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REVIEW

Nontuberculous mycobacterial (NTM) lung disease: The top ten essentials☆

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Summary
This review will utilize essential questions about nontuberculous mycobacterial (NTM) lung disease to succinctly address important new developments in the pathogenesis, diagnosis and management of NTM lung disease with a focus on practical information and "bottom line" answers.

1) **What do I tell my patients who ask, "where did I get this infection" and, "should I take showers"?**
2) **What is the connection between bronchiectasis and the acquisition of NTM lung infection?**
3) **What other factors are important in the pathogenesis of NTM lung disease?**
4) **Why does it seem that am I seeing more new NTM lung disease patients?**
5) **Why is the diagnosis of NTM lung disease so complicated and does the diagnosis of NTM lung infection obligate specific treatment?**
6) **Unlike traditional tuberculosis, what is behind the irrelevance of most in vitro susceptibility testing reports for NTM infections?**
7) **Is there anything new for the management of patients with *Mycobacterium avium complex* lung disease? How does the radiographic appearance influence treatment?**

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8) **Is there anything new for the management of patients with *Mycobacterium abscessus* lung disease?**
9) **What about the management of other NTM respiratory pathogens?**
10) **Is there a role for the use of macrolide monotherapy for non-cystic fibrosis bronchiectasis?**

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Introduction

The NTM are a widely diverse group of organisms with a broad spectrum of virulence and potential for causing disease in humans [1]. A plethora of newly identified NTM species reflects the progress in genomic sequencing techniques applied to the differentiation of mycobacterial species. Clinicians are faced with a steady stream of new NTM species names and the accompanying responsibility for determining the clinical impact of those new species. There is also an increasing awareness that NTM lung diseases are becoming more prevalent. The following discussion will utilize the top ten essential questions about NTM lung disease as a platform to succinctly discuss important new developments in the pathogenesis, diagnosis and management of NTM lung disease with a focus on practical information, the concerns of clinicians, and "bottom line" answers.

1) What do I tell my patients who ask, "where did I get this infection" and, "should I take showers"?

The source of NTM that cause lung disease is still assumed to be the environment, with increasing concern that biofilms that form in municipal water sources may be a significant source for NTM. Feazel et al. analyzed rRNA gene sequences from 45 showerhead sites around the U.S [2]. Sequences indicative of *Mycobacterium avium* were identified in 20% of showerhead swabs. A quantitative PCR with *M. avium* specific primers was also used to screen DNAs from 32 biofilm and 14 water sources and *M. avium* DNA was detected in 20 additional biofilm swab samples in which *M. avium* had not been encountered utilizing the RNA gene libraries [2].

Using microbiologic techniques Nishiuchi et al. reported the recovery of *M. avium* complex (MAC) from residential bathrooms of patients with pulmonary MAC disease [3]. *M. avium* complex was isolated from 10/371 patient residence cultures versus 1/333 control households. Two patients with MAC lung disease were found to have identical sputum and bathroom MAC genotypes. Falkinham also isolated NTM from the household water systems of 59% of NTM patients sampled [4]. In 7 households, the patient isolate and 1 plumbing isolate exhibited similar genotype patterns. Two additional reports have demonstrated identical genotypes of MAC isolated from plumbing and MAC isolates obtained from humans with MAC lung disease, including one with conventional MAC lung infection and one with hypersensitivity-like lung disease [5,6]. These provocative data support the contention that at least some patients acquire NTM pathogens including *M. avium* from household plumbing. It is still unknown, however, how much of a risk NTM in municipal water and household plumbing present and whether these water sources are a significant or common source of NTM for the majority of patients with NTM lung disease [7,8]. It is also not certain that avoidance of showers without avoidance of other potential aerosol generating activities associated with running water in the home would eliminate the risk of household NTM transmission [8]. Interventions such as increasing the temperature of the hot water heater to $\geq$130° Fahrenheit or changing shower heads at regular intervals might decrease risk of NTM transmission but the impact of these steps is not known [4]. Moreover, limited experience suggests that cleaning shower heads with bleach may not result in sustained decreased exposure risk to NTM over time so that no clear recommendations can be made regarding the efficacy or optimal timing of regular cleaning of shower heads with bleach. It is also still unknown whether exposure to specific soil-based sources of NTM organisms may contribute to the development of NTM lung disease. It is important to emphasize, however, that nosocomial NTM disease has been linked to municipal water (tap-water) exposure [1].

