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# Management of pulmonary nontuberculous mycobacterial disease

Kathleen L Horan[1] and Shawn J Skerrett[2]*

Addresses: [1]Division of Pulmonary & Critical Care Medicine, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101, USA; [2]Division of Pulmonary & Critical Care Medicine, University of Washington, Harborview Medical Center, 325 Ninth Avenue, Seattle, WA 98104, USA

* Corresponding author: Shawn J Skerrett (shawn@u.washington.edu)

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## Abstract

Nontuberculous mycobacteria are increasingly recognized as causes of chronic pulmonary disease. Treatment decisions are guided by the clinical presentation, microbial isolate, and condition of the patient. Management may include antibiotic therapy, surgical resection, or observation. Definitive trials are lacking, and optimum management remains uncertain.

## Introduction and context

Nontuberculous mycobacteria (NTM) encompass more than 120 species that are widely distributed in the environment [1]. The isolation of NTM from respiratory samples and the prevalence of NTM pulmonary disease have increased over the past 20 years [1,2]. NTM are opportunistic pathogens, preying upon individuals with underlying structural lung disease such as bronchiectasis, emphysema, and pre-existing cavities from prior infection or pneumoconiosis; persons with chest wall abnormalities such as scoliosis and pectus excavatum; and those with deficiencies of cellular immunity, such as HIV infection and genetic disorders affecting the interferon-gamma pathway [1,3,4].

There are three general patterns of NTM pulmonary disease [1]. The fibrocavitary form involves mainly the upper lobes and commonly occurs in middle-aged male smokers with underlying chronic obstructive pulmonary disease, pneumoconiosis, or healed tuberculosis. The nodular bronchiectatic pattern typically presents in slender, elderly, non-smoking females and is often associated with chest wall deformities such as pectus excavatum. The third form of NTM pulmonary disease is hypersensitivity pneumonitis, which can result from exposure to contaminated hot tubs or industrial coolants. In this report, we will focus on the management of the fibrocavitary and nodular bronchiectatic forms of NTM pulmonary disease as the management of hypersensitivity pneumonitis is centered on the avoidance of aerosolized NTM exposure.

The diagnosis of NTM pulmonary disease is challenging because of the diverse and nonspecific clinical presentation of these infections and the difficulty in separating environmental contamination and transient colonization from active infection. The natural history of NTM disease is also highly variable and is influenced by host- and pathogen-related factors [1,5-7]. Treatment decisions must be tailored to individual patients and focus on three considerations: antibiotic therapy, surgery, and the management of underlying diseases. Successful treatment is hampered by the need for prolonged therapy with poorly tolerated antibiotics. Definitive guidance from controlled trials is lacking, and long-term outcomes often are unsatisfactory.

## Recent advances

The prevalence of NTM in respiratory tract specimens and the number of diagnosed cases of NTM lung disease have steadily increased in recent decades [2,8,9]. A population screening study in the US demonstrated that the prevalence of skin test reactivity to *Mycobacterium intracellulare* antigen increased from 11.2% in 1971-1972 to 16.6% in 1999-2000 [10]. These trends likely result from a combination of factors: increased awareness among clinicians, widespread use of computed tomography, advances in detection of mycobacteria,

increased environmental exposure, and expansion of the at-risk population. In industrialized nations, the burden of NTM disease may soon exceed that of tuberculosis [2,11].

Host factors that predispose individuals to NTM lung disease remain incompletely understood [12]. Damaged airway mucosa and impaired mechanical clearance facilitate NTM infection, which is strongly linked with bronchiectasis and cystic fibrosis [1,12]. Genetic deficiencies in the interleukin-12/interferon-gamma axis predispose patients to severe NTM infection [12], and case reports continue to highlight the risk of NTM disease associated with tumor necrosis factor blockade [13,14]. In most cases, the origin of NTM disease remains enigmatic. A careful study of women with NTM pulmonary disease associated with thoracic cage abnormalities and lingular or middle lobe bronchiectasis (Lady Windermere syndrome) uncovered a high frequency of CFTR (cystic fibrosis transmembrane conductance regulator) mutations and mild impairments in interferon-gamma production, but no specific immunological defects [5].

