Diagnosis and Treatment of Nontuberculous Mycobacterial Lung Disease: Clinicians' Perspectives

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Nontuberculous mycobacteria (NTM) are emerging pathogens that affect both immunocompromised and immunocompetent patients. The incidence and prevalence of NTM lung disease are increasing worldwide and rapidly becoming a major public health problem. For the diagnosis of NTM lung disease, patients suspected to have NTM lung disease are required to meet all clinical and microbiologic criteria. The development of molecular methods allows the characterization of new species and NTM identification at a subspecies level. Even after the identification of NTM species from respiratory specimens, clinicians should consider the clinical significance of such findings. Besides the limited options, treatment is lengthy and varies by species, and therefore a challenge. Treatment may be complicated by potential toxicity with discouraging outcomes. The decision to start treatment for NTM lung disease is not easy and requires careful individualized analysis of risks and benefits. Clinicians should be alert to those unique aspects of NTM lung disease concerning diagnosis with advanced molecular methods and treatment with limited options. Current recommendations and recent advances for diagnosis and treatment of NTM lung disease are summarized in this article.

Keywords: Nontuberculous Mycobacteria; *Mycobacterium avium* complex; *Mycobacterium*; *Mycobacterium kansasii*

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Introduction

Nontuberculous mycobacteria (NTM) are ubiquitous organisms responsible for opportunistic infections with a broad spectrum of virulence. The incidence and prevalence of NTM lung disease continue to increase worldwide, leading to an emerging public health problem[1-3]. Although the distribution of NTM species varies markedly based on geography, *Mycobacterium avium* complex (MAC) is the most common pathogen in most areas followed by *M. abscessus* complex (MABC) and *M. kansasii*[1].

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) published clinical guidelines for NTM in 2007[5]. Because of the difficulty in distinguishing between NTM isolation and disease, clinical and microbiologic criteria are needed for the diagnosis of NTM lung disease. Currently recommended treatment regimens, drug resistance patterns, and treatment outcomes differ according to the NTM species, and management is a lengthy complicated process with limited therapeutic options[5]. However, the current

guidelines rely largely on expert opinion, and some aspects of the recommendations remain controversial[6,7]. In addition, adherence to the guidelines for treating NTM lung disease is suboptimal, or potentially harmful antibiotics regimens are commonly prescribed[8]. Moreover, to date, there have been advances in molecular diagnostic methods for identification of NTM species and drug resistance, and antibiotic treatment of NTM lung disease. Therefore, revised evidence-based guidelines, practical information, and education are needed for practicing clinicians.

In this review, we summarize the recent advances that allow earlier diagnosis, rapid identification of NTM subspecies and improved treatment of NTM lung disease, and recommend a multidisciplinary approach in clinical practice based on updated literature reviews and standard guidelines. This review focuses on the most clinically frequent and significant species of NTM lung diseases in immunocompetent individuals.

Diagnosis of NTM Lung Disease

The isolation of NTM remains a clinical dilemma for clinicians. Because NTM exists naturally in the environment, isolation of NTM from a nonsterile respiratory specimen does not mean they are causative organisms of lung disease[9]. Diagnosis of NTM lung disease requires the clinician to integrate clinical, radiographic, and microbiological data, but, ultimately, diagnosis can be confirmed by (1) at least two positive cultures from sputum, (2) one positive culture in the case of bronchoscopic wash or lavage, or (3) a transbronchial or other lung biopsy with a positive culture for NTM or compatible histo-

