA, O’Connell HA, Lanier WA, Katz LM, Betts RF, Mercurio MG, Scott GA, Lewis MA, Goldgeier MH. Outbreak of Mycobacterium chelonae infection associated with tattoo ink. N Engl J Med 2012;367:1020-4. 
PUBMED | CROSSREF

34. Winthrop KL, Albridge K, South D, Albrecht P, Abrams M, Samuel MC, Leonard W, Wagner J, Vugia DJ. The clinical management and outcome of nail salon-acquired Mycobacterium fortuitum skin infection. Clin Infect Dis 2004;38:38-44. 
PUBMED | CROSSREF

35. Johnson MG, Stout JE. Twenty-eight cases of Mycobacterium marinum infection: retrospective case series and literature review. Infection 2015;43:655-62. 
PUBMED | CROSSREF

36. Sia TY, Taimur S, Blau DM, Lambe J, Ackelsberg J, Yacisin K, Bhatnagar J, Ritter J, Shieh WJ, Muehlenbachs A, Shulman K, Fong D, Kung E, Zaki SR. Clinical and pathological evaluation of Mycobacterium marinum group skin infections associated with fish markets in New York City. Clin Infect Dis 2016;62:590-5. 
PUBMED | CROSSREF

37. Clinical and Laboratory Standards Institute (CLSI). Susceptibility testing of mycobacteria, nocardia, and other aerobic actinomycetes. Approved standard. 2nd ed. M24-A2. Wayne, PA: CLSI; 2011.

38. Friedman ND, Athan E, Walton AL, O’Brien DP. Increasing experience with primary oral medical therapy for Mycobacterium ulcerans disease in an Australian cohort. Antimicrob Agents Chemother 2016;60:2692-5. 
PUBMED | CROSSREF

43. World Health Organization (WHO). Treatment of Mycobacterium ulcerans disease (Buruli ulcer): Guidance for health workers. Geneva: WHO; 2012.

44. World Health Organization (WHO). Buruli ulcer (Mycobacterium ulcerans infection): fact sheet. www.who.int/mediacentre/factsheets/fs199/en/. Accessed 28 February 2017.

45. Lee MR, Chien JY, Huang YT, Liao CH, Shu CC, Yu CJ, Hsieh PR. Clinical features of patients with bacteraemia caused by Mycobacterium avium complex species and antimicrobial susceptibility of the isolates at a medical centre in Taiwan, 2008-2014. Int J Antimicrob Agents 2017;50:35-40. 
PUBMED | CROSSREF

46. Xu HB, Jiang RH, Li L. Treatment outcomes for Mycobacterium avium complex: a systematic review and meta-analysis. Eur J Clin Microbiol Infect Dis 2014;33:347-58. 
PUBMED | CROSSREF
47. Bi S, Hu FS, Yu HY, Xu KJ, Zheng BW, Ji ZK, Li JJ, Deng M, Hu HY, Sheng JF. Nontuberculous mycobacterial osteomyelitis. Infect Dis (Lond) 2015;47:673-85.

48. Goldstein N, St Clair JB, Kasperbauer SH, Daley CL, Lindeque B. Nontuberculous mycobacterial musculoskeletal infection cases from a tertiary referral center, Colorado, USA. Emerg Infect Dis 2019;25:1075-83.

49. Park JW, Kim YS, Yoon JO, Kim JS, Chang JS, Kim JM, Chun JM, Jeon IH. Non-tuberculous mycobacterial infection of the musculoskeletal system: pattern of infection and efficacy of combined surgical/antimicrobial treatment. Bone Joint J 2014;96:1561-5.

50. Zenone T, Boibieux A, Tigaud S, Fredenucci JF, Vincent V, Chidiac C, Peyramond D. Non-tuberculous mycobacterial tenosynovitis: a review. Scand J Infect Dis 1999;31:221-8.

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

52. Lee EY, Rubin DA, Brown DM. Recurrent Mycobacterium marinum tenosynovitis of the wrist mimicking extraarticular synovial chondromatosis on MR images. Skeletal Radiol 2004;33:405-8.

53. Smith DS, Lindholm-Levy P, Huijt GA, Heifets LB, Cook JL. Mycobacterium terrae: case reports, literature review, and in vitro antibiotic susceptibility testing. Clin Infect Dis 2000;30:444-53.

54. Ingraham NE, Schneider B, Alpern JD. Prosthetic joint infection due to Mycobacterium avium-intracellulare in a patient with rheumatoid arthritis: a case report and review of the literature. Case Rep Infect Dis 2017;2017:8682354.

55. Eid AJ, Berbari EF, Sia IG, Wengenack NL, Osmon DR, Razonable RR. Prosthetic joint infection due to rapidly growing mycobacteria: report of 8 cases and review of the literature. Clin Infect Dis 2007;45:867-94.

