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Treatment of Non-Tuberculous Mycobacterial Lung Disease

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Opinion Statement

Treatment of non-tuberculous mycobacterial lung disease (NTM-LD) is challenging for several reasons including the relative resistance of NTM to currently available drugs and the difficulty in tolerating prolonged treatment with multiple drugs. Yet-to-be-done, large, multicenter, prospective randomized studies to establish the best regimens will also be arduous because multiple NTM species are known to cause human lung disease, differences in virulence and response to treatment between different species and strains within a species will make randomization more difficult, the need to distinguish relapse from a new infection, and the difficulty in adhering to the prescribed treatment due to intolerance, toxicity, and/or drug-drug interactions, often necessitating modification of therapeutic regimens. Furthermore, the out-of-state resident status of many patients seen at the relatively few centers that care for large number of NTM-LD patients pose logistical issues in monitoring response to treatment. Thus, current treatment regimens for NTM-LD is largely based on small case series, retrospective analyses, and guidelines based on expert

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Conflict of Interest

Dr. Julie V. Philley, Dr. Jennifer R. Honda, Dr. Michael M. Chan, Dr. Shannon Kasperbauer, Dr. Nicholas D. Walter, and Dr. Edward D. Chan declare that they have no conflict of interest. Dr. Mary Ann DeGroote is a co-PI for the pre-clinical evaluation of new therapeutic entities for NTM therapeutics with Crestonepharma Inc. This is an SBIR phase II grant. There is no overlap with antimicrobial agents described in this review.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

opinions. It has been nearly 10 years since the publication of a consensus guideline for the treatment of NTM-LD. This review is a summary of the available evidence on the treatment of the major NTM-LD until more definitive studies and guidelines become available.

Keywords

antibiotic; atypical mycobacteria; bronchiectasis; *Mycobacterium abscessus* complex; *Mycobacterium avium* complex; pulmonary disease

Introduction

Treatment of non-tuberculous mycobacterial lung disease (NTM-LD) is challenging because different NTM with varying virulence and drug susceptibility are known to be causative agents, the relative resistance of NTM to available antibiotics, requirement of multi-drug regimens for an extended period of time, frequent intolerance of the prescribed regimens, and the relatively high frequency of relapse and/or reinfection. Furthermore, expert-recommended antibiotic regimens are largely based on case series, small randomized studies, expert opinions, and anecdotal clinical experience. Herein, we review the current recommendations on treatment of NTM-LD based on the available evidence.

The prevalence of NTM lung disease and potential sources of infections

Well accepted among the clinical and scientific community is the rising rates of NTM-LD. Because of the chronicity of NTM-LD, the best measures of disease burden in a population are prevalence rates (1). In several countries including Australia, Canada, Germany, and Taiwan, the prevalence has increased by 1.5- to 6-fold over the past decade (2–5). In those >65 years-old in the United States, annual prevalence rates significantly increased from 20 to 47 cases/100,000 between 1997–2007 (an increase of 8% per year) with Hawaii having the highest prevalence at 396 cases/100,000 (6). These numbers are likely underestimated because of a lack of mandatory reporting in the U.S.

There are potentially multiple reasons for the increased number of NTM-LD cases. One possibility is that the true number of cases is not increasing, but rather there are simply more cases being diagnosed due to greater utilization of chest CT scan (prompting sputum cultures in those with abnormalities), more reliance on more sensitive molecular diagnostic techniques, and greater awareness of NTM-LD by clinicians. However, increased exposure to NTM is also a factor as evinced by a study showing that skin test reactivity to purified protein derivative-B (a mixture of antigens from *M. intracellulare*) in the 1999–2000 period (~7,400 subjects) was significantly greater than those tested in the 1971–1972 period (~1,500 subjects) (17% vs. 11%, respectively) (7). Greater exposure may be related to enhanced biofilm development on polyvinyl chloride, steel, and polycarbonate surfaces – where there is greater propensity for NTM biofilm formation compared to copper and glass surfaces (8) – and subsequent inhalation of fractured biofilm carried in fine water aerosols such as that seen with high efficiency showerheads, water misters, and hot tub bubble generators (9). In particular, NTM glycopeptidolipids have been linked to enhanced formation of biofilms (10). The production of extracellular polymeric substances (*i.e.*, lipids,

polysaccharides, and nucleic acids) in a three-dimensional matrix during the production of biofilms is a successful strategy used by NTM for survival in the environment (11). Compared to planktonic bacteria, those residing in biofilms exhibit 10- to 1000- fold greater resistance to antimicrobial agents and decontaminants (8, 12). The close proximity of NTM to each other in biofilms can also promote horizontal gene transfer (*e.g.*, acquisition of drug resistance genes) and switch to slower growth rates that inhibit antibiotic efficiency. With increasing use of chlorination, it is possible that NTM – which are relatively resistant to chlorine except for *M. scrofulaceum* which has virtually disappeared with widespread chlorination – have increased in number because of less competition from chlorine-sensitive organisms. We have also speculated that climate change with global warming and natural disasters may also contribute to increasing infection and prevalence of NTM-LD (13).