pathological features such as granulomatous inflammation or stainable acid-fast bacilli (AFB), and one positive sputum or bronchial wash culture for NTM regardless of the mycobacterial strain[5]. Therefore, symptomatic patients with compatible radiographic findings should meet the microbiological criteria in order to establish a diagnosis of NTM lung disease[5].
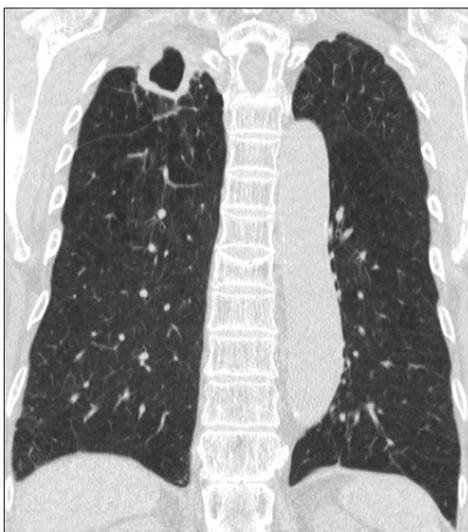
1. Clinical and radiographic manifestations

Diagnosis of NTM lung disease requires considerable time due to its slow growth, and may be misdiagnosed as tuberculosis (TB) or other AFB-positive bacilli[10]. These factors and a low index of clinical suspicion often result in delayed diagnosis. The symptoms are often nonspecific such as chronic cough, increased sputum production, dyspnea, low-grade fever, malaise and weight loss, and overlapping clinical characteristics with pulmonary TB[11,12].

Radiological imaging is important when NTM lung disease is suspected. The broad range of radiological patterns seen in NTM lung disease includes bronchiectasis, nodular lesions, cavitary lesions, and parenchymal consolidation[13]. NTM lung disease has two major manifestations: fibrocavitary and nodular bronchiectatic forms[5]. The fibrocavitary form resembles pulmonary TB and typically affects elderly men with underlying lung disease. This form is characterized by cavities with areas of increased opacity, usually located in the upper lobes (Figure 1). Pleural thickening and volume loss by fibrosis with traction bronchiectasis are frequent. Cavitation is the most typical radiologic feature in pulmonary TB; however, NTM lung disease tends to cause thin-walled cavities, often involving pleura without lymph node calcification, no atelectasis and usually progresses more slowly than pulmonary TB[14,15]. The nodular bronchiectatic form shows bilateral, multilobar

Figure 1. The fibrocavitary form of *Mycobacterium intracellulare* pulmonary disease in a 73-year-old male patient. Chest computed tomography shows a large cavity in the right upper lobe. Note the emphysema in both lungs.

Figure 2. The nodular bronchiectatic form of *Mycobacterium intracellulare* pulmonary disease in a 70-year-old female patient. Chest computed tomography shows severe bronchiectasis in the right middle lobe and the lingular segment of the left upper lobe. Note the multiple small nodules and tree-in-bud appearances suggesting bronchiolitis in both lungs.

bronchiectasis, especially in the middle and lower lung fields, with small nodules on chest radiography and high resolution computed tomography (HRCT) (Figure 2)[16,17]. This pattern of NTM lung disease occurs predominantly in elderly nonsmoking women without underlying lung disease, and appears more commonly in those with a thin body habitus[18,19]. There is evidence for a possible role of NTM infection causing bronchiectasis. On the other hand, bronchiectasis can precede NTM infection in some conditions[20]. A recent meta-analysis showed that the overall prevalence of NTM infection was 9.3% in patients with bronchiectasis[21]. Clinicians should be aware that bronchiectasis and NTM lung disease are connected. Because of considerable overlap in common HRCT findings, it is difficult to differentiate species of NTM lung disease based on radiologic patterns[22,23].

2. Laboratory findings

1) AFB smear and culture

Because NTM are present in the environment, especially in water sources, the careful collection of high-quality respiratory specimens is necessary to avoid contamination. Moreover, the temporary presence of NTM species from environmental sources in the airway may lead to positive samples[9,24]. Therefore, collection of three early-morning specimens on different days is preferred for diagnosis of NTM lung disease[5]. Induction of sputum with hypertonic saline may be used in patients who are unable to produce sputum spontaneously. Two types of AFB stains are commonly used: the carbol fuchsin stain (Ziehl-Neelsen or Kinyoun method) and the fluorochrome procedure (auramine O alone or in combination with rhodamine B). Kinyoun's method appears inferior to both the Ziehl-Neelsen and fluorochrome methods[25,26].

