Nontuberculous mycobacteria: opportunistic environmental pathogens for predisposed hosts

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Nontuberculous mycobacterial (NTM) infections are caused by environmental mycobacteria. Patients with pulmonary NTM disease usually have predisposing lung abnormalities. Diagnostic methods are evolving. Treatment is largely empiric. Data were extracted from peer reviewed publications, guidelines, and case series. Progressive NTM lung disease should be treated. Multidrug regimens are mostly macrolide based and are occasionally complemented by lung resection. Disease persistence and relapse are not uncommon and are a greater problem with so-called rapid-grower NTM infections. Some of the issues considered in this review are: the role of antibiotic susceptibility testing in predicting treatment effectiveness, optimal drug combinations, daily vs. intermittent dosing intervals for different NTM infections and disease severity, when the goal of cure should be replaced with observation or palliation, and patient selection for surgery. Future needs for development and research include improved epidemiology, definition of genetic and other risk factors, definition of predictors of treatment outcome, multicenter treatment studies, new drug discovery and animal models of disease and treatment.

Keywords: nontuberculous mycobacteria/environmental pathogen/pulmonary disease/epidemiology/clinical presentation/diagnosis/treatment

Accepted: September 24, 2010

Introduction

Pulmonary nontuberculous mycobacterial (NTM) disease was first recognized as background infections among a small minority of patients in tuberculosis (TB) sanatoria. In the 1950s, reports began to appear that described NTM disease among patients with underlying lung abnormalities. It was not until disseminated Mycobacterium avium complex (MAC) was recognized as the most common opportunistic bacterial infection in AIDS patients that the low-prevalence
problem of pulmonary NTM disease in immunocompetent patients attracted the attention of the medical community. NTM pulmonary disease and other NTM infections have now been recognized in many parts of the world.

NTM: opportunistic environmental pathogens

NTM infections are acquired from environmental (water, soil) reservoirs and are not transmitted between humans or between animals and humans. NTM infection progression to clinical disease requires one or more predisposing host conditions. What is different from conventional thinking about opportunistic pathogens is that pulmonary NTM disease (outside the context of AIDS) usually occurs in patients who are not obviously immunosuppressed but who almost always have pre-existing, underlying lung abnormalities. Sometimes these pre-existing abnormalities, such as subtle bronchiectasis, require computerized chest tomography for detection. Other, as yet ill-defined, genetic predispositions are likely to be involved in patients with pulmonary NTM disease.

Epidemiology: changing prevalence, geographic distribution and environmental sources

NTM prevalence in developed countries has risen from the obscurity created previously by the high prevalence of TB. In the early 1900s, there were probably 100 cases of TB for every case of NTM disease. Anecdotal lore is that NTM isolated from sputum cultures in that era were considered to be culture contaminants. At present, this TB:NTM disease ratio may be almost reversed, in suburban areas of low TB incidence. In developing countries, where TB is common, NTM disease is less well recognized, for this same reason—but when sought can be found.

There also may be a true increase in NTM disease incidence. However, this conclusion is confounded by the increased awareness of NTM disease since the 1980s and the increased availability and sensitivity of laboratory diagnosis. Nucleic acid amplification testing of sputum for TB, evolution of rapid, liquid culture methods and development of DNA probes for identification allow differentiation of NTM infections from TB. HPLC, PCR and RFLP are also increasing mycobacterial species identification.

There has been a gender shift in patients diagnosed as having NTM disease. Reports from 50 years ago described lung disease of older male patients with predisposing conditions, such as emphysema. In
today’s clinics, approximately 80% of patients with NTM disease are middle aged or elderly females. Some of this shift may be explained by increased female cigarette smoking; however, many females with NTM disease have never smoked. Most female patients have underlying bronchiectasis that can require computerized tomographic (CT) examination for detection and that is associated with previous histories of lung infection or other (often obscure) causes.

