Managing Pulmonary Nontuberculous Mycobacterial Infection

Time for a Patient-centered Approach

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Abstract

The incidence of nontuberculous mycobacteria is increasing worldwide. However, the evidence base for clinical management comprises mostly expert opinion, case series, and few randomized clinical trials. Most currently recommended treatment regimens entail prolonged use of multiple antimicrobial agents associated with multiple self-limited and persistent potential adverse effects, including irreversible impairments of hearing, vision, and kidney function. Yet, little is known about how treatment impacts an individual patient's overall health status. Current treatment guidelines, although of undoubted value, are constrained by these limitations. Here we call for new studies that reassess recommendations for medical management of pulmonary nontuberculous mycobacteria infections, in particular *Mycobacterium avium-intracellulare* complex and *Mycobacterium abscessus* complex. We propose pragmatic, person-centered outcome measures that might be used in clinical assessments and new research studies, including patient-reported experience measures and patient-reported outcome measures. This will enable patients and their health-care providers to make clinical management decisions that derive from a realistic view of what they can hope to achieve from treatment.

Keywords: *Mycobacterium avium* complex; *Mycobacterium avium-intracellulare*; *Mycobacterium abscessus*; *Mycobacterium* infections, atypical; antibacterial agents

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Nontuberculous mycobacteria (NTM) are mycobacterial species other than the *Mycobacterium tuberculosis* complex (i.e., *Mycobacterium tuberculosis*, *Mycobacterium bovis*, and *Mycobacterium africanum*) and *Mycobacterium leprae*. Ubiquitous in the environment and isolated from water, soil, and hospital wards, NTM can persist in humans without causing disease (1). However, with increasing numbers of immunocompromised patients (including those with HIV infection and hematological disorders), as well as patients with cystic fibrosis and chronic lung disorders, the role of N TM as a cause of human, and in particular pulmonary, disease is apparent, with recent reports indicating a worldwide increase (Table 1).

Current treatment guidelines (2, 3) are based on limited data derived mostly from expert opinion, case series, and few randomized clinical trials. Outcome measures used to date have been largely limited to those that are conventionally used to assess curable infections, such as conversion to negative cultures. However, established pulmonary infections with NTM are often not cured. Instead, they persist or recur as chronic diseases more closely resembling diabetes or HIV infection than community-acquired pneumonia. Moreover, many pulmonary NTM infections occur in people with significant comorbidity and are treated for prolonged periods of time with multiple antimicrobial agents that are associated with multiple potential adverse effects, some of which are irreversible.

Although current treatment guidelines, based on conventional measures of infection control or cure rates, have undoubted practical value, they are not necessarily designed to optimize patient-centered outcomes that are particularly relevant to the management of chronic diseases. Here,

Table 1. The increasing incidence and prevalence of nontuberculous mycobacteria isolates is reported from all over the world

Region	Country	Main NTM Species	Trend in Incidence/ Prevalence	Comment
Europe	United Kingdom (31)	MAC (43%) *M. malmoense* (14%) *M. kansasii* (13%)	0.9 per 100,000 (1995) to 2.9 per 100,000 (2006) (Incidence)	It was not possible to assess the clinical significance of these isolates as there was little associated clinical information available
America	Canada (32)	MAC (59%) *M. xenopi* (26%) *M. abscessus* complex, *M. chelonae*, and *M. fortuitum* (13%) *M. kansasii* (2%)	9.1 per 100,000 (1997) to 14.1 per 100,000 (2003) (Prevalence)	The association between NTM isolates and disease was not clarified
	United States (33)	MAC (79–86%) *M. abscessus* complex, *M. chelonae*, and *M. fortuitum* (5–19%)	1.4 per 100,000 (2004) to 6.6 per 100,000 (2006) (Prevalence)	Study across four different U.S. states
Asia (34)	Japan (35)	MAC *M. kansasii*	2.5 per 100,000 (2005) to 5.9 per 100,000 (2007) (Prevalence)	
	South Korea (36)	MAC (65%), *M. abscessus* complex, *M. chelonae*, and *M. fortuitum* (19%)		Absolute number of isolates increasing but no data on incidence/prevalence
	Taiwan (37)	MAC (35%), *M. abscessus* complex (21%)	6.67 per 100,000 (2005) to 9.28 per 100,000 (2008) (Incidence)	Highest incidence recorded
	Oman (38)	MAC	7.6% (2006) to 10.9% (2007)	"Isolation prevalence" data
Australia	Queensland (39)	MAC (72%), *M. kansasii* (8%)	2.2 (1999) to 3.2 (2005) (Incidence)	Authors noted that true number of cases may be an underestimate, and the real prevalence may be much higher
Africa	Zambia (40)	MAC	17% of Patients with active tuberculosis	Only 2% were considered to have NTM disease

Definition of abbreviations: *M.* = *Mycobacterium*; MAC = *Mycobacterium avium-intracellulare* complex.

we review the use of quality measures within current clinical studies and propose that future research on pulmonary NTM infections, in particular *Mycobacterium avium-intracellulare* complex (MAC) and *Mycobacterium abscessus* complex, should incorporate a patient-centered evaluation that combines efficacy of treatment, possible adverse events during therapy, and associated patient comorbidities.

