ANNALSATS SUPPLEMENT

Patient-Centered Research Priorities for Pulmonary Nontuberculous Mycobacteria (NTM) Infection

An NTM Research Consortium Workshop Report

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Abstract

Nontuberculous mycobacteria (NTM) cause an increasingly important chronic and debilitating lung disease in older adults. Diagnosis is often delayed, although awareness among clinicians and patients is increasing. When necessary, treatment often lasts 18–24 months and consists of three or four antibiotics that can have serious side effects. Relapses are common and commonly require resumption of prolonged therapy. Given the need for improved diagnostic techniques and clinical trials to identify new therapies or to improve existing therapies, a group of North American clinicians and researchers formed the NTM Research Consortium (NTMRC) in 2014. The NTMRC recognized the importance of including the patient voice in determining research priorities for NTM. In November 2015, patients, caregivers, patient advocates, clinical experts, and researchers gathered for a 1-day meeting in Portland, Oregon funded by the Patient-Centered Outcomes Research Institute. The meeting goal was to define patient-centered research priorities for NTM lung infections. Patients expressed frustration with the number of people who have endured years of missed diagnoses or inadequate treatment of NTM. Participants identified as top research priorities the prevention of NTM infection; approval of more effective treatments with fewer side effects and easier administration; understanding the best chest physiotherapy methods; validating and using tools to measure quality of life; and developing a disease-specific activity and severity assessment tool. Workshop participants agreed that two complementary objectives are critical to ensure the best achievable outcomes for patients: (*1*) additional clinician education to improve screening and diagnosis of NTM infections; and (*2*) development of a geographically distributed network of experts in NTM disease to offer consultation or direct therapy after a diagnosis is made.

Keywords: nontuberculous mycobacteria; pulmonary disease; quality of life

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Nontuberculous mycobacteria (NTM) are ubiquitous environmental organisms, found in water distribution systems and soil, that cause chronic, debilitating pulmonary disease (1, 2). Patients typically suffer from fatigue, chronic cough, dyspnea, night sweats, weight loss, depression, social anxiety, hemoptysis, wheezing, and other symptoms. Pulmonary NTM disease is increasingly common, with estimates ranging from 15.5 to 26.7 per 100,000 among those more than 50 years of age (3–5). NTM disease disproportionately affects women, incidence increases with age, and it also occurs with chronic underlying lung

disease such as cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease (COPD) (4–6).

For the subset of patients who develop NTM disease requiring treatment, therapy typically includes the use of three or four antibiotics concurrently for 18–24 months without guarantee of cure (2). Side effects are often numerous and may be serious. Many patients fail therapy and more than one-half will have either recrudescent disease or new infection after completing these treatments, and surgical resection is sometimes necessary (2).

Origins and Conduct of the Workshop

The NTM Research Consortium (NTMRC) was formed in 2014 at an Oregon Health & Science University–sponsored NTM Research Retreat by a group of researchers working to improve the care for and outcomes of patients with NTM disease. Although we were able to define key research priorities from a researcher and clinician perspective, one major outcome of this meeting was a desire to involve patients in the process of defining research priorities and future study design and conduct.

In November 2015, a group of 24 patients, caregivers, patient advocates, clinical experts, and researchers met at Oregon Health & Science University in Portland, Oregon for the second annual NTMRC meeting, supported by a Eugene Washington Meeting Award from the Patient-Centered Outcomes Research Institute. The Patient-Centered Outcomes Research Institute is an independent nonprofit nongovernmental organization authorized by the U.S. Congress to promote patient-centered outcomes research.

Attendees included representatives of NTM Info & Research, which is a U.S. national nonprofit organization formed on behalf of patients with pulmonary NTM disease to offer patient support, and to promote medical education and research. Other organizations represented at the meeting included the COPD Foundation, the Bronchiectasis and NTM Research Registry Consortium, and the Cystic Fibrosis Foundation. The goal of the meeting was to define the top patient-centered research priorities for NTM.

Before the meeting we conducted two 15-question needs assessment surveys, one for participating patients and caregivers and one for clinical and expert stakeholders. These are reproduced in the online supplement. The surveys solicited priorities for each of the major topic areas and descriptions of barriers to NTM diagnosis and treatment. The results of that survey were summarized in a slide presentation and provided a starting point for discussion at the meeting.