NTM species that cause pulmonary disease vary by geographic region. MAC is the predominant pathogen in most regions (Table 1). *Mycobacterium kansasii* disease is relatively more common in the middle USA, England and Wales. *Mycobacterium xenopi* disease is more common in the northern USA, Canada, the UK and some regions in Europe. *Mycobacterium malmoense* disease is common in the UK and northern Europe but is uncommon in the USA. *Mycobacterium simiae* disease is more common in arid regions of the southwestern USA, Cuba and Israel. Thus, it is possible that regional variations in environmental conditions may favor differences in the predominant NTM populations in the water and soil reservoirs to which susceptible patients are exposed.

Exposure to NTM may resemble that of other water-borne pathogens, such as *Legionella*. Pathogenic NTM have been isolated from domestic water supplies and water in homes, hot tubs, swimming pools and workplaces, including hospitals. It is not surprising then that NTM have been detected in cooling towers, in association with free-living ameba, and that NTM have been detected in home shower head biofilms. NTM are resistant to chlorine and other disinfectants, and this resistance is increased in biofilms. Also like *Legionella*, NTM are enriched during droplet formation in bioaerosols.

Nosocomial infections with NTM are most commonly associated with rapidly growing mycobacterial species (*Mycobacterium abscessus*, *Mycobacterium fortuitum* and *Mycobacterium chelonae*) but also

<table>
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<th>NTM Classification</th>
<th>Comments on regional disease prevalence</th>
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<tr>
<td>Slowly growing NTM</td>
<td>Most common NTM in most regions</td>
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<tr>
<td><em>M. avium–intracellulare</em></td>
<td></td>
</tr>
<tr>
<td>MAC</td>
<td>Central USA, England, Wales, France</td>
</tr>
<tr>
<td><em>M. kansasii</em></td>
<td>Northern USA, Canada, UK, Paris, some regions of Europe</td>
</tr>
<tr>
<td><em>M. xenopi</em></td>
<td>UK, northern Europe, rare in USA</td>
</tr>
<tr>
<td><em>M. malmoense</em></td>
<td>Arid regions of southwestern USA, Cuba, Israel</td>
</tr>
<tr>
<td><em>M. simiae</em></td>
<td></td>
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<tr>
<td>Rapidly growing NTM</td>
<td>Regional epidemiology less well understood; second to fourth most common NTM in some regions. Increasing in patients with cystic fibrosis (<em>M. abscessus</em>). Increasing RGM speciation, with molecular characterization.</td>
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<tr>
<td><em>M. abscessus, M. chelonae</em> and <em>M. fortuitum</em></td>
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Table 1 NTM that cause pulmonary disease: observations on regional prevalence.
with MAC and *M. xenopi*. *Mycobacterium gordonae* is notorious for contaminating laboratory buffers and clinical water sources, resulting in false-positive clinical cultures. Most nosocomial NTM infections are associated with skin and soft tissue infections acquired during surgical procedures, not pulmonary disease. Examples include cosmetic facial surgery, ophthalmic (including LASIK) surgery, augmentation mammoplasty, median sternotomy, placement of cardiac devices and associated leads, orthopedic surgery and liposuction—i.e. almost any invasive procedure during which environmental NTM might be introduced. There are also reports of NTM transmission with contaminated bronchoscopes. Assistance from hospital epidemiologists and infection control practitioners can help distinguish such pseudoinfections from community-acquired infections, which is important in order to avoid inappropriate therapy with toxic and costly antibiotics.

**Patterns of pulmonary NTM disease**

Recognized patterns of NTM disease presentation have evolved because of increasing awareness of NTM as a lung pathogen and improved lung imaging technology. Original descriptions were of a TB-like picture in middle aged or older males with emphysema or other underlying lung disease. This was the main concept through the early 1980s, when recognition of NTM as pathogens during the AIDS epidemic increased awareness of NTM disease in general. It was not until the report by Prince *et al.* in 1989 that pulmonary NTM disease in females gained widespread attention. The subsequent report by Reich and Johnson in 1991 first described pulmonary MAC disease associated with predominant involvement of the right middle lobe and lingula. The routine use of computerized chest tomography has contributed to the increasing detection of bronchiectasis and associated manifestations of NTM infection. It is now widely recognized that the majority of patients with pulmonary NTM disease are middle aged to elderly females with mid-lung bronchiectasis, among a variety of other pulmonary abnormalities.