AFB staining cannot differentiate between *M. tuberculosis* and NTM. Nucleic acid amplification (NAA) tests for the detection of *M. tuberculosis* are needed. Several commercial tests such as the Xpert MTB/RIF assay (Xpert assay; Cepheid, Sunnyvale, CA, USA), the Cobas TaqMan MTB test (Roche Diagnostics, Rotkreuz, Switzerland), and the Amplified *M. tuberculosis* direct test (Hologic Inc., San Diego, CA, USA) are widely used. Compared with AFB smear microscopy, NAA testing has a greater positive predictive value (>95%) for *M. tuberculosis* with AFB smear-positive specimens in settings in which NTMs are common[27].

Culture remains the gold standard for laboratory confirmation of NTM and is required for genotypic identification and drug susceptibility tests (DST). The culture media are similar to that used for *M. tuberculosis*. Solid media include either egg-based media, such as Löwenstein-Jensen agar, or agar-based media such as Middlebrook 7H10 and 7H11 media. Cultures on solid media allow for the observation of colony morphology, growth rates, species categorization based on pigmentation, and quantitation of the infecting organism.

Solid media also serves as a backup when liquid media cultures are contaminated[25]. Liquid systems are more sensitive and reduce the delay in the detection of NTM but are prone to contamination by other microorganisms and bacterial overgrowth[25]. Therefore, all cultures for mycobacteria should include both solid and liquid media for the detection and enhancement of growth, which was shown to increase the sensitivity of NTM detection by an average of 15%[9]. An incubator system of liquid culture, which contains enriched Middlebrook 7H9 broth, can automatically detect the growth of mycobacteria including NTM in the laboratory. Additionally, there are various commercially available automated culture-reading systems[28].

2) NTM identification

Since treatments and outcomes differ depending on the NTM species, NTM identification is clinically important. Traditional biochemical tests or high performance liquid chromatography for NTM identification have been replaced by molecular methods such as line probe hybridization, polymerase chain reaction (PCR)-restriction fragment length polymorphism analysis, real-time PCR, and DNA sequencing. Some commercial kits are available, including the AccuProbe system (Hologic Inc.), INNO-LiPA Mycobacteria system (Fujirebio Europe, Ghent, Belgium), and GenoType Mycobacterium system (Hain Lifescience, Nehren, Germany)[29].

Gene sequencing is the reference method for the identification of NTM species and may be performed for uncommonly encountered species or precise identification at the subspecies level. Sequencing of the 16S rRNA gene allows discrimination at the species level or to the complex level such as MABC. However, single-target sequencing cannot be used to accurately differentiate species[30], and for a higher level of discrimination up to the subspecies level, gene sequencing of several targets using key genes, such as *hsp65* and *rpoB*, and the 16S-23S internal transcribed spacer, is needed[31-35].

The taxonomy of rapidly growing mycobacteria (RGM), especially MABC, has frequently been revised in recent years, leading to considerable confusion among clinicians[36,37]. Based on whole genome sequencing data, MABC can be divided into at least three close subspecies (subsp.) with regards to the erythromycin ribosomal methyltransferase gene (41) or *erm*(41) sequence: *M. abscessus* subsp. *abscessus* (hereafter *M. abscessus*), *M. abscessus* subsp. *massiliense* (hereafter *M. massiliense*), and *M. abscessus* subsp. *bolletii* (hereafter *M. bolletii*)[38,39].

A recent major advance in MABC was the discovery of inducible macrolide resistance, in which the organism develops resistance to the macrolides *in vitro* after prolonged incubation (susceptible at day 3, but resistant at day 14), or by preincubation in macrolide-containing media[40]. The *erm*(41) gene, encoding a methyltransferase that methylates the site of action of macrolides at the 23S rRNA level, is present in sev-

eral species in RGM, and confers natural inducible resistance to macrolides.