While a link has been made to water and associated biofilms as potential sources of NTM lung infections (14), a recent study found that *M. intracellulare* – a member of the *Mycobacterium avium* complex (MAC) group of organisms and historically the most common cause of NTM-LD in the U.S. – was not commonly found in water biofilms; instead, *M. chimaera* (another MAC organism) was found in household water and biofilm samples (15). However, since traditional non-sequencing methods of NTM identification cannot speciate *M. chimaera* with any reliability, it is likely that a significant number of isolates previously classified as *M. avium* or *M. intracellulare* were in fact *M. chimaera* or another species under the MAC umbrella (16). Indeed, a report from Germany showed that 143/166 (85%) of *M. intracellulare* isolates initially identified by *16S rRNA* gene-based methods were actually misidentified and were reclassified as *M. chimaera* after multilocus sequence analyses including a combination of 16S rRNA gene and 16S–23S internal transcribed spacer (ITS) region sequencing (17). Furthermore, *rpoB* gene and 16S–23S ITS multilocus sequence analyses used to speciate 448 clinical MAC isolates in the U.S. revealed the dominant MAC to be *M. avium* (54%), *M. chimaera* (28%), and *M. intracellulare* (18%) (18). Thus, since a significant number of previously identified *M. intracellulare* clinical isolates may actually be another MAC species, the infrequent finding of *M. intracellulare* in water biofilms should not diminish the importance of water and their associated biofilms as sources for NTM infections.

Brief synopsis of NTM identification and diagnosis of NTM lung disease

Determining the precise NTM species and even subspecies is critical since the antibiotic regimen and prognosis varies with the responsible NTM. Newer molecular techniques that allow more precise identification include line probe hybridization and PCR. For the most precise identification of NTM species and subspecies, sequencing of *hsp65* and *rpoB* genes, as well as the 16S-23S ITS is recommended (19–23). Furthermore, the infrequent use of NTM genotyping in the clinical setting makes it difficult to ascertain whether recurrent disease is due to a relapse or a new infection acquired from the environment.

There is no reliable biomarker that distinguishes NTM colonization vs. NTM-LD. Thus, after identification of NTM from the respiratory tract, other clinical factors must be considered to determine if the isolated NTM is clinically relevant. A guideline published jointly by the American Thoracic Society/Infectious Diseases Society of America (ATS/

IDSA) espoused that, at a minimum, NTM-LD can be diagnosed when NTM-positive patients are symptomatic (*e.g.*, cough, sputum, fatigue) and have radiographic features that are consistent with NTM-LD (*e.g.*, nodules, bronchiectasis, tree-in-bud opacities, cavities). The NTM species can also help predict the clinical relevance; *e.g.*, at one end of the spectrum, *M. gordonae* almost always is a laboratory contaminant and not a culprit organism whereas the presence of *M. kansasii* is a better predictor of NTM-LD (Table 1).

Even if one has established the presence of NTM-LD, patient factors such as age, co-morbid conditions, life expectancy, and goals of care (*e.g.*, curative vs. symptom control) are important to consider since treatment for NTM-LD entails multiple antibiotics for an extended period of time (months to several years).

Treatment of NTM-LD is based on small clinical studies and expert opinion

Although treatment trials have been performed on patients with MAC-LD, participant numbers are generally small and often single-centered (24–28). Large, multi-center, prospective trials reminiscent of the studies performed on tuberculosis in Hong Kong, East Africa, U.S., and several other countries have not been done with NTM-LD. Challenges to conduct such studies include the relatively few NTM-LD patients at most centers, out-of-state resident status of many patients at the few centers that care for large number of NTM-LD patients, the difficulty of distinguishing relapse and reinfection with standard laboratory techniques, and the relatively high frequency of intolerance or toxicity to various antibiotic regimens in an older population, often necessitating temporary or permanent discontinuation of certain drugs or modification of regimens based on co-morbid conditions or drug-drug interactions. It has been nearly 10 years since the publication of the ATS/IDSA guidelines in the diagnosis and treatment of NTM-LD (29). Yet, Admejian *et al* recently showed that following the treatment guidelines is poor among clinicians who treat such patients (30). We discuss below the treatment of NTM-LD caused by MAC, *M. kansasii*, *M. malmoense*, *M. xenopi*, *M. szulgai*, *M. simiae*, and *M. abscessus* complex.

Treatment for *Mycobacterium avium* complex (MAC)

MAC has traditionally been comprised of several well-known species, including *M. avium* and *M. intracellulare* but more recently, also include a third group known as MAC “X”, comprised of at least eight less common MAC species (15). In the U.S., standard laboratory testing is completed by partial sequencing and subsequent phylogenetic analysis of the *16S rRNA* gene and thus the delineation of different strains of MAC is frequently unavailable. Currently, all species within MAC are similarly treated according to standard ATS/IDSA guidelines (29). But clearly, different “MAC strains” are associated with differential virulence (31); if future analyses find the virulence of MAC species significantly differs, distinguishing these MAC species may ultimately prove useful for prognosticating and perhaps guiding therapy (32, 33).