There are three main radiographic manifestations of NTM infection that can be superimposed upon bronchiectasis or on a variety of other pre-existing lung abnormalities. NTM can induce nodular reactions, patchy air space disease and cavitory lesions. Clusters of small- to medium-sized lung nodules can appear in regions of bronchiectasis or endobronchial spread. Larger nodules and mass-like lesions can make the distinction between NTM disease and malignancy difficult. NTM infection can induce patchy areas of lung infiltrate, which can range from hazy abnormalities to dense consolidation. Classical lung cavities can occur and also can be mimicked by cavity-like lesions resulting
from infection-induced enlargement of cystic areas of bronchiectasis or pre-existing lung blebs. Various causes of lung scarring can provide foci for NTM infection. Examples include idiopathic pulmonary fibrosis, radiation-induced fibrosis, old tuberculosis and areas of postoperative scarring. Reactive pleural thickening adjacent to underlying NTM-induced parenchymal lesions is common; pleural effusion and empyema are not.

These radiographic changes are typical for pulmonary MAC disease.9,10 *Mycobacterium kansasii* and *Mycobacterium xenopi* infections more commonly cause upper lobe cavitory lung disease.11 Lung disease caused by rapidly growing mycobacteria, such as *M. abscessus* infection, is most commonly associated with nodular lung abnormalities in the context of bronchiectasis but can also cause cavities. Some other mycobacterial species, such as *Mycobacterium marinum* and *Mycobacterium hemophilum*, rarely (if ever) cause lung disease, which might be explained partly by their optimal growth at low temperatures (e.g. in areas of skin infection).

One NTM disease in which pre-existing lung pathology is not required is NTM-induced hypersensitivity pneumonitis (HSP).12 These patients have a typical HSP presentation with cough and dyspnea and usually have a history of exposure to an indoor water reservoir that is contaminated with NTM, such as a hot tub, swimming pool or contaminated industrial water source.1 The question is whether NTM-induced HSP is the result of an infection, an immunological reaction to NTM, or (more likely) both.13

**Genetic predispositions to bronchiectasis and NTM disease**

The association between bronchiectasis and NTM disease is clear. It is therefore not surprising that patients with cystic fibrosis14 and alpha-1 antitrypsin deficiency15 can have pulmonary NTM disease, since both conditions are associated with bronchiectasis. There are initial reports indicating that these associations may be more complex than would be suggested by the simple interpretation that the reduced secretion clearance associated with bronchiectasis enables NTM airway colonization and disease. There is one report that alpha-1 antitrypsin inhibits infection of human macrophages with *M. abscessus*, suggesting that deficiency of this protease inhibitor may increase mycobacterial pathogenesis.16 There also are initial reports of NTM-disease-linked polymorphisms associated with proinflammatory signaling receptor (toll-like receptor-2 [TLR]),17 signaling pathway (natural resistance-associated macrophage protein-1 [NRAMP])18,19 and inflammatory cell ligand (MHC class I-related chain A [MICA], a ligand for the
NKG2D receptor). These are probably the tip of the iceberg of the complex interactions between NTM infection and innate immune reactions that mediate host defense and immunopathogenesis.

**Diagnosis**

Pulmonary NTM disease diagnosis often results from patient presentation with a persistent cough that may or may not be productive. There may be no other symptoms, or, if patients have been ill for many months or years, they may note increasing ease of fatigue, night sweats, intermittent hemoptysis and weight loss. These symptoms, coupled with various radiographic abnormalities, suggest a chronic pneumonia that could be caused by NTM disease, infections with endemic fungi or noninfectious etiologies. Patients with pulmonary NTM disease may not have acid-fast bacillus (AFB) smear-positive sputum, and several weeks may elapse before culture results identify the NTM pathogen. If the patient is seen by a pulmonary specialist, evaluation may proceed to bronchoscopy with bronchoalveolar lavage and transbronchial biopsy. Although commonly done in resource-rich settings, it is unclear how often bronchoscopy is needed to diagnose NTM disease, since serial voluntary sputums or saline-induced sputums may be sufficient.