In addition, *M. abscessus* strains have a T or C polymorphism at the 28th nucleotide on *erm*(41): T28 strains demonstrate inducible clarithromycin resistance, while C28 strains are susceptible[41,42]. *M. bolletii* strains have *erm*(41) sequences similar to the sequence of the T28 *M. abscessus* group, associated with inducible clarithromycin resistance[41]. *M. abscessus* possesses a novel *erm*(41) gene and the production of Erm41 methyltransferase is predictive of clinical failure with clarithromycin[40]. *M. massiliense* has a dysfunctional *erm* gene and exhibits susceptibility to macrolides[41,43].

To date, gene sequencing is the most accurate method for identifying NTM species; however, species-level discrimination may require analysis of several genes and has been limited to specialized laboratories. In recent years, the matrix-associated laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) method is increasingly being applied clinically for bacterial and fungal infections, and its utility for the identification of NTM has emerged as a potential tool for NTM identification in a limited scope. The MALDI-TOF MS method is a method of identifying target bacterial species by comparing the mass spectral patterns of molecules, mainly ribosomal proteins, specific to NTM species, in a library of known NTM strains with unquestionable reliability and cost-effectiveness[44]. In recent comparative studies of MALDI-TOF MS and conventional real-time PCR methods, the GenoType *Mycobacterium* system or 16S rRNA gene sequencing for the evaluation of NTM suggested that MALDI-TOF MS is a valuable tool for the identification of these groups of organisms[45-47]. MALDI-TOF was found to be an accurate, rapid, and cost-effective system for identification of NTM species. However, MALDI-TOF MS requires a moderate amount of organism, unlike sequencing where only scant growth is needed[45]. Furthermore, the discrimination power of MALDI-TOF MS largely depends on the quality of the databases and cannot accurately differentiate MABC to a subspecies level. Therefore, further study is required to validate these results in clinical practice[9,45].

3) Drug susceptibility test

The role of a DST is to guide the design of optimal treatment regimens. However, the DST for NTM is difficult and controversial because of discrepancies between *in vitro* and *in vivo* clinical outcomes, with the exception of macrolides and amikacin[48]. Among slow-growing mycobacteria (SGM), clear correlations have been established for macrolides and amikacin in MAC lung disease and for rifampicin in *M. kansasii* lung disease. Macrolide resistance in MAC is caused by a mutation in the 23S rRNA gene macrolide binding site, usually selected due to macrolide monotherapy[49]. Only routine macrolide susceptibility testing for all MAC isolates is advised and clarithromycin is the preferred class representative according to

the Clinical and Laboratory Standards Institute[50]. In the case of macrolide resistance, moxifloxacin and linezolid should be tested.

Given that treatment failure is associated with rifampin resistance and drug treatment histories are generally unavailable during laboratory procedures, rifampin and clarithromycin are the currently recommended drugs for primary susceptibility testing for *M. kansasii*[5]. *M. kansasii* isolates resistant to rifampin should be tested against a panel of secondary agents, including rifabutin, ethambutol, isoniazid, clarithromycin, fluoroquinolones, amikacin, and sulfonamides[5]. For RGM, agents that should be tested are amikacin, cefoxitin, ciprofloxacin, clarithromycin, doxycycline (or minocycline), imipenem, linezolid, moxifloxacin, trimethoprim-sulfamethoxazole, and tobramycin[50]. In addition, it is recommended that the final reading for clarithromycin be at least 14 days, unless resistance is recognized earlier, to detect inducible macrolide resistance in RGM, especially *M. abscessus*[50].