Bottom Line: In our opinion it is too early to make broad conclusions or recommendations about the risk of showering, or other municipal water exposure, in patients with NTM lung disease and underlying diseases such as bronchiectasis. Concerned patients could consider raising hot water heater temperatures, treating shower heads with bleach monthly or even changing shower heads at regular intervals although the effectiveness of these interventions for preventing NTM lung disease is unknown.

2) What is the connection between bronchiectasis and the acquisition of NTM lung infection?

Bronchiectasis and pulmonary NTM infection are inextricably linked. Twenty per cent of cystic fibrosis patients and 10% of primary ciliary dyskinesia patients have NTM recovered from respiratory specimens, which strongly suggests, at least for some patients, a predisposing alteration in airway-surface defenses [1]. Kim et al. from the National Institutes of Health (NIH) reported a study of 63 patients (95% female) with a characteristic body habitus and NTM lung disease [8]. In this referral population, the BMI was significantly lower and the height significantly greater than matched controls. This population also had higher rates of scoliosis (51%), pectus excavatum (11%), and mitral valve prolapse (9%). There were no recognized immune defects such as cell-mediated dysfunction or cytokine-pathway abnormalities identified in these patients. In another similar recent report investigators from National Jewish Health (NJH) again noted the characteristic body habitus of female MAC lung disease patients but found, in contrast to the NIH study, decreased cytokine (interferon-gamma and IL-10) response of stimulated peripheral blood monocytes from MAC patients compared with controls [9]. The NIH study also noted a higher incidence of cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations (36%) compared with a matched control population. There was no consistent correlation between sweat chloride concentrations and CFTR variants. It has recently been noted in Japan that patients presenting with pulmonary NTM disease have mutations in the CFTR gene significantly more frequently than in the general population [10]. In a recent study, patients heterozygous for CFTR mutations were found to have abnormal nasal potential differences compared to controls suggesting a subtle mucosal ion transport abnormality and possible mechanism for developing bronchiectasis [11]. To date, however, there are no clear mechanistic connections between single CFTR mutations, the characteristic body habitus described above and the pathogenesis of bronchiectasis.

In some patients with NTM lung disease, primarily nonsmoking adult women, nodular infiltrates often precedes the development of cylindrical bronchiectasis which is in contrast to cystic fibrosis patients in whom NTM lung disease develops distinctly and consistently after bronchiectasis is long established. It is likely that the answer to the "chicken or egg" question of whether bronchiectasis or NTM infection comes first is "yes". That is to say there may be many phenotypic pathways to the development of bronchiectasis with or without NTM lung disease.

Bottom Line: Pre-existing bronchiectasis is an important predisposition for acquiring NTM respiratory infection. Female patients with a specific morphotype appear to be predisposed to the development of bronchiectasis with or without NTM lung diseases although the exact pathophysiologic mechanisms are still being investigated. Patients with known bronchiectasis for any reason should be screened for NTM infection and should be considered for evaluation of genetic or hereditary causes of bronchiectasis. The natural history of the development of NTM lung disease and/or bronchiectasis remains incompletely understood at this time.

3) What other factors are important in the pathogenesis of NTM lung disease?

As with *Mycobacterium tuberculosis*, tumor-necrosis factor alpha (TNF-α) blockers are a potent predisposition for NTM infections. Winthrop et al. recently published data from the United States Food and Drug Administration (FDA) MedWatch database for reports of NTM disease in patients receiving TNF-α blocker therapy [12]. NTM infections were associated with all available TNF-α blockers and MAC was the NTM species most commonly implicated. Extrapulmonary disease was common (44%) and 9% of patients had died at the time their infection was reported. TNF-α blockers are unquestionably an important predisposing factor for potentially serious, even fatal, NTM infection and must be used with extreme caution in patients with NTM disease.