The latest American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guidelines suggest that pulmonary NTM disease can be diagnosed when patients have two positive sputum cultures or one positive bronchoalveolar lavage culture or when a transbronchial biopsy is culture positive or yields pathology characteristic for mycobacterial disease, with one or more positive sputum cultures. Patients with multiple positive cultures for the same NTM pathogen and cavitary lung disease or major areas of bronchiectasis usually require therapy. A more difficult decision arises when patients have no or few symptoms and a single positive culture for a potential NTM pathogen and also have no evidence of progressive pulmonary pathology on serial chest imaging studies. There is no urgency in making a therapeutic decision in this circumstance. It is reasonable to monitor symptoms, periodic sputum cultures and chest imaging studies at several month intervals. This rationale is applicable for suspected disease caused by MAC, and most other slowly growing NTM and rapidly growing mycobacteria, but the mycobacterial species identified may affect the decision to treat. Since *M. kansasii* may be the most pathogenic of the NTM species, patients with repeated positive cultures for this organism will usually require therapy. As previously noted, cultures for *Mycobacterium gordonae* are almost always the result of laboratory contamination and rarely require therapy.
Detailed discussion of laboratory methods of NTM diagnosis is beyond the scope of this review. However, a few points may be useful for clinicians who must discuss diagnosis with laboratorians. Decontamination procedures for sputum AFB studies were created for TB. NTM are more susceptible to inactivation by NaOH compared with TB; thus, laboratory personnel should be aware that NTM are being considered in the diagnosis so that strict attention can be paid to processing methods to avoid false-negative cultures. In patients with sputum cultures positive for multiple Gram-negative pathogens (e.g. cystic fibrosis patients with *Pseudomonas* colonization), 5% oxalic acid can be added as a means of ‘double decontamination’ to reduce overgrowth by Gram-negative bacteria that reduces NTM detection. Clinicians should be aware of the capabilities of their microbiology laboratory for sputum nucleic acid amplification testing (to identify or exclude the TB), molecular testing of positive NTM cultures (commonly done for MAC, *M. kansasii* and *M. gordonae*) and HPLC methods for NTM speciation.

The value for clinical decision-making of antibiotic susceptibility testing of different NTM species is an area of ongoing discussion. There is little information at present that can be used to assess the predictive value of *in vitro* antibiotic susceptibility results. It is accepted that clarithromycin susceptibility testing should be done with MAC isolates, based upon the large body of data collected during studies of clarithromycin therapy of disseminated MAC infection in AIDS patients. Rifampin susceptibility testing is a key for decision-making regarding treatment of *M. kansasii* disease, since rifampin is the keystone for treatment of this infection. A third generalization is that MIC determinations using the broth microdilution method are the standard for susceptibility testing of rapidly growing mycobacteria (i.e. *M. abscessus*, *M. chelonae* and *M. fortuitum*). The agar culture proportion method that is used for TB antibiotic susceptibility studies is inappropriate for testing antibiotic susceptibility of most NTM pathogens. Since susceptibility testing of NTM is in evolution, various methods may be used by different laboratories, all of which might be reported in a simple ‘S’ (susceptible), ‘R’ (resistant) or ‘I’ (intermediate) format. This underscores the importance of good communication between the clinician and the microbiology laboratory to understand the value and limitations of the data.

**Treatment**

The history of treatment of pulmonary NTM disease caused by infection with slowly growing NTM (notably MAC) can be divided into
pre-macrolide and post-macrolide eras. In the pre-macrolide era, aggressive treatment with multiple drugs was associated with high rates of initial treatment failure, disease relapse and 40% of patients died during long-term follow-up. The post-macrolide era followed observations of clarithromycin effectiveness in treating high-level bacteremia in AIDS patients with disseminated MAC. This single observation resulted in a pivotal change in the perspective on treating pulmonary NTM disease in immunocompetent patients. Using macrolide-based regimens, most patients who can tolerate therapy experience symptomatic improvement, although the long-term prognosis is still dependent on multiple other factors, especially the extent of disease at diagnosis. The advent of macrolide therapy for NTM diseases caused by MAC infection has stimulated a rapid increase in reports of experiences with pulmonary NTM treatment. The most important result of this increased information has been development of consensus-based treatment guidelines, such as the ATS/IDSA guidelines. These documents provide a rich resource for background information and references on various NTM infections, along with guidelines for clinical decision-making that are rated based upon supporting evidence.