Treatment of NTM Lung Disease

The management of NTM lung disease is a challenge that should be undertaken by experienced clinicians at centers equipped with reliable laboratory services for mycobacterial cultures and *in vitro* DST as it the requires prolonged use of costly combinations of multiple drugs with a significant potential for toxicity. The diagnosis of NTM lung disease does not obligate the initiation of therapy against NTM species, and a decision must be made based on the potential risks and benefits of therapy for individual patients[5]. Unlike pulmonary TB, clinicians may observe patients with minimal symptoms and stable radiographic disease closely without invasive work-ups or treatment, provided the patients do not have decreased host immunity towards NTM and avoid aggravating factors through education. However, once the clinician decides to start treatment, the goal of curative therapy in NTM lung disease is 12 months of culture negativity, and therefore, frequent sputum sampling every 1–2 months is needed[5]. Simultaneously, clinicians should consider quality of life and a patient-centered approach rather than solely expecting microbiologic erradication[51].

1. Treatment of MAC lung disease

Macrolides (clarithromycin and azithromycin) are the cornerstones of treatment for MAC lung disease[52]. The standard optional regimen includes a rifamycin (rifampin or rifabutin), ethambutol, and a macrolide administered for 18–24 months, including 12 months of sputum culture negativity[5]. Considering potential toxicity, intolerance, and costs of daily therapy with macrolide-based regimens, current guidelines recommended three-times-weekly intermittent therapy with a

macrolide (clarithromycin 1,000 mg or azithromycin 500 mg), rifampin 600 mg, and ethambutol at 25 mg/kg for the initial treatment of non-cavitary nodular bronchiectasis NTM lung disease[5]. Recent studies have shown that intermittent thrice-weekly therapy is effective and better tolerated compared with daily therapy in non-cavitary nodular bronchiectatic MAC lung disease[53,54]. There were no differences in response between clarithromycin and azithromycin regimens[53]. However, for patients with fibrocavitary forms or cavitary nodular bronchiectatic disease, daily therapy is recommended with clarithromycin (1,000 mg/day) or azithromycin (250 mg/day), rifampin (10 mg/kg/day, maximum 600 mg/day) or rifabutin (150–300 mg/day), and ethambutol (15 mg/kg/day), and amikacin or streptomycin could be added for the first 2 or 3 months of therapy in severe disease[5].

For patients failing standard therapy, the addition of moxifloxacin to multidrug regimens may improve treatment outcomes, but there has been little evidence to support the use of these regimens[55,56]. With the requirement of prolonged treatment of aminoglycosides in cases of refractory MAC lung disease, inhaled amikacin can be used as an alternative to parenteral use, even with limited evidence[57]. Clofazimine can be used as an effective alternative to rifamycins or in refractory MAC disease[58-60]. Ultimately, optimal therapeutic attempts and avoidance of the emergence of macrolide-resistant MAC strains is critical for successful treatment of MAC lung disease.

2. Treatment of *M. kansasii* lung disease

M. kansasii remains a relatively easily treatable pathogen in NTM lung disease and often has a similar presentation to that of pulmonary TB with fibrocavitary lesions in the upper lobes[5]. *M. kansasii* is sensitive to standard anti-TB drugs except for pyrazinamide, and there is good correlation between *in vitro* and *in vivo* susceptibility, especially for rifampicin[48]. The recommended regimen for treating *M. kansasii* lung disease includes daily isoniazid 300 mg, rifampicin 600 mg, and ethambutol 15 mg/kg for 12 months after sputum culture conversion[5]. Recently, a favorable experience with a low relapse rate in a 12-month fixed-course treatment regimen, including rifampin, isoniazid, and ethambutol, supplemented with streptomycin during the first 2–3 months, was reported[61]. Because of the excellent activity of the macrolides for *M. kansasii*, a macrolide-containing regimen has also been suggested[62-64].