The extent to which other immunosuppressive regimens and biologic agents increase risk is less well defined although some increased risk is clearly present. Prototypically, disseminated NTM disease is common in those with advanced HIV infection or congenital IL-12 or interferon gamma defects [1]. Conversely, there appears to be little risk associated with older, "non-biologic" immune suppressive agents used for rheumatoid arthritis such as azothiaprine and methotrexate [12].

Bottom Line: Patients who receive TNF-α blockers must be evaluated for NTM disease as well as tuberculosis with initiation of appropriate treatment for the NTM infections to avoid severe or even fatal NTM disease. Appropriate diagnostic and therapeutic considerations should also be proportionately applied to those receiving other biologic agents or immunosuppressive regimens in the presence of known or suspected NTM disease.

4) Why does it seem that I am seeing more new NTM lung disease patients?

Available data supports the contention that NTM disease prevalence is increasing. Determining the incidence and prevalence of NTM lung disease remains difficult because disease reporting is not mandatory in the U.S., and there must be an assessment of the clinical significance of individual NTM isolates, as opposed to *M. tuberculosis*, where each isolate is assumed to be associated with true disease.

In an insightful analysis, Iseman and Marras suggested that while the incidence of NTM lung disease may be comparable to tuberculosis, the true prevalence of NTM lung disease is almost certainly higher than tuberculosis due to the difficulty in curing patients with NTM lung disease, versus the relatively high cure rates for tuberculosis patients, and the subsequent accumulation of NTM patients who have indolent but essentially incurable disease [13]. The prevalence of NTM lung disease exceeds incidence given the chronic nature of NTM lung disease.

In a report of four regional healthcare systems based primarily on NTM laboratory isolation prevalence, the mean annual NTM disease prevalence was estimated to be 5.5/100,000, ranging from 1.7/100,000 in Southern

Colorado to 6.7/100,000 in Southern California [14]. This study suggested an annual increase in prevalence of 2.6% over the study period. MAC was the most common species identified in pulmonary cases (4.7cases/100,000 population). In perhaps the best and most rigorous NTM prevalence study to date, Winthrop et al. took the next important but more difficult step of matching NTM isolates with the clinical history and radiographic findings of individuals from whom the NTM isolates had been obtained. In this analysis the prevalence of NTM lung disease was found to be 8.6/100,000 overall and 20.4/100,000 in those 50 years of age or older over the 2005—2006 study period [15].

Bottom Line: NTM lung disease is currently more common in the U.S. than tuberculosis and appears to be increasing in prevalence. For post menopausal women, NTM lung disease associated with bronchiectasis may be a common and often unrecognized explanation for chronic cough.

5) **Why is the diagnosis of NTM lung disease so complicated and does the diagnosis of NTM lung infection obligate specific treatment?**

The NTM share an important characteristic: they are all found in the environment so that isolation of any NTM species can be the consequence of environmental contamination, especially contamination by nonsterile (tap) water sources including shower heads as well as other household water, municipal water and environmental sources. Hence, diagnostic criteria for respiratory NTM isolates remain necessary to help determine which NTM isolates are clinically significant [1]. Overall, this decision must be based on the potential virulence of the NTM isolated, the host from which the organism was isolated and the source of the clinical specimen from which the NTM was isolated [16]. Clinicians must remain knowledgeable about the disease causing potential of at least the most commonly isolated NTM species.

There are NTM species such as *Mycobacterium kansasii* and *Mycobacterium szulgai* that are almost always associated with significant disease when isolated from respiratory specimens [1,16]. In some cases, lung disease might be diagnosed on the basis of one positive culture for these organisms (especially *M. kansasii*) [1]. Conversely, there are also NTM such as *Mycobacterium simiae* and *Mycobacterium fortuitum* that are usually not respiratory pathogens, even if the NTM diagnostic criteria are met [17,18]. Lastly, there are NTM species such as *Mycobacterium gordonae* and *Mycobacterium terrae* complex that almost always represent contamination of respiratory specimens [1]. Substantial geographic differences are present in the distribution of the most common NTM lung disease pathogens intra-continentally as well as inter-continentally. The approach to NTM lung disease warrants consideration of these differences and underscores the importance of microbiologic confirmation of specific NTM lung disease prior to instituting treatment.