A few fundamental questions can be raised for decision-making on pulmonary NTM disease therapy. Does the patient have symptoms, radiographic and culture data that justify therapy. Is there only a single positive culture? If the patient has no or minimal symptoms, will he/she benefit from multidrug antimycobacterial therapy, or could the patient be observed over several months to consider the evidence for NTM disease establishment and progression? Will therapy be more debilitating than the disease, especially for elderly patients with minimal symptoms? If pulmonary NTM disease has caused localized lung destruction (e.g. of a single lung lobe), would a combined medical/surgical approach be worth considering? There is rarely any urgency in making these decisions or initiating therapy for pulmonary NTM disease. Therefore, time is available for observation, review and consultation with an expert in the field as appropriate.

Approaches to multidrug therapy of pulmonary NTM disease, as summarized in the latest ATS/IDSA guidelines, involve seven basic concepts (Table 2). The first six concepts are generalizations relating to treatment of infections caused by slowly growing NTM. The seventh concept provides perspective about differences in treatment of infections caused by rapidly growing NTM.

First, clarithromycin-based regimens are suggested for treatment of infections caused by most slowly growing NTM. Since there has been no direct comparison of clarithromycin vs. azithromycin therapy, it is unclear whether one or the other macrolide is preferable. The usual approach is to use clarithromycin as the macrolide core of therapy,
unless the patient can only tolerate azithromycin or there is a clarithromycin drug–drug interaction that favors azithromycin therapy.

Second, ethambutol is usually added to multidrug regimens as an ‘enhancing’ drug for treatment of infections caused by slowly growing NTM. The cell-wall inhibitory activity of ethambutol may account for its enhancing effect on the in vitro antimycobacterial activities of partner drugs. This ethambutol synergy has been demonstrated for MAC, M. kansasii and M. malmoense25–29 and might be a factor in other NTM therapy.

Third, either rifampin or rifabutin is usually added as a third drug in a multidrug regimen for infections caused by slowly growing NTM. This is not based on evidence that three-drug regimens are better than two-drug regimens but on the unproven concern that two-drug therapy might be more likely to result in evolution of macrolide resistance.

Fourth, it is recommended to consider adding a parenteral aminoglycoside (e.g. amikacin or streptomycin) during the first few months of therapy, especially for patients with severe clinical illness and advanced pulmonary NTM disease. However, it is not clear, in the post-macrolide era, whether the cost, inconvenience and side effects of aminoglycoside therapy are warranted, especially in the elderly. Therefore, aminoglycosides should be considered as ancillary treatment on a case-by-case basis.

Fifth, it remains uncertain whether daily therapy or intermittent therapy of pulmonary NTM disease is preferable, and the optimal dosing interval for intermittent therapy is unknown. It is reasonable to consider intermittent treatment strategies, since they have been so successful for TB. The most encouraging observations for pulmonary NTM disease come from the studies of Griffith et al.22,30 who have

Table 2 Seven concepts on treatment of pulmonary NTM disease.

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<thead>
<tr>
<th>NTM classification</th>
<th>Concepts regarding therapy</th>
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<tbody>
<tr>
<td>Slowly growing NTM</td>
<td>1. Clarithromycin (azithromycin)-based regimens recommended for most infections</td>
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<tr>
<td>(SG NTM)</td>
<td>2. Ethambutol added as an ‘enhancing’ drug</td>
</tr>
<tr>
<td></td>
<td>3. Rifampin or rifabutin added as a third drug</td>
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<td></td>
<td>4. Parenteral aminoglycoside (e.g. amikacin) may be added initially (1–3 months) for severe illness or cavitary disease.</td>
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<td></td>
<td>5. Dosing frequency: uncertain whether daily or intermittent dosing is preferable, but the latter can be effective and has reduced cost and toxicity.</td>
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<td></td>
<td>6. Treatment duration: initial goal = 12-month therapy beyond sputum conversion to smear negative. Re-assessment of disease status at the end of this period of therapy is important.</td>
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<tr>
<td></td>
<td>7. Different regimens compared with for SG NTM disease. Initial therapy may include several months of parenteral therapy with cefoxitin-amikacin or imipenem-amikacin. Relapse is common. Long-term oral suppressive therapy may be required. Expert consultation recommended.</td>
</tr>
<tr>
<td>Rapidly growing NTM</td>
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NTM: opportunisitic environmental pathogens
reported initial studies showing that thrice weekly therapy can be effective in achieving clinical responses with pulmonary MAC and *M. kansasii* disease. Whether intermittent therapy will be successful in long-term cure and whether such therapy is as effective as daily therapy in patients with more advanced NTM disease or diseases caused by rapidly growing NTM is uncertain.