3. Treatment of MABC lung disease

For the treatment of MABC lung disease, the strategy should be individualized based on *in vitro* DST results and patient tolerance. The therapy for *M. abscessus* lung disease remains a difficult problem and more clinical trials are needed because of the poor outcomes and paucity of treatment success[65]. Current guidelines suggest an oral macrolide with two parenteral agents for several months to symptomatically improve and slow down the disease progression for *M. abscessus* lung disease[5]. The most active parenteral agents include amikacin (10–15 mg/kg/day or 15–25 mg/kg thrice weekly), cefoxitin (200 mg/kg/day up to 12 g/day in divided doses), imipenem (500–1,000 mg[2] to four times daily), and tigecycline (50 mg once or twice daily)[65]. The role of inhaled amikacin has yet to be defined[57]. Although more than half of the *M. abscessus* isolates are moderately susceptible to moxifloxacin in some studies[66,67], the results are controversial[68]. Moreover, regarding the bactericidal effects of amikacin and moxifloxacin against *M. abscessus*, none of these drugs showed bactericidal activity[69-71]. Considering drug toxicity and inconvenience, aggressive parenteral therapy was suggested for 2–4 months, followed by macrolide therapy with additional oral agents such as a fluoroquinolone, linezolid, clofazimine, or inhaled amikacin as a step-down therapy[65].

In a recent comparative study between clarithromycin and azithromycin, clarithromycin induced greater *erm*(41) expression with higher macrolide resistance than azithromycin in *M. abscessus* infection[43]. However, more recent studies do not support the suggestion of preferential use of azithromycin over clarithromycin[72]. Therefore, the choice of macrolide depends on tolerability. *M. massiliense* isolates do not show inducible resistance to macrolides, and treatment outcomes showed favorable responses in *M. massiliense* lung disease[73-75]. The inducible macrolide resistance may explain disappointing treatment responses to macrolide-based regimens against *M. abscessus* lung disease. Because reliably effective medical therapy for *M. abscessus* lung disease remains elusive, surgical resection should be considered, especially in focal disease[76].

4. Adverse reaction and drug-drug interactions

Multiple drug therapy in NTM lung disease can cause adverse effects, which leads to treatment discontinuation or patient nonadherence[52]. Current guidelines recommend monitoring for drug toxicity at repeat intervals[5]. Gastrointestinal side effects with oral agents are common. Due to severe gastrointestinal disturbances, the use of macrolides may require dose adjustment[5]. Drug-induced hepatotoxicity due to rifampin, macrolides, imipenem, or tigecycline should be monitored by liver function tests, and monitoring complete blood count when using rifampin, imipenem, or tigecycline is recommended due to hematologic disturbances such as leukopenia or thrombocytopenia[52]. Renal function testing is also needed, especially in aminoglycosides[52]. Due to the risk of ototoxicity such as hearing loss, tinnitus, or vestibular toxicity, patients who receive streptomycin or amikacin should be educated regarding the signs and symptoms of toxicity with audiometry testing at the start of therapy and again on subsequent visits with discontinuation, or a decrease in dosage

or frequency if signs suggestive of toxicity occur[52]. Macrolides can also cause ototoxicity or vestibular dysfunction[52]. Because optic neuritis and peripheral neuropathy are important side effects with ethambutol and linezolid, patients should be tested at baseline and periodically during treatment[52]. Patients should visit clinicians immediately for ototoxicity or optic neuritis-related symptoms.

Clinicians should consider drug-drug interaction following comorbidities and associated concomitant therapies, especially in elderly patients with NTM lung disease[77]. Concomitant use of rifampin often leads to reduced peak serum levels for macrolides and moxifloxacin, which could partially explain the poor outcomes of currently recommended treatment regimens[78,79]. Concomitant use of macrolides and warfarin or new oral anticoagulants can increase bleeding risk[80]. Rifamycins may decrease the anticoagulative effect of warfarin because rifamycins are strong inducers of the cytochrome P-450 enzyme[52]. However, clarithromycin is both a substrate for and an inhibitor of cytochrome P 3A enzymes, whereas azithromycin is not. Thus, azithromycin is often preferred, in order to avoid drug interactions, including interactions with rifamycins[52]. As a result, the medication list of patients with NTM lung disease should be reviewed before starting antimicrobial therapy, and potential drug-drug interactions should be monitored. Especially in patients receiving multiple medications for comorbidities, gradual introduction at 1 to 2 weekly intervals is advisable in order to evaluate tolerance to each medication and medication dose.