The clinician evaluating these patients frequently has to take into account a number of factors not explicitly addressed in the NTM diagnostic criteria [1]. One frequently encountered scenario is the isolation of an NTM species from a patient undergoing therapy for tuberculosis. Jun et al. reported 958 patients with tuberculosis, of whom 68 (7.1%) had NTM also isolated during tuberculosis therapy [19]. Most patients (71%) had only one positive NTM culture and only two patients (3%), both with *Mycobacterium abscessus* isolates, were felt to have progressive NTM disease after completion of tuberculosis therapy. The authors concluded that isolation of NTM in patients with tuberculosis was not uncommon but was rarely due to invasive or progressive NTM disease. Completion of TB treatment generally trumps consideration of treatment of concomitant NTM lung disease when present. Nevertheless, these patients required follow-up after completion of tuberculosis therapy, especially with isolation of potentially virulent NTM species.

In other instances more than one NTM species is present either synchronously or metachronously. This raises even more complex questions about appropriate treatment regimens in these circumstances. No expert consensus or actual data exists to direct the unfortunate clinician dealing with more than one NTM organism. In some instances combination regimens may need to be considered but for now, those circumstances must be evaluated on an individual basis.

Newer diagnostic techniques to augment the current diagnostic criteria are clearly needed and some are under investigation. One novel approach to possibly assist in establishing a diagnosis of NTM lung disease is a serologic test based on an enzyme immunoassay kit (EIA) detecting serum IgA antibody to glycopeptidolipid core antigen specific for MAC [20]. To date the role of this test is not sufficiently sensitive or specific in the diagnosis of MAC lung disease to be incorporated into current clinical practice.

Even in the setting of an established diagnosis of NTM lung disease treatment may not always be needed. The natural history of NTM lung disease remains elusive including the specific factors that may be associated with disease progression. Likewise, treatment of NTM lung disease involves prolonged multidrug regimens with substantial potential side effects and costs. The NTM lung disease patient and physician must be a priori in clear agreement that the risks and benefits of NTM lung disease favors treatment taking into account patient preferences and expectations. If a component of the decision to proceed with treatment for NTM lung disease is based on improving symptoms the clinician should be clear to discern that these symptoms (e.g. cough) are not attributable to the presence of frequently concomitant diagnoses of bronchiectasis, sinus disease, and/or gastroesophageal reflux disease.

If a diagnosis of NTM lung disease is present and treatment not started patients must be followed longitudinally so as to assess for progressive symptomatic and/or radiographic lung disease warranting reassessment of the risks and benefits of treatment.

Bottom Line: The diagnosis of NTM lung disease depends on meeting established diagnostic criteria however, the decision about whether to treat a patient who meets those criteria still requires considerable clinical judgment. For most patients with typically indolent NTM lung disease there is adequate time to carefully consider the clinical significance of respiratory NTM isolates and weigh the pros and cons of prolonged and potentially toxic therapy.

6) **Unlike traditional tuberculosis, what is behind the irrelevance of most in vitro susceptibility testing reports for NTM infections?**

Perhaps the most frustrating problem in the management of patients with NTM diseases is the observation that in vitro susceptibility testing may not be a guide for effective in-vivo response to antibiotics, as it is in the therapy of tuberculosis [1]. The most clinically important example of this phenomenon is MAC, where there is, so far, only evidence to support a correlation between in vitro macrolide susceptibility and in vivo clinical response which has been confirmed in multiple studies [1]. Both the Clinical and Laboratory Standard Institute (CLSI) and the American Thoracic Society (ATS) recommend that new MAC isolates should be tested in vitro only for susceptibility to macrolides [1,21]. Understandably, clinicians still cling to in vitro susceptibility reports for MAC isolates that list multiple agents as either 'susceptible' or 'resistant' based on in vitro MICs, even though those MICs have not been shown to correlate with in vivo response to the antibiotics tested. One of several examples of this phenomenon was reported from Japan by Kobashi et al. in a recent study showing a lack of correlation between in vitro susceptibility for MAC and in vivo response to rifampin, ethambutol and streptomycin [22–25].