56. Henry MW, Miller AO, Kahn B, Windsor RE, Brause BD. Prosthetic joint infections secondary to rapidly growing mycobacteria: two case reports and a review of the literature. Infect Dis (Lond) 2016;48:453-60.

57. Kim CJ, Kim UJ, Kim HB, Park SW, Oh MD, Park KH, Kim NJ. Vertebral osteomyelitis caused by non-tuberculous mycobacteria: Predisposing conditions and clinical characteristics of six cases and a review of 63 cases in the literature. Infect Dis (Lond) 2016;48:509-16.

58. Hogan JI, Hurtado RM, Nelson SB. Mycobacterial musculoskeletal infections. Infect Dis Clin North Am 2017;31:369-82.

59. Haverkamp MH, Arend SM, Lindeboom JA, Hartwig NG, van Dissel JT. Nontuberculous mycobacterial infection in children: a 2-year prospective surveillance study in the Netherlands. Clin Infect Dis 2004;39:450-6.

60. Anonymous. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. This official statement of the American Thoracic Society was approved by the Board of Directors, March 1997. Medical Section of the American Lung Association. Am J Respir Crit Care Med 1997;156:51-25.

61. Thegerström J. Pinpointing the source of infection of Mycobacterium avium hominissuis in children. Infect Dis (Lond) 2017;49:617-24.

62. Ding LW, Lai CC, Lee LN, Huang LM, Hsueh PR. Lymphadenitis caused by non-tuberculous mycobacteria in a university hospital in Taiwan: predominance of rapidly growing mycobacteria and high recurrence rate. J Formos Med Assoc 2005;104:987-904.

63. Hassell M, French MA. Mycobacterium avium infection and immune restoration disease after highly active antiretroviral therapy in a patient with HIV and normal CD4+ counts. Eur J Clin Microbiol Infect Dis 2001;20:889-91.
64. Lindeboom IA, Kuijper EJ, Bruinesteijn van Coppenraet ES, Lindeboom R, Prins JM. Surgical excision versus antibiotic treatment for nontuberculous mycobacterial cervicofacial lymphadenitis in children: a multicenter, randomized, controlled trial. Clin Infect Dis 2007;44:1057-64.

65. Lindeboom IA, Lindeboom R, Bruinesteijn van Coppenraet ES, Kuijper EJ, Tuk J, Prins JM. Esthetic outcome of surgical excision versus antibiotic therapy for nontuberculous mycobacterial cervicofacial lymphadenitis in children. Pediatr Infect Dis J 2009;28:1028-30.

66. Tumbarello M, Tacconelli E, de Donati KG, Bertagnolio S, Longo B, Ardito F, Fadda G, Cauda R. Changes in incidence and risk factors of Mycobacterium avium complex infections in patients with AIDS in the era of new antiretroviral therapies. Eur J Clin Microbiol Infect Dis 2001;20:498-501.

67. Chaisson RE, Benson CA, Dubé MP, Heifets LB, Korvick JA, Elkin S, Smith T, Craft JC, Sattler FR. Clarithromycin therapy for bacteremic Mycobacterium avium complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. AIDS Clinical Trials Group Protocol 157 Study Team. Ann Intern Med 1994;121:905-41.

68. Dubé MP, Sattler FR, Torriani FJ, See D, Havlir DV, Kemper CA, Dezfoul MG, Bozzette SA, Bartok AE, Leedom JG, Tilles JG, McCutchan JA. A randomized evaluation of ethambutol for prevention of relapse and drug resistance during treatment of Mycobacterium avium complex bacteremia with clarithromycin-based combination therapy. California Collaborative Treatment Group. J Infect Dis 1997;176:1225-32.

69. Benson CA, Williams PL, Currier JS, Holland F, Mahon LF, MacGregor RR, Inderlied CB, Flexner C, Neidig J, Chaisson R, Notario GF, Hafner R; AIDS Clinical Trials Group 223 Protocol Team. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated Mycobacterium avium complex disease in persons with acquired immunodeficiency syndrome. Clin Infect Dis 2003;37:1234-43.

70. Kaplan JE, Benson C, Holmes KK, Brooks JT, Pau A, Masur H; Centers for Disease Control and Prevention (CDC); National Institutes of Health; HIV Medicine Association of the Infectious Diseases Society of America. Guidelines for prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. MMWR Recomm Rep 2009;58:1-207.

71. Brode SK, Jamieson FB, Ng R, Campitelli MA, Kwong JC, Paterson JM, Li P, Marchand-Austin A, Bombardier C, Marras TK. Increased risk of mycobacterial infections associated with anti-rheumatic medications. Thorax 2015;70:677-82.