5. Recent advances in antibiotic therapy for refractory NTM lung disease

Amikacin is an effective drug against most NTM species, but daily or intermittent use of systemic amikacin can have undesirable adverse effects such as ototoxicity and nephrotoxicity[52]. The current guidelines recommend only systemic use of aminoglycosides[5], but recent data have shown that inhaled amikacin is effective in the treatment of refractory NTM lung disease with less toxicity than systemic amikacin[57]. Although these data are based on a small sample size and retrospective analysis, amikacin inhalation treatment could overcome the side effects of systemic use and could be effective as an adjunctive therapy for treatment of NTM lung disease[79]. Liposomal amikacin for inhalation could be more effective than free amikacin in eliminating NTM species *in vitro* and in animal studies[81]. A multicenter, randomized, double blind, placebo-controlled phase 2 study of liposomal amikacin for inhalation treatment of refractory NTM lung disease has been recently completed (http://www.clinicaltrials.gov; identifier: NCT01315236).

Linezolid, the first oxazolidinone antibacterial agent approved for clinical use, has excellent potential against multidrug-resistant (MDR) TB and some species of NTM, and the oral agent is completely absorbed with near 100% bioavailibility[52]. However, the clinical use of linezolid for treatment of NTM lung disease has been limited because of the lack of long-term safety data, concern over limiting adverse hematologic events, and cost[82].

Tigecyline is active against many gram-positive and -negative organisms in skin and soft tissue infections as a parenteral therapy and shows good *in vitro* activity against *M. abscessus*[83]. A recent study has shown a favorable response to tigecyline salvage treatment in patients with *M. abscessus* and *M. chelonae* infections as part of multidrug regimens[84]. However, due to significant nausea and vomiting, reduced dosage adjustment from 100 to 50 mg per day may be needed for tolerability[84]. Combined with clarithromycin, tigecycline has high synergistic activity against RGM, but should be used with caution in combination with amikacin because of antagonistic activity with low synergistic activity[85].

Clofazimine is an anti-leprosy drug that has been used occasionally in the treatment of MDR-TB and NTM infections[52]. Clofazimine is administered orally, most often at doses of 100 mg daily[52]. Common adverse effects with clofazimine are discoloration and dryness of skin, photosensitivity, and gastrointestinal problems[86]. To date, clofazimine has been difficult to obtain because it is a non-commercial drug, and there are few clinical data regarding clofazimine use for salvage therapy of NTM infection[56], but clofazimine and amikacin show significant synergistic activity against both SGM and RGM[58,87].

Bedaquiline is an oral antimycobacterial agent, recommended for MDR-TB, and showed potential promise for advanced NTM lung disease in a recent small preliminary report[88]. A total of 10 patients with failed NTM lung disease treatment completed 6 months of bedaquiline therapy, and 60% had a microbiologic response while 90% showed symptom improvement. There were no severe complications including QT prolongation[88].

Biofilms are microcolonies of bacteria embedded in the extracellular matrix that provide stability and resistance to human immune mechanisms[89]. In recent years, some species of NTM have been shown to form biofilms that enhance resistance to disinfectants and antimicrobial agents[90,91]. In clinical practice, poor drug penetration and resistance due to biofilm formation of the respiratory tract is an important barrier to treating NTM lung disease. Moreover, lack of correlation between *in vitro* and *in vivo* susceptibility could be related to biofilms. A biofilm is mainly composed of extracellular DNA, proteins and polysaccharides, and extracellular DNA plays a major role in resistance; destruction of extracellular DNA *in vitro* was found to increase the efficacy of antimicrobial agents[92]. Therefore, a combination of DNase with antimicrobial agents could be a more effective treatment strategy for future treatment of NTM infection within biofilm formation[93].

