Management of pulmonary nontuberculous mycobacterial disease

Kathleen L Horan¹ and Shawn J Skerrett^{2*}

Addresses: ¹Division of Pulmonary & Critical Care Medicine, Virginia Mason Medical Center, 1100 Ninth Avenue, Seattle, WA 98101, USA;

²Division 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)

F1000 Medicine Reports 2009, **1**:99 (doi:10.3410/M1-99)

The electronic version of this article is the complete one and can be found at: <http://F1000.com/Reports/Medicine/content/1/99>

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.

Acknowledgments

Supported in part by funding from the National Institutes of Health (Bethesda, MD, USA).

References

- Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ Jr, Winthrop K: **An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases.** *Am J Respir Crit Care Med* 2007, **175**:367-416.
- Iseman MD, Marras TK: **The importance of nontuberculous mycobacterial lung disease.** *Am J Respir Crit Care Med* 2008, **178**:999-1001.
- Glassroth J: **Pulmonary disease due to nontuberculous mycobacteria.** *Chest* 2008, **133**:243-51.
- Piersimoni C, Scarparo C: **Pulmonary infections associated with non-tuberculous mycobacteria in immunocompetent patients.** *Lancet Infect Dis* 2008, **8**:323-34.
- Kim RD, Greenberg DE, Ehrmantraut ME, Guide SV, Ding L, Shea Y, Brown MR, Cherrick M, Steagall WK, Glasgow CG, Lin JP, Jolley C, Sorbara L, Raffeld M, Hill S, Avila N, Sachdev V, Barnhart LA, Anderson VL, Claypool R, Hilligoss DM, Garofalo M, Fitzgerald A, Anaya-O'Brien D, Darnell D, DeCastro R, Menning HM, Ricklefs SM, Porcella SF, Olivier KN, et al: **Pulmonary nontuberculous mycobacterial disease, prospective study of a distinct preexisting syndrome.** *Am J Respir Crit Care Med* 2008, **178**:1066-74.
- Kikuchi T, Watanabe A, Gomi K, Sakakibara T, Nishimori K, Daito H, Fujimura S, Tazawa R, Inoue A, Ebina M, Tokue Y, Kaku M, Nukiwa T: **Association between mycobacterial genotypes and disease progression in *Mycobacterium avium* pulmonary infection.** *Thorax* 2009, **64**:901-7.
- The Research Committee of the British Thoracic Society: **Pulmonary disease caused by *Mycobacterium avium-intracellulare* in HIV-negative patients: five-year follow-up of patients receiving standardised treatment.** *Int J Tuberc Lung Dis* 2002, **6**:628-34.
- Marras TK, Chedore P, Ying AM, Jamieson F: **Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997-2003.** *Thorax* 2007, **62**:661-6.
- van Ingen J, Bendien SA, de Lange WCM, Hoefsloot W, Dekhuijzen PNR, Boeree MJ, van Soolingen D: **Clinical relevance of non-tuberculous mycobacteria isolated in the Nijmegen-Arnhem region, the Netherlands.** *Thorax* 2009, **64**:502-6.
- Khan K, Wang J, Marras TK: **Nontuberculous mycobacterial sensitization in the United States. National trends over three decades.** *Am J Respir Crit Care Med* 2007, **176**:306-13.
- Arend SM, van Soolingen D, Ottenhoff TH: **Diagnosis and treatment of lung infection with nontuberculous mycobacteria.** *Curr Opin Pulm Med* 2009, **15**:201-8.
- Sexton P, Harrison AC: **Susceptibility to nontuberculous mycobacterial lung disease.** *Eur Respir J* 2008, **31**:1322-33.
- Salvana EMT, Cooper GS, Salata RA: ***Mycobacterium* other than tuberculosis (MOTT) infection: an emerging disease in infliximab-treated patients.** *J Infect* 2007, **55**:484-7.
- Winthrop KL, Yamashita S, Beekman SE, Polgreen PM: ***Mycobacterial* and other serious infections in patients receiving anti-tumor necrosis factor and other newly approved biologic therapies: case finding through the emerging infections network.** *Clin Infect Dis* 2008, **46**:1738-40.