Not surprisingly, there are multiple other NTM species and pathogens that share this frustrating property with MAC (including *Mycobacterium xenopi*, M. *malmoense*, *M. simiae*, etc.) and while the explanation(s) are not yet forthcoming, recent work with rapidly growing mycobacteria (RGM) may offer a window into the complex relationship between in vitro responses and in vivo effect of antibiotics for NTM. Macrolide antimicrobial agents act by binding to the 50S ribosomal subunit and inhibiting peptide synthesis. Erythromycin methylase (*erm*) genes, a diverse collection of methylases that impair binding of macrolides to ribosomes, reduce the inhibitory activity of these agents. The primary mechanism of acquired clinically significant macrolide resistance for some mycobacteria, especially RGM, is the presence of an inducible *erm* gene (*erm* 41) [26,27]. All isolates of *M. abscessus* ssp *abscessus*, *M. fortuitum* and several other RGM, but not *Mycobacterium chelonae*, contain an inducible *erm* gene. Parenthetically, there is also a novel *erm* gene in *M. tuberculosis*, which explains the poor response of *M. tuberculosis* to macrolide antibiotics. The most interesting aspect of this inducible gene is that if an *M. fortuitum* or *M. abscessus* ssp *abscessus* isolate is exposed to macrolide, the *erm* gene activity is induced with subsequent in vivo macrolide resistance which may not be reflected by the initial in vitro MIC of the organism for the macrolide! In other words, the organism may appear to be susceptible in vitro to the macrolide but will not respond to the macrolide in vivo. It appears to be one mechanism for the discrepancy between in-vitro susceptibility results and in vivo responses for *M. abscessus* ssp *abscessus* and *M. fortuitum*.

This in vivo macrolide resistance that does not affect the initial in vitro MIC for macrolide has been termed 'cryptic resistance', and requires incubation of an NTM isolate with macrolide prior to determining an MIC for the macrolide. Increasing numbers of mycobacteriology laboratories are now incubating RGM clinical isolates with macrolide prior to testing macrolide "susceptibility" and reporting final macrolide susceptibility.

While there is no *erm* gene in MAC, could there be other similar inducible genes that confer in vivo resistance to other antibiotics for MAC? It is an intriguing, if unproven, possibility. Van Ingen et al. have recently published a concise review of the multiple factors that are likely contributors to the paradox of poor correlation between in vitro antibiotic susceptibility and in vivo response to the same antibiotics [28].

Bottom Line: Macrolide susceptibility is currently the only drug category relevant to clinical outcomes in MAC lung infections. In contrast, treating clinicians must be aware that the inducible erm gene carried by some RGM invalidates macrolide susceptibility results certain species.

7) **Is there anything new for the management of patients with *M. avium complex* lung disease? How does the radiographic appearance influence treatment?**

MAC lung disease is associated radiographically with upper lobe fibrocavitary densities, which occurs primarily in men with underlying obstructive lung disease or nodules and bronchiectasis which occurs primarily in women without other underlying pulmonary disease. These latter patients are associated with a specific morphotype, including low BMI, tall stature, scoliosis, pectus excavatum and mitral valve prolapse as previously discussed. Most clinicians rely heavily on CT scan appearances in order to assess disease type and severity and to determine the choice of treatment regimens. Most experts agree that the pathophysiology and clinical behavior of the two groups should be viewed separately. Ito et al. described predictors of 5-year mortality in patients with MAC lung disease [29]. After adjusting for multiple cofounders, the presence of cavitary disease was associated with a higher mortality thus emphasizing that "patients with cavitary lesions require immediate treatment for sputum culture conversion and to improve their chances of survival." The decision to treat patients with the nodular/bronchiectatic form of MAC lung disease, should be based on potential risks and benefits of therapy for individual patients as noted previously.