Current Guidelines, Research Studies, and Their Limitations

The American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) 2007 guideline is the most current available and covers prevention, diagnosis, and treatment of NTM infections (2). The British Thoracic Society guideline (1999) is more concise but less up to date (3). The ATS/IDSA guideline itself highlights failings in the current evidence base, as many of the recommendations arise from expert opinion or single-center studies and not large-scale randomized, controlled trials. In addition, most treatment studies report clinical outcomes, such as sputum conversion rate or cure and mortality rates at the end of treatment. These are generally objective measures that do not directly capture the patient experience before, during, or after a given therapy. There are few studies that document treatment-related changes in quality of life or health status (4, 5). Despite the anecdotal high frequency of adverse events during therapy (6), surprisingly few data are available that objectively quantify toxicity, tolerability (which is often poor), and possible hypersensitivity reactions. Examples of these include abnormal liver and renal function (often due to rifampicin, clarithromycin, streptomycin, or amikacin), peripheral neuropathy and impaired visual acuity (ethambutol), or severe nausea and gastrointestinal disturbances (clarithromycin) (7–10).

There is no doubt that treatment response can sometimes be very good. A U.S. study of MAC lung disease demonstrated sputum conversion rates up to 90% in subjects with no history of previous treatment failure and (importantly) an ability to tolerate a clarithromycin-containing multidrug regimen (11). However, of the 39 who took more than 5 months of treatment, more than 40% had to discontinue at least one drug because of severe adverse events. Furthermore, 6 of the original 50 (12%) enrolled subjects stopped all drug therapy due to adverse events within the first months of treatment. Unfortunately many cases of MAC are not successfully treated, and where there is drug resistance or advanced disease, the prognosis is still very poor. Parenteral drugs and surgical treatment may be needed (12).

Less successful results are reported for *M. abscessus* complex. A study by Jarand and colleagues (13) on pulmonary disease reported a conversion to negative sputum without relapse in 48% of patients, although many required surgical treatment, and

postoperative complications arose in 25% of the cases. Also, adverse events or toxicities were severe enough to stop at least one drug in 65% of patients. Cefoxitin and amikacin were the least well tolerated (producing rash and hearing problems, respectively).

Studies to minimize drug-related toxicity (and hence its impact on individual health status) are limited, with the exception of intermittent administration of azithromycin/clarithromycin in MAC infection (14–16).

The duration of treatment is also yet to be definitively established. Typically this is 18 to 24 months, although for pulmonary NTM a further 12 months from negative sputum cultures is often recommended (Table 2). Hence, the total time on therapy may be considerably longer than 2 years. Thus, despite little supporting data, patients may be started on multiple drugs of uncertain efficacy and significant toxicity, which can be continued for a protracted (and potentially open-ended) length of time.

An Increased Focus on Quality

To better understand the impact of both NTM infection and its treatment on an individual, a structured quality framework is needed that incorporates clinical outcome as well as patient-reported measures (17). The typical duration of treatment (18–24 mo) defines pulmonary NTM by U.S. National Center for Health Statistics criteria as a chronic illness. In conditions such as Parkinson disease and arthritis there are a number of well-established and standardized quality-of-life tools (18, 19). A range of measures can be used, including patient-reported experience measures and patient-reported outcome measures (20). Questionnaires are available that can accurately evaluate patient experience. These cover different health domains, including dignity, as well as emotional and physical symptoms. In HIV infection, the Medical Outcome Study (MOS)-HIV Health Survey has been used in clinical trials, with extensive evidence regarding its reliability and validity as a measure of patient experience (21).

Many of the questionnaires already in use could be easily modified and incorporated into assessment tools for NTM disease when considering therapy and also during treatment. This would enable the patient to state what they hope to gain from treatment and serve to set out their own criteria for starting or stopping therapy. The assessments would also allow the clinician to indicate the likely chance of achieving "success" using the patient's definition of treatment benefit. This has been rarely used in clinical studies. An evaluation of NTM infection symptom and health status outcome was performed within a Canadian clinical trial in HIV-infected individuals with disseminated MAC (4). Here MOS-HIV and Karnofsky scores helped to establish the superiority of a three-drug regimen against four drugs in terms of impact on symptoms, function, and other aspects of health status.

A recent study from the Mayo Clinic, currently published as an abstract (5), described a 12-month pilot project in which a pharmacist took increased responsibility for the management of NTM lung infections. This involved training to identify, resolve, and prevent drug-related adverse events. More than 96% of patients (n = 61) were "very satisfied" or "satisfied" with the service provided and their clinical outcome, suggesting that successful treatment can be facilitated by the use of a robust, person-centered framework that recognizes different comorbidities and treatment-adverse events. The approach also highlights the importance of a dedicated point of contact for the patient. In many conditions this is already acknowledged through the use of specialist nonphysician health-care workers who are involved over the longer term across the patient journey. They can also act, when needed, as both a patient's support and advocate (22).