Below, we summarize the discussions and resulting patient-centered research priorities for each major topic area: prevention, diagnosis, health-related quality of life, treatment, and clinical outcomes. Thirteen patient-centered research priorities and specific research questions identified during the NTMRC workshop are listed in Table 1.

Prevention Priorities

Strengthen the Role of Patients in Preventing NTM Infection or Reinfection

The natural history of NTM lung disease is not well understood, although NTM are ubiquitous throughout the world (7). The workshop discussion focused on the prevention of reinfection, given that patients with prior or current infection were included. There is currently little consensus on how to prevent infection and reinfection with NTM. As a result, patients reported that they have adopted a "careful way of living." Given ongoing environmental exposure, prevention efforts typically focus on reducing exposure to aerosolized water and soil. However, underlying conditions and health have also been associated with pulmonary *Mycobacterium avium* complex, suggesting that interventions should also focus on overall health and immunosuppression (8, 9). Patients specifically questioned whether aspiration had a role in NTM infection and reinfection.

Limit the Risk of Patient-to-Patient Transmission of NTM Infection in Cystic Fibrosis Clinics

For patients with cystic fibrosis, there may be a risk of transmission in cystic fibrosis clinics. Workshop attendees agreed that more research is needed to determine the risk of person-to-person or indirect transmission in cystic fibrosis clinics. Several reports have been published regarding clusters of *Mycobacterium abscessus* subspecies *massiliense* in a Seattle cystic fibrosis clinic and at a U.K. cystic fibrosis center documented by molecular methods (10, 11). The U.S. Cystic Fibrosis Foundation and European Cystic Fibrosis Society consensus recommendations include standard infection control precautions to minimize the potential for cross-infection with NTM in cystic fibrosis clinics (12), although there have not been any trials to compare interventions or to identify situations in which additional precautions are necessary.

Diagnosis Priorities

Improve the Timeliness of Diagnosis and Develop Molecular Techniques for Rapid Species Identification and Susceptibility

Patients expressed frustration with misdiagnosis and slow culture results once the correct test is ordered. Workshop participants identified major issues with the process of diagnosis, beginning with who is tested, the time to culture, and the difficulty of collecting an adequate sputum specimen from many patients.

The "gold standard" for NTM diagnosis is culture, which can take 1–2 weeks for rapid-growing NTM such as *Mycobacterium abscessus* or up to 6 weeks for slow-growing NTM such as *Mycobacterium avium* complex species. After culture growth, species are identified with DNA probes available for *Mycobacterium avium* complex or using molecular techniques performed at specialized reference laboratories to identify other species.

It is important for treatment and prognostic purposes to be able to identify NTM species and subspecies, particularly *Mycobacterium abscessus*. Ideally, new diagnostic tests will speed up identification and include susceptibility testing, as has been done for diagnosing *M. tuberculosis* (TB) and rifampin susceptibility with results available within 2 hours, using the GeneXpert system (Cepheid, Sunnyvale, CA). These tests are being developed for NTM, but still need to be validated. In contrast to tuberculosis, for which recovery of *Mycobacterium tuberculosis* indicates active disease, it is more complicated to distinguish between indolent and active NTM disease. Susceptibility testing of NTM

Table 1. Nontuberculous mycobacterial lung disease: patient–centered research priorities by topic area