Treatment for MAC lung disease is long, expensive, and frequently associated with drug-related toxicities. Clinical improvement and 12 months of sputum culture negativity while on therapy are the goals, although this is frequently not achievable. Treatment regimens for MAC should consist of a rifamycin (rifampicin or rifabutin), ethambutol and a macrolide (azithromycin or clarithromycin) [1]. Therapy can be given daily or intermittently, depending on the disease type and severity. Nodular bronchiectasis patterns by radiography can usually safely be treated by intermittent or three times weekly therapy [30]. Fewer side effects and cost make intermittent therapy a more palatable option for many patients. Intermittent therapy has been shown to be less effective for individuals with cavitary MAC lung disease, especially if they are accompanied by a history of COPD, bronchiectasis or previous treatment for MAC

lung disease [31]. Therapy for cavitary MAC lung disease, severe nodular/bronchiectatic disease or disease of either type unresponsive to initial therapy currently involves daily three drug therapy as outlined above in addition to IM streptomycin or IM/IV amikacin usually given TIW [1]. The optimal duration for parenteral therapy is unknown and may require 6 months or longer of the agent. The initial use of parenteral agents has been shown to increase culture conversion rates, but not improve long-term outcome [32]. Barriers to initiating therapy for cavitary disease include difficulty obtaining and monitoring drug levels, side effect profiles of aminoglycosides and patient desires. There is no evidence to support the use of fluoroquinolones as first line agents for treating MAC lung disease. The use of macrolide and fluoroquinolone may be associated with cardiac toxicity and puts the patient at risk for development of macrolide resistant MAC disease [33]. Limited data suggests that for patients who do not tolerate rifamycins, clofazimine may provide an effective alternative, combined with ethambutol and a macrolide [34]. Adjunctive surgery for selected patients is associated with favorable treatment outcomes although experienced mycobacterial lung disease surgeons remain an important factor for successful outcomes [35,36].

The role for the inclusion of inhaled amikacin in a treatment regimen for advance or recalcitrant NTM lung disease remains uncertain with little available published data [37]. An ongoing multicenter clinical trial investigating the addition of inhaled liposomal amikacin for recalcitrant MAC and *M. abscessus* lung disease to a stable regimen promises to shed important light onto this unanswered question.

An additional critical element in the management of patients with MAC lung disease is prevention of the emergence of macrolide resistance. While the role of in vitro susceptibility for other agents remains controversial, it is clear that the development of macrolide resistance in a MAC isolate (MIC $>$ 16 μg/ml) is strongly associated with treatment failure and increased mortality [33]. The most important risk factors for developing macrolide resistant MAC are macrolide monotherapy and the combination of macrolide and fluoroquinolone without a third companion drug [33].

Recent data has shown that currently recommended macrolide-based treatment regimens for MAC are associated with important pharmacologic interactions with resulting low plasma concentrations of essentially all drugs including macrolides [38]. Targeted pharmacodynamic indices for essentially all drugs commonly used in MAC treatment regimens are seldom met. These findings may at least partly explain the poor outcomes of the currently recommended MAC treatment regimens. It is noteworthy that improvement in these pharmacodynamic parameters would almost certainly entail increased dosages of the MAC medications which would be a formidable obstacle to overcome for many patients with MAC lung disease [39].

The timing of when to repeat imaging after the initiation of treatment can be confusing with no established guidelines available as the clinical disease course can vary from one individual to another. While the desired response is sputum conversion and imaging improvement, the radiographic evolution, especially with nodular bronchiectasis, is unclear and often unrewarding. With increasing evidence to suggest that the cumulative radiation dose is associated with increased risk of cancer, the need to limit unnecessary radiographic studies is pertinent to the field of NTM lung disease [40].

Bottom Line: The management of MAC lung disease is dependent on in vitro susceptibility of MAC isolates for macrolides and the inclusion of macrolides in the treatment regimen with companion medications adequate to prevent the emergence of macrolide resistance. Surgery for highly selected patients by experienced thoracic surgeons can also improve MAC treatment outcomes. Cavitary MAC lung disease is associated with a higher mortality and should prompt initiation of aggressive therapy which would likely include an aminoglycoside and consideration of *surgical* intervention.

8) Is there anything new for the management of patients with *M. abscessus* lung disease?