Sixth, 18–24 months of therapy has been considered standard for pulmonary NTM disease. This evolved from observations on treatment of TB and multidrug-resistant TB and not from clinical trials on optimal duration of therapy of pulmonary NTM disease. The current standard for duration of therapy is to complete at least 12 months of therapy beyond sputum culture conversion to negative. This is a reasonable initial endpoint but should include careful assessment of disease status at the end of treatment.

Treatment of *M. kansasii* and *M. simiae* pulmonary disease may (or may not) be exceptions to these basic approaches. Historically, rifampin has become the keystone of therapy for *M. kansasii* disease, and a 12-month INH/rifampin/ethambutol regimen may be sufficient for cure. Evolving information suggests that macrolide and fluoroquinolone antibiotics may be reasonable additions to a rifampin-based regimen if INH cannot be tolerated or there is not a good clinical response to the INH-containing regimen. There are limited data on drug combinations for treatment of *M. simiae* disease. As for other slowly growing NTM, a clarithromycin/ethambutol core of therapy is reasonable. What little information there is suggests that addition of a fluoroquinolone antibiotic to this two-drug core might be useful.

Seventh, treatment of pulmonary disease caused by rapidly growing mycobacteria is approached differently from therapy of slowly growing NTM species. Of all pulmonary NTM diseases, these are the most difficult to treat successfully, with therapy often resulting in initial clinical improvement but not long-term cure. Anecdotal experience is that patients with progressive pulmonary disease caused by rapidly growing NTM usually respond to initial, combination therapy with parenteral amikacin plus cefoxitin or imipenem. However, the long-term benefit of such therapy is uncertain and is limited by high cost and drug-related side effects. Because of the high rate of disease relapse after stopping such parenteral therapy, continued oral suppressive treatment is usually required, and repeated parenteral therapy may be needed periodically during long-term follow up. Management of patients with these rapid-grower NTM infections may benefit from collaborative interactions between primary care physicians and consultants with experience in treating rapid-grower NTM disease. The poor outcomes of treatment also may warrant increased consideration of combined medical/surgical therapy, if the disease is localized.
Information is limited on the use of other drugs to treat pulmonary NTM disease. These medications are usually used in retreatment regimens and therefore might be best considered in collaboration with a consultant with expertise treating refractory pulmonary NTM disease. Moxifloxacin may be the best of the fluoroquinolone antibiotics, as a component of multidrug therapy for pulmonary NTM disease. It has shown promise in clinical trials of TB therapy with good efficacy and improved sputum sterilization rates.33 Clofazimine is an anti-leprosy drug that often shows excellent in vitro activity against MAC isolates. It has therefore been considered as a possible alternative component of multidrug therapy in patients with refractory pulmonary MAC disease. But its value in therapy is uncertain, and its use can be complicated by limited availability and problems with unusual side effects that might require support of an expert in its use. Linezolid34 and tigecycline35,36 have been reported to have good in vitro activity against some isolates of rapidly growing mycobacteria, and it has been hoped that these drugs would provide effective alternatives for treatment of rapid-grower-induced pulmonary NTM disease. However, long-term linezolid therapy is complicated by its hematological and neurological side effects, and tigecycline therapy is complicated by gastrointestinal intolerance, especially in elderly patients, and adds considerable expense to a disease that requires many months (and sometimes years) of therapy.