In contrast to treatment for tuberculosis, where *in vitro* susceptibility testing is a useful guide for effective *in vivo* response to antibiotics (29), the Clinical Laboratory Standards Institute and ATS/IDSA guidelines recommend testing MAC susceptibility only to clarithromycin (or

azithromycin) (29). This recommendation is based on studies showing a relationship between clinical efficacy and minimum inhibitory concentration (MIC) for clarithromycin, but not for rifampicin, ethambutol or streptomycin (34–38). No studies have established superiority of one macrolide over another (28). Combined rifampin and ethambutol drug susceptibility testing has shown mutual lowering of the individual drug MIC, but the clinical importance of this *in vitro* synergy is controversial (39, 40). Susceptibility to amikacin (≤ 16 μg/mL for susceptible, 32 μg/mL for intermediate, and ≥ 64 μg/mL for resistant) may also help predict treatment success (41).

Two major radiographic phenotypes of NTM-LD are seen – nodular-bronchiectasis often involving the right middle lobe and lingula segment and the fibrocavitary form often involving the upper lobes – although patients may have features of both. For patients with nodular-bronchiectasis MAC-LD without cavitation, it is acceptable to treat with a macrolide, rifamycin, and ethambutol – the standard three-drug regimen – thrice weekly (Table 2) (29, 42–44). In a study that compared such dosing in 180 MAC-LD patients with nodular-bronchiectasis who completed >12 months of multidrug therapy, thrice weekly dosing was as good as daily dosing with combined treatment success rate of 84% (sputum conversion with no evidence of microbiologic relapse) (28). Interestingly, most of the recurrences (75%) were due to new infections rather than a true relapse (25%) (28). Overall, the standard three-drug regimen of a macrolide, rifamycin, and ethambutol gives a durable culture conversion rate of ~60–80% (25, 28, 34, 35, 37, 45).

For those with fibrocavitary disease, daily dosing rather than intermittent therapy with the standard three-drug regimen is recommended (Table 2) (43). With more severe disease, addition of an aminoglycoside during the first 2–3 months of therapy is recommended based on a study showing that addition of streptomycin to the standard three-drug regimen significantly improved the sputum conversion rates, albeit long-term outcome was not significantly better (27). There are small case series describing inhaled amikacin to treat MAC-LD with varying success (46–48). An ongoing multicenter study is recruiting patients to determine if inhaled liposomal amikacin helps for MAC-LD recalcitrant to the standard three-drug regimen (http://www.insmed.com/clinical-trials/).

Commensurate with the importance of a macrolide in the treatment of MAC-LD, the development of macrolide resistance in a MAC isolate is strongly associated with treatment failure and increased mortality (49). Factors associated with emergence of macrolide resistance include macrolide monotherapy and dual therapy with a macrolide and fluoroquinolone (49). Thus, avoiding these practices is a critical element in the management of patients with MAC-LD. However, once macrolide resistance develops, aggressive therapy, usually including use of an injectable aminoglycoside and possibly lung resection should be considered (49).

Second-line agents for MAC are generally reserved for those with disease recalcitrant to first-line treatment, intolerance or unacceptable adverse effects to one or more of the first line agents, and/or macrolide resistance. For patients intolerant to rifamycins, substitution with clofazimine is a viable option with prolonged sputum conversion rates for clofazimine, macrolide, and ethambutol or minocycline to be ~65%, similar to that seen with rifampin-

based three-drug therapy (25, 45, 50–53). Clofazimine synergizes with clarithromycin or amikacin against MAC (50, 52). The use of linezolid was assessed in a retrospective multicenter study across six NTM centers in over one hundred patients, 33% of whom had MAC-LD (54). Many of these patients had stable or improved disease on treatment but significant side effects occurred in about half. Bedaquiline, approved by the FDA in 2013 for the treatment of multidrug-resistant tuberculosis, appears to be well-tolerated in patients with refractory MAC-LD (55). A U.K. study compared 24 months of treatment for MAC-LD with either ciprofloxacin-ethambutol-rifamycin or macrolide-ethambutol-rifamycin and found similar and very low cure rates for both arms (23–24%) but this may be due to the fact that two-thirds had cavitary disease (26), a sign of more severe disease. While this finding suggests that ciprofloxacin is equivalent to clarithromycin in efficacy, experts in North America and several other regions still consider clarithromycin or azithromycin the most important drug available for MAC. Moxifloxacin has been used with some success in MAC-LD patients who failed clarithromycin-based therapy (56). Thus, for refractory or resistant MAC-LD, there is little published data for treatment options apart from ATS/IDSA guidelines.