New clinical studies (in particular on MAC and *M. abscessus* complex infections) should include standardized measures for clinical and patient-reported outcomes (Table 3). In particular, they should provide information on treatment success rates, adverse event profile, and its frequency, and also serve as practical tools to evaluate health status and patient experience. This will allow transparent decision making that acknowledges the individual nature of the condition before any proposed treatment. This will help the person considering therapy to work with the health-care team in making decisions about their care. It also facilitates data comparison between different centers and provides the opportunity to create a robust international dataset that can underpin new guidelines and so build on current clinical practice.

Table 2. Combination treatment and duration from American Thoracic Society/Infectious Disease Society of America and British Thoracic Society guidance

NTM Species	Antibiotic Regimen	Comments
Mycobacterium avium-intracellulare complex	ATS/IDSA: macrolide (clarithromycin or azithromycin), rifampicin/rifabutin, and ethambutol plus streptomycin or amikacin in advanced/extensive disease BTS: rifampicin and ethambutol, ± isoniazid	Duration not definitively established (18–24 mo)
Mycobacterium kansasii	ATS/IDSA: isoniazid, rifampicin, and ethambutol BTS: rifampicin and ethambutol only	Treat for 12 mo after sputum cultures negative (often total of 18–24 mo)
Rapidly growing mycobacteria	Combination treatment dependent on the species isolated and the site of infection	Minimum 6 mo treatment

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Disease Society of America; BTS = British Thoracic Society; NTM = nontuberculous mycobacteria.
Data from References 2 and 3.

Table 3. Summary of key recommendations

New research studies should include:
1. Standardized measures for clinical and patient reported outcomes:
Clinical outcomes can be reported as sputum conversion rate or cure and mortality rates at the end of treatment
A range of patient-reported measures can be used: PREMs, PROMs, QALY, MOS-HIV Health Survey, and Karnofsky score
2. Person-centered framework that acknowledges different comorbidities and treatment adverse events
3. Strategies to minimize toxicity (e.g., intermittent administration)
4. Cost-effectiveness and cost–benefit assessment
In addition, new research studies should enable:
5. Data registries on clinical relevance and patient's treatment and outcome to be commenced and easily populated
6. Epidemiological/surveillance data on likelihood of adverse events to be made easily available to patients and health-care providers

Definition of abbreviations: MOS-HIV = Medical Outcomes Study HIV; PREMS = patient-reported experience measures; PROMS = patient-reported outcome measures; QALY = quality-adjusted life years.

Cost-effectiveness and cost–benefit assessments are a natural consequence of this. It is of interest that tuberculosis programs are now adopting complex evaluation tools that link performance scores and expenditures (i.e., Report of Performance Measure [23]). At present, there are few data regarding the cost of treatment of NTM infections (24, 25) or its associated benefit. Established measures, such as the quality-adjusted life years measure, could also be used to assess this (26). The reporting of outcome measures is an essential first step when determining value—defined as an improvement in outcome in the most efficient and pragmatic way (27). Long-term conditions (such as NTM infections) represent an opportunity to maximize value over time because of their prolonged morbidity and costs. A whole-pathway quality measure approach (determined by summing clinical and patient-reported outcomes plus patient experience, divided by the cost of care over a 1-year period) is a useful framework within which outcomes and costs may be equitably linked (28). It also enables the patient and his or her health-care provider to obtain a clear picture of the local availability of services, technology, and personnel, all of which can influence decisions regarding current and future management.

The necessary political will to change the current treatment paradigm for NTM disease exists, although it requires reframing specifically for this chronic condition. In the United Kingdom, the Department of Health is undertaking a program promoting the routine collection and use of information derived from patient-reported outcome measures completed by patients undergoing selected National Health Service–funded elective procedures (e.g., hip replacement, as well as chronic obstructive pulmonary disease and diabetes care [but not pulmonary NTM]) (29). In the United States, the Patient-Centered Outcomes Research Institute (PCORI) (30) is authorized by Congress to conduct research to provide information about the best available evidence to help patients and their caregivers make informed decisions regarding their health and health care. To date, 51 awards with a total value of US $88.6 million have been made. None of these are for chronic infections, although pulmonary NTM would seem an attractive area to study.

Conclusions

NTM infections are now more frequently encountered worldwide by both clinicians and microbiologists. Treatment outcome measures, such as prevention of adverse events or improvement in health status, are rarely covered by clinical studies reported to date and so limit current guidelines. New research should contain a robust, person-centered management framework that encompasses clinical data, potential drug toxicity, and patient-reported experience. This will enable patients and their health-care providers to make decisions regarding their health that derive from a realistic view of what they hope to achieve from treatment. It also provides the opportunity to set boundaries for success and potential therapeutic failure. Establishing new international research databases that systematically record this information would be a key first step in understanding current and future health-care demands, the costs associated with NTM, and the value of treatment. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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