Topic	Priority	Potential Specific Questions and Next Steps
Prevention	1. Strengthen the role of patients in preventing NTM infection or reinfection	Evaluate whether aspiration increases the risk of NTM infection or reinfection
	2. Limit the risk of patient-to-patient transmission of NTM infection in cystic fibrosis clinics	Estimate the risk of person-to-person or indirect transmission in CF clinics
		Comparative effectiveness of standard and expanded infection control precautions
Diagnosis	3. Improve the timeliness of diagnosis and develop molecular techniques for rapid species identification and susceptibility	Validate molecular diagnosis techniques being developed by National Jewish Healthcare
	4. Develop a screening algorithm for patients at risk for pulmonary NTM disease	Predictors of positive culture
		Predictors of meeting ATS disease criteria at diagnosis
	5. Develop better methods for sputum collection and testing	Identify techniques that improve sputum collection
		Develop new collection devices
Quality of life	6. Reduce the impact on patients of anxiety and depression	Evaluate anxiety and depression after diagnosis or during treatment in patients with NTM disease
		Association between anxiety/depression and poorer treatment adherence
	7. Develop an NTM-specific Health-Related Quality of Life tool	Validate NTM Symptom Module* tool
	8. Promote quality-of-life measures for assessing the effectiveness of treatment	Validate correlation between NTM Symptom Module and clinical outcomes
Treatment	9. Reduce the burden of antibiotic treatment for NTM disease	Develop and evaluate alternative delivery systems for intravenous antibiotics
		Repurpose existing therapies
		Develop new, more effective drugs with a shorter therapy duration
	10. Develop and test the efficacy of nonpharmacological therapies and holistic medicine approaches	Comparative effectiveness of exercise and lung clearance devices, taking into account ease of use and affordability
	11. Improve understanding of who needs or benefits from antibiotic therapy	Role of therapy in mild cases to prevent disease progression
		Predictors of treatment response
Clinical outcomes	12. Develop a composite measure of disease activity or severity	Develop a composite index of disease activity or severity that includes microbiological, chest imaging, and quality of life measures
	13. Identify and validate biomarkers associated with disease risk, prognosis, and treatment response	Identify biomarkers associated with disease risk, prognosis, or treatment response

Definition of abbreviations: ATS = American Thoracic Society; CF = cystic fibrosis; NTM = nontuberculous mycobacteria.
*From Reference 22.

isolates for antimicrobial agents other than macrolides and amikacin must be interpreted cautiously, because they are not necessarily associated with response to therapy.

Develop a Screening Algorithm for Patients at Risk for Pulmonary NTM Disease

Improved education of primary care providers about NTM symptoms and screening, as well as pulmonologists and infectious disease physicians, is critical. In adults with cystic fibrosis, the prevalence is approximately 20% and NTM is difficult to distinguish from other infections (13, 14). Accordingly, the Cystic Fibrosis Foundation has released screening guidelines that include a recommendation for annual NTM cultures in patients with cystic fibrosis, as long as they can produce sputum (12).

For patients without cystic fibrosis, screening occurs when an astute clinician recognizes a patient profile suggestive of NTM infection, such as a patient with a persistent productive cough that does not improve with ordinary antibiotics, a positive smear for acid-fast bacilli or culture of mycobacteria on a patient sample obtained routinely during hospitalization, or incidental discovery of a pattern suggestive of NTM infection on a computed tomographic (CT) imaging study of the chest.

Workshop attendees agreed that universal screening of all patients with chronic cough is cost prohibitive and not necessary for a relatively infrequent infection such as NTM. Instead, NTM Info & Research currently encourages testing for NTM when patients have had at least two lower respiratory infections in the prior 12 months, frequent coughing, and night sweats, although this algorithm has not been evaluated in a clinical setting.

Develop Better Methods for Sputum Collection and Testing

Workshop participants discussed how difficult it is for some patients to expectorate an adequate sputum specimen. Limitations to current methods for sputum collection create challenges for diagnosing lung NTM lung disease, monitoring untreated infection, and confirming response to

treatment. Clinicians rely on skilled personnel to assist patients with sputum collection. Identifying techniques that are used by health-care workers who are able to collect sputum from patients experiencing difficulty would be useful. Improved methods and devices for sputum collection without risk of contamination are needed.

Quality-of-Life Priorities

Reduce the Impact on Patients of Anxiety and Depression

NTM lung infection is a chronic disease requiring long-term therapy that causes or amplifies negative emotions for many patients. Patients are particularly concerned about anxiety and depression and the effects of mental health challenges on medication adherence and quality of life (15, 16). Patient participants in the workshop described the difficulties of adding NTM therapy to the daily treatment burden, which may exacerbate issues with adherence, observed in patients with bronchiectasis with chronic *Pseudomonas* infections (17, 18). More work needs to be done to address these concerns.