In 2007, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) published an updated statement that streamlined the diagnostic criteria for NTM disease and that provided evidence-based guidelines for treatment [1]. This very thorough and well-referenced document should be required reading for health care providers involved in the management of patients with NTM infections. The modified diagnostic criteria include clinical and radiographic features that are compatible with NTM disease, convincing microbiological evidence (isolation of NTM from ≥2 sputum samples or from lung washings or tissue biopsies), and the exclusion of other diagnoses. Most patients from whom NTM is isolated from respiratory tract samples will not meet these criteria for NTM disease [8,9,15].

The optimum antimicrobial treatment for NTM pulmonary disease has not been determined. The antibiotic regimens recommended in the ATS/IDSA statement based on the available evidence are pathogen- and syndrome-specific and guided by targeted antimicrobial sensitivity testing. Pulmonary infection with *Mycobacterium avium* complex (MAC) is the most common cause of NTM lung disease and serves as a paradigm for the management of other NTM infections. For initial therapy for MAC pulmonary disease, susceptibility testing for clarithromycin is recommended as resistance to this agent predicts treatment failure and relapse, whereas susceptibility testing to rifamycins, ethambutol, and streptomycin does not predict clinical efficacy [1,16-18]. Patients with the nodular bronchiectatic form of MAC pulmonary disease of mild-to-moderate severity can be treated with an intermittent regimen of thrice-weekly macrolide (clarithromycin or azithromycin), ethambutol, and rifampicin [1,19,20]. Daily treatment is recommended for the fibrocavitary form and for severe/progressive cases of nodular bronchiectatic disease. The addition of an injectable antimicrobial such as streptomycin should be considered for advanced disease. Treatment for NTM pulmonary disease should be continued for 12 months following sputum conversion to culture negative.

Recent gains in the management of pulmonary MAC infections have been modest. A randomized controlled trial of thrice-weekly streptomycin added to thrice-weekly clarithromycin, rifamycin, and ethambutol showed improved microbiological efficacy in sputum conversion (71% versus 50%), but no difference in symptoms or time to relapse [21]. Inhaled aminoglycosides are a promising alternative to intravenous therapy in some cases, but experience is limited [22]. Immunotherapy with *Mycobacterium vaccae* was tested in an open-label trial but did not improve outcome over antibiotic therapy alone [23]. Drug intolerances that lead to interruptions in treatment and antibiotic substitutions remain common in the management of NTM pulmonary disease, at considerable economic cost [1,23-25].

Surgery can play an important role in the management of localized NTM pulmonary disease in patients with adequate cardiopulmonary reserve. Resection should be considered in cases of treatment failure and in patients at high risk of treatment failure, such as infection with macrolide-resistant MAC or *Mycobacterium abscessus* [1,3]. Surgical case series have reported sputum clearance rates of 88-100% and relapse rates of 0-9.5% [26-30]. However, surgical management of NTM lung disease is associated with substantial risks. In the largest reported case series (in which 236 patients were treated from 1983 to 2006), operative mortality was 2.6% and morbidity was 18.5%, and bronchopleural fistulae complicated one-third of right pneumonectomies [31].

## Implications for clinical practice

NTM pulmonary disease is increasingly common. The recently published ATS/IDSA statement provides useful criteria for the diagnosis of NTM disease and rational guidelines for treatment. However, these recommendations are based largely on observational studies and expert opinion, rather than controlled trials. Current antibiotic regimens often are poorly tolerated, and

long-term efficacy is uncertain, particularly for less commonly encountered species of NTM. Surgery has a role in some patients with predominantly focal disease but should be limited to centers with expertise in both medical and surgical management of NTM disease. There is an urgent need for further investigation to better define optimal antimicrobial regimens and identify new and more effective treatments.

## Abbreviations

ATS, American Thoracic Society; IDSA, Infectious Diseases Society of America; MAC, *Mycobacterium avium* complex; NTM, nontuberculous mycobacteria.

## Competing interests

The authors declare that they have no competing interests.

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