- Bodle EE, Cunningham JA, Della-Latta P, Schluger NW, Saiman L: **Epidemiology of nontuberculous mycobacteria in patients without HIV infection, New York City.** *Emerg Infect Dis* 2008, **14**:390-6.
- Wallace RJ Jr, Brown BA, Griffith DE, Girard WM, Murphy DT: **Clarithromycin regimens for pulmonary *Mycobacterium avium* complex: the first 50 patients.** *Am J Respir Crit Care Med* 1996, **153**:1766-72.
- Tanaka E, Kimoto T, Tsuyuguchi K, Watanabe I, Mastsumoto H, Niimi A, Suzuki K, Murayama T, Amitani R, Kuze F: **Effect of clarithromycin regimen for *Mycobacterium avium* complex pulmonary disease.** *Am J Respir Crit Care Med* 1999, **160**:866-72.
- Kobashi Y, Yoshida K, Miyashita N, Niki Y, Oka M: **Relationship between clinical efficacy of treatment of pulmonary *Mycobacterium avium* complex disease and drug-sensitivity testing of *Mycobacterium avium* complex isolates.** *J Infect Chemother* 2006, **12**:195-202.
- Griffith DE, Brown BA, Girard WM, Griffith BE, Couch LA, Wallace RJ Jr: **Azithromycin-containing regimens for treatment of *Mycobacterium avium* complex lung disease.** *Clin Infect Dis* 2001, **32**:1547-53.
- Lam PK, Griffith DE, Aksamit TR, Ruoss SJ, Garay SM, Daley CL, Catanzaro A: **Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease.** *Am J Respir Crit Care Med* 2006, **173**:1283-9.
- Kobashi Y, Matsushima T, Oka M: **A double-blind randomized study of aminoglycoside infusion with combined therapy for pulmonary *Mycobacterium avium* complex disease.** *Respir Med* 2007, **101**:130-8.
- Davis KK, Kao PN, Jacobs SS, Ruoss SJ: **Aerosolized amikacin for treatment of pulmonary *Mycobacterium avium* infections: an observational case series.** *BMC Pulm Med* 2007, **7**:2.
- Jenkins PA, Campbell IA, Banks J, Gelder CM, Prescott RJ, Smith AP: **Clarithromycin and ciprofloxacin as adjuncts to rifampicin and ethambutol in treating opportunist mycobacterial lung diseases and an assessment of *Mycobacterium vaccae* immunotherapy.** *Thorax* 2008, **63**:627-34.
- Murray MP, Laurenson IF, Hill AT: **Outcomes of a standardized triple-drug regimen for the treatment of nontuberculous mycobacterial pulmonary infection.** *Clin Infect Dis* 2008, **47**:222-4.
- Ballarino GJ, Olivier KN, Claypool RJ, Holland SM, Prevots DR: **Pulmonary nontuberculous mycobacterial infections: antibiotic treatment and associated costs.** *Respir Med* 2009, **103**:1448-55.
- Nelson KG, Griffith DE, Brown BA, Wallace RJ Jr: **Results of operation in *Mycobacterium avium-intracellulare* lung disease.** *Ann Thorac Surg* 1998, **66**:325-30.
- Shiraishi Y, Nakajimi Y, Takasuna K, Hanaoka T, Katsuragi N, Konno H: **Surgery for *Mycobacterium avium* complex lung disease in the clarithromycin era.** *Eur J Cardiothorac Surg* 2002, **21**:314-8.

F1000 Factor 3.0 Recommended
Evaluated by Shawn Skerrett 16 Dec 2008

28. Shiraishi Y, Nakajimi Y, Katsuragi N, Kurai M, Takahashi N: **Pneumonectomy for nontuberculous mycobacterial infections.** *Ann Thorac Surg* 2004, **78**:399-403.
29. Watanabe M, Hasegawa N, Ishizaka A, Asakura K, Izumi Y, Eguchi K, Kawamura M, Horinouchi H, Kobayashi K: **Early pulmonary resection for *Mycobacterium avium* complex lung disease treated with macrolides and quinolones.** *Ann Thorac Surg* 2006, **81**:2026-30.
30. Koh W-J, Kim YH, Kwon OJ, Choi YS, Kim K, Shim YM, Kim J: **Surgical treatment of pulmonary diseases due to nontuberculous mycobacteria.** *J Korean Med Sci* 2008, **23**:397-401.
31. Mitchell JD, Bishop A, Cafaro A, Weyant MJ, Pomerantz M: **Anatomic lung resection for nontuberculous mycobacterial disease.** *Ann Thorac Surg* 2008, **85**:1887-93.