Overall, the treatment of *M. abscessus* lung disease remains difficult with inconsistent results. Jeon et al. recently reported the results of therapy for a series of 69 patients (84% female, mean age 56 years) with *M. abscessus* lung disease [41]. These authors treated the patients with a regimen consisting of an initial 1 month of parenteral therapy with amikacin 15 mg/kg/day and cefoxitin 200 mg/kg/day while hospitalized, in combination with oral medications including clarithromycin 1000 mg/day, ciprofloxacin 1000 mg/day, and doxycycline 200 mg/day for more than 12 months (median 24 months). Forty-seven of 69 patients (68%) converted sputum to negative with a median time of 1 month. Sputum conversion with macrolide resistant strains occurred in 27% of patients vs. 71% with macrolide susceptible strains. Additionally, relapse occurred in 100% of patients with macrolide resistant strains. These sputum conversion rates are somewhat surprising given the in-vitro susceptibility pattern of *M. abscessus* previously reported (with 0% isolates susceptible in vitro to fluoroquinolones, and less than 5% isolates susceptible in vitro to doxycycline) and the relatively short period of parenteral therapy. These results, once again, challenge conventional assumptions about the utility of in-vitro susceptibility testing in the therapy of NTM disease.

These results also highlight the importance of differentiating between *M. abscessus* isolates with (*M. abscessus* ssp *abscessus*) and without (*M. abscessus* ssp *bolletii* aka *Mycobacterium massiliense*) an active *erm* gene. Subsequent work has shown that patients with *M. abscessus* ssp *bolletii* (*M. massiliense*) have a much more favorable response to macrolide-based therapy, presumably due to an inactive *erm* gene, than patients infected with *M. abscessus* ssp *abscessus* [42,43]. In another interesting recent twist it has also been recently reported that clarithromycin induces greater *erm* gene activity than azithromycin and thus higher macrolide resistance than azithromycin [44]. They concluded that azithromycin may be more effective against *M. abscessus* ssp *abscessus* than clarithromycin whereas both macrolides appear to be equally effective against *M. massiliense* (*M. abscessus* ssp *bolletii*).

For unclear reasons, in the United States as opposed to Korea, there appears to be more lung disease caused by *M. abscessus* ssp *abscessus* than *M. abscessus* ssp *bolletii* (*M.*

massiliense). However, there is a clear treatment advantage with macrolide-based regimens for *M. abscessus* organisms without an active *erm* gene. Even if a laboratory is unable to identify *M. abscessus* isolates to the subspecies level, any laboratory should be capable of determining the MIC for macrolide for an *M. abscessus* isolate after incubation of that isolate in the presence of macrolide.

Akin to the approach towards recalcitrant cavitary MAC lung disease, surgical resection may warrant consideration in select *M. abscessus* (especially ssp *M. abscessus* patients) with localized or cavitary disease.

Bottom Line: The optimal therapy for *M. abscessus* ssp *abscessus* lung disease remains problematic and usually requires one or more parenteral agents. *M. abscessus* ssp *bolletii* (*M. massiliense*) responds in a more predictably favorable manner to macrolide-containing regimens. Mycobacterial laboratories must provide sufficient information to the clinician to allow determination of the *erm* gene activity of an *M. abscessus* isolate.

9) What about the management of other NTM respiratory pathogens?

M. kansasii remains the most easily treatable of the NTM pulmonary pathogens. As opposed to most other NTM, there is a good correlation between in-vitro susceptibilities and in-vivo response for a variety of antimicrobial agents including rifamycins, macrolides and fluoroquinolones.

A prospective study of 106 patients with *Mycobacterium malmoense* lung disease was performed over a 5-year period by the British Thoracic Society (BTS) [45]. The results of 2 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. In a follow-up study, the BTS randomly assigned 167 patients with *M. malmoense* lung disease 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 [46].

In an uncontrolled retrospective study of 136 patients with *M. xenopi* pulmonary infection, the absence of treatment was associated with a poor prognosis; median survival was 10 months in untreated patients compared with 32 months in treated patients [47]. Combination therapy with a rifamycin-containing regimen was associated with improved survival. These outcomes were not adjusted for comorbidities; therefore, the difference in survival cannot be definitively attributed to treatment. In a similar study from the Netherlands, multiple different treatment regimens were used in 49 patients with *M. xenopi* lung disease, but no specific drug combination showed consistently superior results [48].