Develop an NTM-Specific Health-Related Quality-of-Life Tool

A. Quittner (University of Miami, Coral Gables, FL), one of the stakeholder attendees, has developed disease-specific assessment tools for patients with cystic fibrosis (CFQ-R) and for patients with bronchiectasis (QOL-B). She and others are working on an NTM Symptom Module that can be used in addition to those tools or alone, depending on the patient's underlying diagnosis (19–22).

The NTM Symptom Module measures NTM-specific symptoms, including loss of appetite, feverishness or chills, bad taste in the mouth, and problems with memory. The overwhelming fatigue associated with NTM comes and goes and is an often-overlooked characteristic of the disease, but was one of the most frequently mentioned effects on health-related quality of life. Patients and clinicians are interested in specific interventions that can address this fatigue.

Promote Quality-of-Life Measures for Assessing the Effectiveness of Treatment

In October 2015, the U.S. Food and Drug Administration conducted a public meeting on patient-focused drug development for treatment of NTM lung infections, which included discussion of microbiological and other clinical outcomes for clinical trials (23). In response, much of the discussion at the NTMRC meeting focused on measuring quality of life. Workshop participants agreed that including patient-reported outcomes in future therapeutic trials is critical to understanding tradeoffs between relief of symptoms of NTM disease and reduced quality of life resulting from medication side effects.

Quality of life is relatively easy to measure and does not require in-person visits to collect data, contributing to patient-friendly clinical trial design. The CFQ-R is used to evaluate therapies in clinical trials for patients with cystic fibrosis, and the U.S. Food and Drug Administration has been increasingly willing to use improvement in patient-reported outcomes (i.e., respiratory symptoms) as an outcome measure to obtain drug approval. The NTM Symptom Module, once validated, and other appropriate health-related quality-of-life tools should be incorporated in future clinical trials, in addition to traditional microbiological outcomes (22).

Treatment Priorities

Reduce the Burden of Antibiotic Treatment for NTM Disease

There is a clear need for less toxic, more effective antibiotic therapies for NTM disease. Patients expressed a need for reducing the treatment burden, which includes reducing the duration of treatment, identifying drugs with fewer side effects, and eliminating the need for intravenous administration of drugs, particularly for those with cystic fibrosis, who already have a high treatment burden.

Workshop participants discussed the model of tobramycin, approved in 1976 for intravenous administration against *Pseudomonas aeruginosa* infections in patients with cystic fibrosis. Home administration was made possible in 1997 with the approval of inhaled tobramycin (24). In 2013 a nonnebulized dry-powder formulation was approved and welcomed by the cystic fibrosis community as an even more patient-friendly method of therapy administration (25).

At present, patients with *Mycobacterium abscessus* disease may require several months of intravenous antibiotic therapy administered in combination with oral agents during an intensive phase of treatment, which has a negative impact on daily life (12). After the intensive period most patients switch to combined inhaled and oral antibiotics for the duration of therapy.

Develop and Test the Efficacy of Nonpharmacological Therapies and Holistic Medicine Approaches

Patients expressed a need for clinicians to treat the whole body, not just the lung infection. Patients strongly believed that exercise and airway clearance techniques improve function, and probiotics help patients feel better. Patients with cystic fibrosis are experienced in managing excess mucus production and have access to a variety of proven medications and techniques for their disease. It is also important to clear mucus from the lungs in patients with NTM disease who have excess mucus production.

Clinician participants opined that one limitation of the current treatment guidelines for NTM lung infections sponsored by the American Thoracic Society and the Infectious Diseases Society of America (2) is that the guidelines focus on controlling infection with antimicrobial or surgical therapy and only briefly mention other ways to improve the health of patients with NTM disease. Although adjunctive treatments such as airway clearance, exercise, and probiotics are standard of care for the clinical experts at the workshop, the clinicians advised that the role of these treatments for NTM disease and associated symptoms and the prevention of reinfection remains largely untested scientifically. Clinicians would like to know which adjunctive therapies are "best," see more evidence of clinical benefit, and know how hard to push patients to incorporate adjunctive treatments into daily routines.