Areas of controversy and research development

The epidemiology and natural history of pulmonary NTM disease is a patchwork of observations, with no centralized database for reference. A standardized database for national and international collection of information on NTM disease could be highly informative for understanding risk factors, genetic and other predisposing conditions and regional differences in patterns of NTM species-related disease, among many other possible parameters. Such a centralized registry could be critical to progress in this field, where disease incidence in any institution or region is insufficient to provide the broad perspective needed for hypothesis formulation and testing.

Multicenter studies are needed to answer many questions about NTM diagnosis and therapy. Beyond the emerging consensus that a macrolide/ethambutol core is a reasonable starting place for drug regimen design for disease caused by slowly growing NTM, what are the optimal drug combinations and dosing intervals for treatment of pulmonary disease caused by different NTM species? Specifically, can antibiotic dosing be done on less than a daily or thrice weekly schedule and still result in
good treatment outcomes for some pulmonary NTM infections? Comparative NTM treatment studies like those done for TB by the British Medical Research Council could be done if sufficient numbers of patients could be entered into treatment protocols. What is the proper role of in vitro antibiotic susceptibility testing for different NTM species? There is increasing experience with MIC determinations for selected antibiotics with MAC, M. kansasii and rapidly growing mycobacteria, but the utility of most of these data as predictors of treatment outcome remains unclear. Again, multicenter comparative studies would be needed to generate adequate power for such analyses. What is the role of therapeutic drug monitoring in optimizing treatment of pulmonary NTM disease? The technology for pharmacokinetic and pharmacodynamic studies has been developed over the past 20 years and has been used on a case-by-case basis to try to optimize drug dosing. A better understanding of the application of these data would be facilitated by large, clinical studies comparing dosing, drug–drug interactions and treatment outcomes. What are the predictors of treatment outcome that can be identified during initial patient evaluations or during re-evaluation of patients who have experienced treatment failures with initial, multidrug regimens? A better understanding of the clinical, radiographic and microbiological parameters that predict response to therapy or disease persistence despite therapy would be useful for patient counseling, multidrug treatment design and long-term disease management.

Most important is the need for increased drug discovery and translational research to develop new compounds that might be useful for pulmonary NTM disease therapy. There has been no targeted drug discovery for NTM disease. The greatest hope comes from the possibility that the increasing efforts toward drug discovery for TB might identify compounds with collateral anti-NTM activity. Development of an interrelationship between TB drug discovery and NTM drug development could lead to the next breakthrough in NTM therapy—like that which resulted from the accidental, yet pivotal, discovery of the efficacy of macrolide antibiotics for NTM therapy.

**Conclusions**

Pulmonary NTM disease is not a single entity but a group of different infections that are lumped together because they are ‘not TB’—i.e. mostly because of what they are not rather than what they are. These different mycobacterial diseases may be caused by combinations of overlapping, but in some cases different, pathogenic mechanisms and host inflammatory responses. These opportunistic pathogens do not appear to cause latent infection in humans but instead to be acquired
Little is known about the environmental reservoirs of the NTM species that cause human disease, but what is known suggests that these reservoirs are diverse and complex. Beyond the obvious lung abnormalities that are associated with NTM disease, the key predisposing host risk factors for establishment of NTM infection and progression to disease are poorly defined. A few genetic defects have been identified (in very small numbers of patients) that predispose to systemic NTM disease, but much more must be learned about the predisposition to pulmonary disease. Treatment of pulmonary NTM disease has evolved indirectly by assumptions derived from experiences treating drug-resistant tuberculosis and clinical trials of therapy for disseminated MAC infections in AIDS patients, not from controlled clinical trials of pulmonary NTM therapy. There is a great deal of room for progress in definition of genetic risk factors, earlier disease diagnosis, optimal medical and surgical therapy and drug discovery. However, the low disease prevalence, the lack of a public health imperative and the limited antibiotic pipeline have created orphan disease status for this group of infections. It is therefore unlikely, given limited resources and other high-profile, public health and global infectious diseases priorities, that major progress will be made in the near future in needed research on pulmonary NTM diseases. It will require the concerted efforts of multiple collaborating organizations and institutions in multiple world regions to create the momentum needed to change this prospect. The question is, where will the support come from that stimulates and supports such an enterprise?

**Funding**

Supported in part by the James A. and Marion C. Grant Fund for Infectious Diseases and Immunology Research.

**References**