Although pulmonary *M. szulgai* disease is rare, *M. szulgai* isolates are usually clinically significant. Disease occurs most commonly in patients with underlying lung disease. In a study that included 12 patients treated for *M. szulgai* infection, patients responded well to multiple treatment regimens, usually including rifampin, ethambutol, and either clarithromycin or ciprofloxacin [16]. Patients with *M. szulgai* lung disease appear more likely to respond to therapy than patients with *M. malmoense*, *M. xenopi*, or *M. simiae* infection.

M. simiae, when isolated in clinical samples, is more often a contaminant than a true pathogen. When it is a true pathogen, however, it is extremely difficult to treat effectively. To date, there are no predictably effective drug combinations for treating *M. simiae* [17]. The treatment of RGM pulmonary disease is highly dependent on the species isolated, the source of the RGM species isolated and, as noted earlier, the presence of inducible resistance genes for macrolides.

M. fortuitum is a low-grade pathogen that infrequently causes progressive pulmonary disease and usually does not require specific antibiotic therapy [18]. Clinicians should be very careful when evaluating the clinical significance of *M. fortuitum* respiratory isolates. Overall, it is important to be confident about the diagnosis, base therapy on in-vitro susceptibility, use at least two non-macrolide agents with in-vitro activity against the clinical *M. fortuitum* isolate, treat for at least 12 months of negative sputum cultures while on therapy (as is recommended for other nontuberculous respiratory isolates) and avoid macrolides if possible (especially for empiric therapy). Evaluation and treatment of esophageal disease when present is warranted in those with *M. fortuitum* lung disease given the known close association.

Bottom Line: Multi-drug macrolide-containing regimens remain the cornerstone of therapy for most slowly growing nontuberculous mycobacterial pathogens. Effective therapy for *M. abscessus*, the most important rapidly growing nontuberculous mycobacterial pathogen, remains elusive. Better therapeutic approaches are urgently needed for almost all NTM respiratory pathogens.

10) Is there a role for the use of macrolide monotherapy for non-cystic fibrosis bronchiectasis?

Recent data have been published regarding the benefits of the use of macrolide monotherapy to decrease rates of exacerbations in patients with COPD and non-cystic fibrosis-related bronchiectasis [49,50]. Increasing interest and ongoing multicenter studies are hoping to answer whether there may be a role for macrolide monotherapy to improve the natural course of adult non-CF bronchiectasis patients. The relative tolerance and potential benefit raises complex questions grounded in the relationship between bronchiectasis and NTM lung disease as well as the deleterious risk of creating macrolide-resistant NTM lung disease as discussed above. Without clear data or recommendations available to direct the clinician, a common approach to the adult non-CF bronchiectasis patient is similar to the CF patient and macrolide monotherapy. Specifically, prior to consideration of the start of macrolide monotherapy NTM lung disease should be excluded on clinical, radiographic, and as appropriate, microbiological criteria. Caution should be exercised before starting macrolide monotherapy in those adult non-CF bronchiectasis patients with past history of NTM lung disease given the real possibility of subsequent relapse or reinfection with the same or different NTM organism and risk of creating macrolide resistant NTM lung disease. The use of macrolide monotherapy in those with established macrolide resistant NTM lung disease for

immunomodulatory purposes is also undefined but at least superficially appears to be justifiable.

Bottom Line: Use of macrolide monotherapy in adult non-CF bronchiectasis should be cautiously approached given lack of data thus far from ongoing studies. If considered, NTM lung disease should be excluded prior to the start of macrolide monotherapy to avoid creating macrolide resistant lung disease, especially macrolide resistant MAC lung disease. Likewise, caution should be exercised in those with a history of past NTM lung disease.

Summary

Nontuberculous mycobacterial lung diseases are encountered with increasing frequency by clinicians in the U.S. where the prevalence of NTM lung disease appears to exceed that of tuberculosis, and at this point represents an important public-health threat. The recognition and diagnosis of NTM lung diseases seems to be improved, perhaps as a result of increased familiarity, but reliable and effective treatment of NTM, especially MAC, remains problematic. It is still frustrating that NTM generally do not respond to antimicrobials based on in-vitro susceptibility testing. Recent insights into molecular mechanisms of in-vivo drug resistance in RGM may provide clues to this poorly understood and vexing process.

Conflict of interest

None.

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