Treatment for *M. kansasii*

M. kansasii is one of the more common cause of NTM-LD in the Western hemisphere but is less common in Asia (58). *M. kansasii* is phylogenetically the most closely related NTM species to *M. tuberculosis* (59). It is considered the most virulent NTM and classically causes upper lobe fibrocavitary lung disease similar to tuberculosis. Historically, isolation of *M. kansasii* has been considered to almost always predict true NTM-LD. However, a recent review of 19 papers published over the course of 60 years found that 1,008 of 2,672 patients (38%) evaluated after isolation of *M. kansasii* isolation did not meet clinical criteria for disease (60).

There are no randomized trials comparing treatment regimens for *M. kansasii*. Fortunately, *M. kansasii* is among the most antibiotic-responsive NTM species with a low rate of treatment failure or relapse (<1%) among patients who completed the ATS/IDSA recommended treatment of daily isoniazid, rifampin, and ethambutol until cultures are negative for at least 12 months (Table 3) (29). Rifampin is the most important agent in this regimen as cure was uncommon in the pre-rifampin era (61).

M. kansasii is also typically susceptible to macrolides, fluoroquinolones, and the aminoglycosides but is intrinsically resistant to pyrazinamide. Susceptibility testing should be performed for rifampin and clarithromycin (62). Because isoniazid activity is lower for *M. kansasii* than for *M. tuberculosis* and macrolides have strong *in vitro* activity, an alternative regimen is replacing isoniazid with a macrolide. Indeed, two studies used a regimen of clarithromycin, rifampin and ethambutol daily or thrice weekly for at least 12 months of culture negativity while on treatment and identified no relapses after a long period of follow-up (63, 64). Patients receiving shorter courses (9 to 12 months) with different regimens have experienced unacceptable rates of relapse (6–10%) (65, 66). Earlier regimens also included streptomycin in the first three months (61, 67) but since high cure rates are typically achieved with oral regimens, aminoglycosides are rarely necessary. For rifampin-

resistant *M. kansasii*, ATS/IDSA recommends a combination of clarithromycin, moxifloxacin, and a third agent with *in vitro* susceptibility such as ethambutol or sulfamethoxazole (29).

Treatment for *M. malmoense*

M. malmoense is an uncommon pathogen in the U.S., but is a more common cause of NTM-LD in Europe. It grows more slowly than MAC in liquid media and historically, it is a difficult species to treat. Similar to MAC, many clinicians cannot correlate *in vitro* susceptibilities with an *in vivo* response. A prospective study of 106 patients with *M. malmoense*-LD was performed over a 5-year period by the British Thoracic Society (BTS) (68). The results of two years of treatment with rifampin plus ethambutol were equivalent to rifampin, ethambutol plus isoniazid, although only 53% of patients were alive at 5 years and 44 of the original 106 patients (42%) were cured of the infection (68). In a follow-up study, the BTS randomly assigned 167 patients with *M. malmoense*-LD to clarithromycin, rifampin, and ethambutol, or ciprofloxacin, rifampin, and ethambutol. Overall response rates were low, but the group receiving clarithromycin had slightly better clinical response and lower mortality (26). There have been several other retrospective studies with varying success to rifampicin and ethambutol with or without a macrolide (45, 69, 70). Overall, the optimum antibiotic regimen to treat *M. malmoense* remains unknown but based on available evidence, standard MAC therapy is a reasonable place to start (Table 4).

Treatment of *M. szulgai*

M. szulgai, an organism closely related to *M. malmoense* (71), is one of a few NTM that possess the ESAT-6 and CFP-10 – small secretory proteins produced by *M. tuberculosis* but only by a few NTM – indicating that it may contain virulence genes similar to *M. tuberculosis* (72). Consistent with this hypothesis is that isolation of *M. szulgai* from a patient generally indicates actual disease (73). *M. szulgai* is known to cause chronic lung disease and skin and soft-tissue infections. Treatment regimens that consist of clarithromycin, rifampin, and ethambutol (± ciprofloxacin) have been used successfully (Table 5) (73, 74).

Treatment of *M. xenopi*

M. xenopi is named for its isolation from the toad *Xenopus laevis* (75). It is mainly isolated from water sources (29) and clinically more relevant in certain parts of the world including Europe (76–78).

M. xenopi is often recalcitrant to treatment, with correspondingly lower sputum conversion rates, reduced long-term cure rates, and associated with higher mortality (24, 26, 45, 78, 79). There is real resistance to typical anti-tuberculosis drugs such as rifampin, isoniazid, and ethambutol (80); however, the rifabutin MIC_{50} for a small number of strains tested was < 0.5 (81). In time-kill kinetic studies, moxifloxacin and clarithromycin are equally effective (82). *In vitro* activity with ciprofloxacin and amikacin was limited (83), whereas no *in vitro* synergy between rifampin and ethambutol was seen (39). Andrejak and co-workers

performed a comprehensive study of antimicrobials using drugs *in vitro*, sera of treated mice to assess antimicrobial activities *ex vivo*, and *in vivo* murine models to test drug activities (84). They found that *in vitro*, two-drug combinations of ethambutol plus either rifamycin or moxifloxacin, and of clarithromycin plus moxifloxacin showed the best bactericidal activities; *ex vivo*, a three-drug combination of ethambutol plus a rifamycin and either clarithromycin or moxifloxacin was best (84). Interestingly, for the *in vivo* studies, amikacin-containing regimen had the greatest bactericidal activity with no difference in regimens containing clarithromycin or moxifloxacin (84). Based on a few trials, isoniazid is not effective and may in fact be associated with worse outcomes (24, 85). Short of more robust studies, the most efficacious drugs are the rifamycins, macrolides, and the fluoroquinolones (26, 29, 45, 78, 86). Thus, based on available evidence, it is recommended that *M. xenopi*-LD be treated with a combination of a macrolide, rifamycin, ethambutol ± a fluoroquinolone (Table 6) (26, 45).