Improve Understanding of Who Needs or Benefits from Antibiotic Therapy

The decision to start antibiotic therapy is based on clinical experience and judgment. Patients and physicians struggle to make informed decisions regarding risks and benefits. Treatment recommendations in the 2007 American Thoracic Society/ Infectious Diseases Society of America

guidelines on treatment of NTM lung infections (2) were based largely on expert opinion, and are currently being updated.

The evidence base for antibiotic therapy is still lacking; although the first randomized controlled clinical trial for NTM therapy in HIV-negative patients was published in 2001, relatively few others have been performed (26). Many questions remain. We do not have reliable indicators about who will progress and who will not. We do not have adequate knowledge about which patients benefit from therapy and at what point in the disease course treatment is indicated to prevent progression and lung damage.

Given the complexity of treatment regimens, workshop participants agreed that clinicians who are not familiar with NTM should consult with experts in the field regarding treatment options before initiation of therapy, or refer complicated patients to experts.

Clinical Outcomes and Prognosis

Develop a Composite Measure of Disease Activity or Severity

Given that NTM lung disease is often not curable and is thus similar to other chronic diseases, workshop participants agreed that a composite measure of disease activity or severity would be useful for trials and in clinical practice.

As an example of what is needed for NTM disease, there are several validated measures of disease outcomes for rheumatoid arthritis, including the ACR20 and Disease Activity Score (27). Disease activity scales measure manifestations of inflammation and are used to measure response to therapy in clinical trials as well as in clinical practice when treating patients with rheumatoid arthritis. For NTM disease, a composite score would likely incorporate microbiological, chest imaging, and health-related quality-of-life measures.

Identify and Validate Biomarkers Associated with Disease Risk, Prognosis, and Treatment Response

Development of clinically useful biomarkers for NTM lung disease has been restrained by limited knowledge of the pathogenesis of pulmonary NTM disease and of host responses to NTM exposure and infection. However, clinical and epidemiologic observations regarding pulmonary NTM, as well as related mycobacterial diseases such as nonpulmonary NTM infection and tuberculosis, suggest the likelihood that host immune and genetic factors predispose to disease. Expansion of this knowledge may lead to the identification of biomarkers for risk and prognosis.

There is evidence that patients with pulmonary NTM have impaired mucociliary function and more low-frequency variants in genes associated with immune, cystic fibrosis transmembrane conductance regulator, cilia, and connective tissue gene sets (28, 29). In addition, there may be immunological markers that distinguish disease from airway colonization. Human data regarding the importance of helper T-cell type 1 immune responses in protection against NTM are limited, although similar to that seen with *M. tuberculosis*.

Anti–tumor necrosis factor therapies used in the treatment of rheumatic diseases and other chronic inflammatory conditions are recognized as risk factors for pulmonary NTM disease, suggesting that defects in these immune pathways may explain pulmonary NTM pathogenesis in some patients (30–32).

Further, work evaluating $CD8^+$ mucosal-associated invariant T (MAIT) lymphocytes, in patients with active tuberculosis, suggests that MAIT cells correlate with invasive and active infection and may serve as a biomarker for mycobacterial disease (33–35).

Summary

Top priorities identified by the participants in the 2015 NTMRC workshop for advancing control of NTM lung disease include prevention of NTM infection, approving more effective treatments with fewer side effects and that are easier to administer, understanding the best lung clearance methods, validating and using tools to measure health-related quality of life, and developing a disease activity and severity measurement tool.

Patients are frustrated by the length of time (sometimes years) during which a diagnosis of NTM is missed or NTM lung infection is improperly treated. Accordingly, there is a pressing need to educate physicians and primary care providers about NTM disease, including primary care physicians and mid-level practitioners who see patients with recurrent pneumonia or pneumonia that does not respond to first-line antibiotics, radiologists who see characteristic changes on chest CT examinations, and gastroenterologists who see patients with reflux and related pneumonia. Workshop participants agreed that it is important for community clinicians to consult with or refer patients to experts in NTM treatment after diagnosis is made to ensure that clinicians and patients are fully informed of the options.

The priorities for research and education generated from this workshop should provide much-needed data to better inform clinician and patient decision-making and to improve treatment and outcomes for patients with NTM disease.

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