6. Surgery

Except for *M. kansasii*, NTM lung disease is difficult to control with antimicrobial therapy alone[94]. Although the role of adjunctive surgical approaches remains unclear, surgery can be effective in cases of significant drug resistance or failure of medical treatment. In the case of localized lesions, appropriate surgical treatment could improve the rate of treatment success in patients with NTM lung disease. To slow disease progress, debulking surgery of the worst area of the destroyed lung may be indicated in selected patients. Additionally, in terms of symptom control such as massive hemoptysis, surgery may be helpful[95].

Successful treatment outcomes with sputum conversion can be achieved in 81%–100% of patients after adjuvant surgical resection[96-98]. Despite the favorable treatment success rate, postoperative complications were not uncommon and recent data showed 7%–25% morbidity and 0%–3% mortality[96-98]. Therefore, clinicians should carefully select patients for surgery after discussion in a multidisciplinary setting and comprehensive preoperative evaluation is needed[95]. Moreover, surgery without combination antimicrobial therapy could not achieve acceptable results. It is important to maintain perioperative antimicrobial therapy throughout the postoperative period[95]. The optimal duration of antimicrobial therapy before and after surgery remains a topic of debate[96-98]. However, patients are considered to have failed treatment without response after 6 months of appropriate medical therapy or without sputum conversion after 12 months of appropriate therapy[99]. Therefore, clinicians should consider the potential role of surgery in these cases[100]. Additionally, even in focal disease, aggressive medical therapy of at least 2 months should be performed before surgery[65]. Moreover, current guidelines recommend that medical therapy should be continued until the patient has persistently negative sputum cultures for 12 months while undergoing treatments, including surgery[5].

Summary

The prevalence of NTM lung disease is increasing worldwide, even in immunocompetent individuals. NTM lung disease is becoming a greater public health problem and the financial costs are substantial, particularly in elderly patients. Because NTM is a ubiquitous pathogen, isolation from a respiratory specimen does not necessarily indicate NTM lung disease. Clinical, microbiologic, and radiographic criteria should all be met to make a diagnosis of NTM lung disease. Treatment regimen and response rates differ according to NTM species; therefore, molecular methods for identification of NTM species and DST for optimal treatment regimens are ultimately needed. The diagnosis of NTM lung disease depends on meeting established diagnostic criteria; however, treatment decisions are difficult and still require considerable clinical judgment. Management of NTM lung disease is mainly carried out by medical therapy, a lengthy, expensive, and time-consuming process. Macrolides remain the most effective agents available against SGM and some RGM. Multiple drug therapy with a macrolide, ethambutol and a rifamycin is recommended, and an initial 2–3 months of aminoglycosides may be needed depending on the disease severity of MAC lung disease. Although optimal therapeutic regiments have yet to be established and effective agents are lacking, with frequent side effects in MABC lung disease, treatment with a macrolide and two parenteral agents (amikacin plus cefoxitin or imipenem) has shown favorable outcomes in species of *M. abscessus erm*(41) C28 sequevar or *M. massiliense* species with nonfunctional *erm*(41) gene. There is a lack of evidence and few randomized clinical trials to guide the management for refractory NTM lung disease, macrolide-resistant NTM, or *M. abscessus erm*(41) T28 sequevar with active *erm*(41) gene, resulting in inducible resistance to macrolides. However, multiple combination regimens with inhaled amikacin following initial treatment with parenteral aminoglycosides, tigecycline and other promising oral antibiotics such as linezolid, clofazimine, and bedaquiline, and surgical intervention in selected cases have shown promising results. A multidisciplinary approach is important in the diagnosis and treatment of NTM lung disease and improved management of NTM lung disease allows for more comprehensive care. Newer antimicrobial agents and clinical trials are needed in order to improve patient management.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

Acknowledgements

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