Treatment of *M. simiae*

M. simiae is isolated from water sources in the environment (29, 71) and is capable of, but rarely causes disease; *i.e.*, a positive culture is a low predictor of having actual NTM-LD (87, 88). When implicated in pulmonary disease, its clinical presentation has similarities to that seen with MAC-LD (89). This organism is resistant to many of the standard tuberculosis drugs such as isoniazid, rifamycin, ethambutol, and para-aminosalicylic acid (81, 90). In one report, 27 of 86 isolates (31%) were susceptible to streptomycin (91). Agents that have *in vitro* activity include ofloxacin, amikacin, clarithromycin, ethionamide, cycloserine, and clofazimine (92). Like *M. xenopi*, no *in vitro* synergy was seen between rifampin and ethambutol (39); however, synergy could be demonstrated between amikacin and clofazimine (52). Jeong *et al* recently reported the first confirmed South Korean patient with *M. simiae*-LD who, despite receiving 12 month treatment with azithromycin, rifampin, ethambutol, and moxifloxacin, failed to achieve culture conversion (93). ATS/IDSA guidelines primarily suggest a clarithromycin-based, multiple drug regimen, citing that drugs such as moxifloxacin, sulfamethoxazole/trimethoprim, or linezolid have activity against *M. simiae* (Table 7) (29). For cavitary disease, extrapolation for MAC treatment suggests amikacin for a period of time could be helpful. Overall, the results of therapy are often disappointing and treatment for *M. simiae* remains problematic (57).

Treatment for *M. abscessus* complex and *M. chelonae*

Among the rapidly growing mycobacteria (RGM) – defined historically as observable growth from a subculture on solid medium in < 7 days – those belonging to the *M. abscessus* complex are the most clinically relevant to humans. Whole genome sequencing support categorizing *M. abscessus* complex into three distinct subspecies: *M. abscessus* sensu stricto, *M. bolletii*, and *M. massiliense* (94). In the clinical laboratory, distinguishing these three *M. abscessus* complex subspecies can be difficult and often requires sequencing of *hsp65*, *rpoB*, *secA*, erythromycin ribosomal methylase 41 (*erm41*), and/or *16S-23S rRNA ITS*.

Pang and co-workers performed *in vitro* susceptibility testing of 40 international reference RGM to 20 antimicrobial agents and found amikacin, tigecycline, and linezolid had potent

activities and that the fluoroquinolones, cefoxitin, and meropenem had good activities (95). Although the Clinical and Laboratory Standards Institute recommends drug susceptibility testing to 10 antimicrobial agents (amikacin, cefoxitin, clarithromycin, ciprofloxacin, doxycycline or minocycline, imipenem, linezolid, moxifloxacin, trimethoprim-sulfamothoxazole, and tobramycin) for *M. abscessus* complex isolates (96, 97) and recommended by some experts (94, 98), others cite insufficient evidence that *in vitro* susceptibility correspond with *in vivo* response with the exception of the macrolides (99). The method of drug susceptibility testing (*e.g.*, disc diffusion *vs.* broth dilution methods with the latter method preferred) may account for differences in drug susceptibility and hence, differences in reliability of the results in predicting outcome (96). One study from South Korea noted sputum conversion and maintenance of negative sputum cultures for more than 12 months were significantly lower in patients whose isolates were resistant to clarithromycin (2/12, 17%) compared with those whose isolates were susceptible or intermediate to clarithromycin (21/33, 64%) (100).

A distinguishing feature of *M. abscessus* sensu stricto and *M. bolletii* from *M. massiliense* is that the first two RGM have poor treatment outcomes. The reason for this is the presence of the functional *erm41* gene in both *M. abscessus* sensu stricto and *M. bolletii*, which, upon exposure to macrolides, modifies the binding site for macrolides and induces resistance (101). Clarithromycin may have greater propensity to induce greater erm41 expression resulting in greater macrolide resistance than azithromycin in *M. abscessus* sensu stricto infection (102) although others have not found a difference in the two macrolides to induce such resistance (103). Additionally, *M. abscessus* sensu stricto possesses other enzymes and efflux pumps that may confer *in vivo* antibiotic resistance (36).

Koh *et al* summarized the four studies (three from South Korea and one from Denver, Colorado) examining the treatment outcome for *M. abscessus*-LD (94). In the three studies that did not distinguish the subspecies of *M. abscessus* complex, the sputum conversion rate without evidence of relapse was 50–70%. In contrast, in the one study from South Korea where *M. massiliense* was distinguished from *M. abscessus* sensu stricto, the sputum conversion rate was significantly more favorable for *M. massiliense* (88%) than for *M. abscessus* sensu stricto (25%) (104). This finding indicates that the presence of the *erm41* gene may be the reason for the generally poor response of *M. abscessus* sensu stricto to medical therapy as oppose to the more favorable outcomes in the treatment of lung disease due to *M. massiliense* (104–106). Thus, this is a good example where distinguishing the subspecies has important prognostic implications for patients.

The only oral drugs with reliable activity against *M. abscessus* complex organisms are the macrolides and clofazimine, although others that have been used in treatment include ciprofloxacin, moxifloxacin, linezolid, or doxycycline (107). Similar to that for MAC, clofazimine was found to synergize with clarithromycin or amikacin against *M. abscessus* (50). Parenteral drugs used in the treatment of *M. abscessus* complex include cefoxitin, imipenem, tigecycline, and amikacin.

Current guidelines recommend an initial intensive phase of daily clarithromycin or azithromycin and two parenteral drugs for 2–4 months (*e.g.*, amikacin thrice weekly plus

daily imipenem or cefoxitin in divided doses) followed by macrolide therapy with at least one other oral agent (fluoroquinolone, linezolid, clofazimine) or inhaled amikacin (45, 108, 109). If the isolate is identified as *M. abscessus* sensu stricto or *M. bolletii*, then the macrolide should not be used and inhaled amikacin plus clofazimine should be considered in the continuation phase (Table 8). The total duration of therapy is based on culture conversion, typically treating for ≥12 months of negative sputum cultures. On the other hand, if the goal is symptom control and not intent to cure, then the continuation phase can be shortened to a few months.

In contrast to *M. abscessus* sensu stricto, *M. chelonae* – a much less common cause of lung disease – does not have an active *erm41* gene and thus should not have inducible macrolide resistance.

Role of resectional lung surgery

Surgical resection can play an important adjunctive role in the management of NTM-LD (29, 110). However, there is a paucity of robust evidence to guide the calculation of risks and benefits of selecting NTM-LD patients for lung resection. A number of single-center, retrospective case series have reported long-term microbiological success after lung resection for NTM-LD (111–119). Case series of *M. abscessus* patients have suggested improved outcomes with surgical resection relative to antibiotic treatment alone (100, 108, 120). Nonetheless, several caveats are critical in interpretation of these data. First, these reports come from centers with extensive experience with surgical techniques specific to infectious lung disease. Results should not be extrapolated to centers with less experience in these highly specialized techniques. Second, patients seen in these centers are highly selected and may not be representative of NTM patients generally.

Expert opinion emphasizes consideration of surgical resection under the following circumstances: *(i)* for pathogens that are less amenable to medical therapy such as *M. abscessus* or macrolide-resistant MAC organisms, *(ii)* for severely involved but localized disease (*e.g.*, focal bronchiectasis or cavitation), and/or *(iii)* for patients who have responded poorly to initial medical treatment and for life-threatening complications such as hemoptysis (29, 110). Patients are typically treated with intensive antibiotic regimens for 2–3 months prior to surgery to maximally reduce bacterial burden (110). ATS/IDSA guidelines conclude that – in light of the lack of widely-accepted criteria for patient selection and the high potential morbidity – decision-making regarding surgical resection should optimally be made in conjunction with experienced NTM treatment centers (29).

Adjunctive treatment

In addition to antimicrobial therapy, avoidance of potential sources of exposure (*e.g.*, aerosolized water, soil, and biofilms) is necessary to prevent re-infection. In patients who are on inhaled corticosteroids, a trial to limit their use may potentially help with treatment as inhaled corticosteroids have been shown to be a risk factor for acquiring NTM-LD and by inference, presumably may hinder response to therapy (121). Moreover, measures to improve airway clearance in the bronchiectatic airways are essential adjunct to drug

treatment – *e.g.*, airway clearance devices (Acapella®, Aerobika®, TheraVest®), agents to enhance expectoration of mucous (*e.g.*, inhaled hypertonic saline or mannitol), and optimization of nutrition. Other measures to maximize favorable treatment outcome are listed in Table 9.

Traditional and more novel predictors of treatment outcome

Traditional factors that may contribute to suboptimal outcome include innate and acquired resistance including to the endogenous antimicrobial peptide cathelicidin (36, 127), under-dosing of antimicrobials (122), the presence of other pathogens in the respiratory tract (NTM or non-NTM bacteria or fungi), and newly-acquired NTM infections during treatment or after completion.

In 72 Japanese patients with MAC-LD on triple drug regimen, in whom 51% experienced treatment success – defined as sputum conversion without relapse – low soil exposure (defined as ≤ 2 hrs of soil-related activities per week) was associated with significantly greater sputum conversion, lower rates of relapse, and higher treatment success rates than those with high soil exposure (>2 hours per week) (123). This finding is consistent with the long-standing observation with now experimental proof that a substantial number of recurrences are due to a new infection rather than a true relapse (28).

While treatment outcome is most often discussed in the context of the antibiotic regimen used and perhaps drug susceptibility, some investigators have examined the association between outcome and genotype of the organisms. Kikuchi and co-workers categorized patients with *M. avium-LD* as having a therapeutic responsiveness (defined as microbiologic and radiologic improvement) or unresponsiveness and then retrospectively determined whether there was an association between the *M. avium* genotype of the variable number tandem repeats (VNTR) at 16 minisatellite loci and responsiveness to therapy (128). Performing principal component analysis of the raw VNTR data, they were able to identify genetic features that were associated with therapeutic response to clarithromycin-containing regimen. Subsequently, they constructed a multivariate model to predict therapeutic responsiveness using VNTR data from only four minisatellite loci (128). This study would lend credence to the notion that different strains of NTM – even within the same species — may have differential virulence. In contrast, Kim S-Y *et al* found no association between the clinical characteristics, drug susceptibility, disease progression and *M. intracellulare* cluster based on VNTR genotyping (129).

Conclusions and Future Developments

In conclusion, we summarized the treatment of NTM-LD based on available data with the caveat that many of the recommendations are based on clinical experience, small clinical studies, and expert opinions. Systematic, multi-center studies are needed to provide more robust evidence-based recommendations for treatment and outcome analysis of NTM-LD.

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Table 1

Relative likelihood that NTM isolated from respiratory tract indicate disease

Organisms recovered	Relative likelihood of disease
M. kansasii	High
MAC, *M. abscessus* complex, *M. chelonae*, *M. malmoense*, *M. szulgai*, *M. xenopi*	Intermediate depending on imaging, symptoms, and repeated isolation; *M. szulgai* in certain regions is considered to be more pathogenic
M. simiae, *M. fortuitum, M. terrae*	Low
M. gordonae	Very low

Table 2

Treatment of *Mycobacterium avium* complex (MAC)

Regimen	Drug	Dose and schedule*	Known adverse effects
Fibrocavitary disease: daily three drug regimen ± thrice weekly	Azithromycin *or* clarithromycin *and*	250 mg QD 1000 mg QD	Diarrhea, hearing loss, metallic taste, QT prolongation
aminoglycoside for at least 12 months of negative sputum cultures.	Rifampin *or* rifabutin** *and*	10 mg/kg QD (maximum 600 mg) *or* 150–300 mg QD	Hepatitis, drug-drug interactions, fever, chills, arthralgias, thrombocytopenia, leukopenia, acute hemolytic anemia, uveitis, decreases clarithromycin levels
	Ethambutol	15 mg/kg QD (max 2.4 grams)	Optic neuritis (color blindness, scotoma, decreased visual acuity and/or visual defect), hepatitis
	± Amikacin or streptomycin	10–25 mg/kg*** IV or IM TIW for the first 2–3 months	Renal failure, cranial VII (vestibular and cochlear) toxicity, hypomagnesemia
	Clofazimine (for intolerance to rifamycins)	100–300 mg QD	GI intolerance (abdominal pain, nausea, vomiting, diarrhea –occurring in 40–50%), skin discoloration, QT prolongation
Nodular-bronchiectasis: thrice weekly for at least 12 months of negative sputum cultures.	Azithromycin *or* clarithromycin *and*	500 mg TIW 1000 mg TIW	See above
	Rifampin *or* rifabutin* *and*	600 mg TIW 150–300 mg TIW	See above
	Ethambutol	25 mg/kg TIW	See above

Key References: (29, 45, 57)

* Unless indicated, all dosages are given orally.

** Reserve rifabutin for advanced or previously treated disease. Rifabutin levels may be increased by macrolides. Hematologic complications is more common with rifabutin than rifampin.

*** Some centers favor lower doses for better tolerability. Monitor peak aminoglycoside level weekly.

IV = intravenous; IM = intramuscular; QD = once daily, TIW = thrice weekly

Table 3

Treament of *Mycobacterium kansasii*

Regimen	Drug	Dose and schedule	Known adverse effects
Daily for 12 months of negative cultures	Isoniazid * *and*	300 mg QD	Hepatotoxicity, peripheral neuropathy, drug-induced lupus, agranulocytosis
	Rifampin *and*	600 mg QD	See above
	Ethambutol	15 mg/kg QD (max 2.4 grams)	See above
	Azithromycin or clarithromycin may be substituted for isoniazid	250 mg QD 1000 mg QD	See above

Key References: (29, 45)

* Consider adding pyridoxime 20 mg QD to lower risk of INH-induced peripheral neuropathy

Table 4

Treament of *Mycobacterium malmoense*

Regimen	Drug	Dose and schedule	Known adverse effects
Daily therapy for at least 12 months of negative sputum cultures	*Clarithromycin or azithromycin *and*	1000 mg QD or 250 mg QD	See above
	Rifampin *and*	600 mg QD	See above
	Ethambutol	15 mg/kg QD	See above
	Moxifloxacin in place of the macrolide	400 mg QD	Tendonitis, QT prolongation, photosensitivity

Key References: (45, 69)

*Fluoroquinolones may be used as an alternative in those intolerant to macrolides

Table 5

Treatment of *Mycobacterium szulgai*

Regimen	Drug	Dose and schedule	Known adverse effects
No proven regimen. Daily therapy for > 12 months of negative cultures.	Clarithromycin *and*	1000 mg QD	See above
	Rifampin *and*	10 mg/kg QD (max 600 mg)	See above
	Ethambutol *and*	15 mg/kg QD (max 2.4 gram)	See above
	± Ciprofloxacin	250–750 mg BID	See moxifloxacin above

Key References: (73, 74)

Table 6

Treatment of *Mycobacterium xenopi*

Regimen	Drug	Dose and schedule	Known adverse effects
No proven regimen. Daily therapy for > 12 months of negative cultures.	Clarithromycin *and*	1000 mg QD	See above
	Rifampin *and*	10 mg/kg QD (max 600 mg)	See above
	Ethambutol	15 mg/kg QD (max 2.4 grams)	See above
	± Moxifloxacin	400 mg QD	See above
	± amikacin *	10–25 mg/kg IV or IM TIW for the first 2–3 months	See above

Key References: (26, 45)

* Based on an *in vivo* murine study (84)

Table 7

Treatment of *Mycobacterium simiae*

Regimen	Drug	Dose and schedule	Known adverse effects
No proven regimen. Relationship of *in vitro* susceptibility and clinical outcome is not clear.	Clarithromycin *and*	1000 mg QD	See above
	Rifampin *and*	10 mg/kg QD (max 600 mg)	See above
	Ethambutol	15 mg/kg QD (max 2.4 grams)	See above
	± Moxifloxacin	400 mg QD	See above
	± Trimethoprim-sulfamethoxazole	One double-strength tablet BID	Hypersensitivity, rash, myelosuppression, interstitial nephritis, increased liver function tests

Key References: (29)

Table 8

Treatment of *Mycobacterium abscessus* complex

M. abscessus* sensu stricto or *M. abscessus* subsp *bolletii			
Regimen	**Drug**	**Dose and schedule**	**Known adverse effects**
A reasonable regimen includes clofazimine, cefoxitin, and amikacin initially, then clofazimine, IV or inhaled amikacin, and ± linezolid for >12 months of negative culture. If the goal is symptom control, length of treatment can be shortened.	Clofazimine *and*	100–300 mg QD	See above
	Cefoxitin or	2 grams IV BID or TID	Thrombophlebitis, induration, hypotension, and rash
	Imipenem *and*	500–1000 mg QID IV (BID also used)	Seizures, bone marrow suppression, increased liver function tests
	Amikacin	15–25 mg/kg IV TIW	See above. *M. abscessus* can acquire resistance due to mutation of the 16S rRNA gene
	± Tigecycline	50 mg IV QD or BID	Hepatotoxicity, pancreatitis, photosensitivity, tooth discoloration, and anorexia
	± Linezolid	600 mg PO BID	Serotonin syndrome, myelosuppression, neuropathy, metabolic acidosis
M. abscessus* subsp. *massiliense			
Regimen	**Drug**	**Dose and schedule**	**Known adverse effects**
Daily regimen of macrolide + cefoxitin or imipenem ± thrice weekly amikacin for at least 12 months of negative culture.	Azithromycin or clarithromycin *and*	250 mg QD 1000 mg QD	See above
	Cefoxitin or	2 grams BID or TID IV for ≥ 2 months	See above
	Imipenem	500-1000 mg QID IV (BID also used)	See above
	Amikacin	15–25 mg/kg IV TIW	See above
	± Moxifloxacin	400 mg QD	See above

Key References: (29, 45, 107)

Table 9

Measures to maximize favorable treatment outcome

Measures	Key references
Test NTM for resistance to macrolide and possibly the aminoglycosides	(27, 34, 35, 41)
Use at least a three-drug regimen of azithromycin, rifampin, and ethambutol for MAC-LD, thrice weekly for non-cavitary minimal disease and daily for cavitary and more severe disease	(29, 42–44)
If rifampin is used with macrolides, the dose of macrolides may need to be increased and preferably, macrolide levels checked	(34, 45, 122)
Consider including intravenous or inhaled amikacin for those with more severe or cavitary disease	(27, 47, 48)
Take measures to avoid re-exposure such as avoidance of aerosolized soil and water	(123)
Consider increasing hot water heater temperature to 130°F	(124, 125)
Airway clearance mechanisms for bronchiectasis (*e.g.*, Acapella® valve, Aerobika®, TheraVest®, hypertonic saline)	(126)
Surgical lung resection for severe but localized disease in selected patients	(29, 110)