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Pulmonary Nontuberculous Mycobacterial Disease: New Insights into Risk Factors for Susceptibility, Epidemiology, and Approaches to Management in Immunocompetent and Immunocompromised Patients

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Abstract

Nontuberculous mycobacteria (NTM) are ubiquitous in the environment and cause a wide range of diseases in humans. Pulmonary involvement, the most common disease manifestation of NTM infection, is being increasingly encountered in clinical settings. In addition, specific phenotypic and genetic characteristics of persons predisposed to contract pulmonary NTM disease are now beginning to be recognized. Prior to treatment, patients should meet clinical and microbiologic criteria for NTM disease. Treatment involves prolonged courses of antibiotics in various combination regimens that are often discontinued because of serious side effects. In some cases, complete cure of pulmonary disease is difficult to achieve. Rather, clinical improvement may be a more feasible goal. Surgical treatment is warranted for select patients.

Keywords

Nontuberculous mycobacteria; Bronchiectasis; *Mycobacterium avium* complex; *Mycobacterium abscessus*; *Mycobacterium kansasii*; Cystic fibrosis

Introduction

Nontuberculous mycobacteria (NTM) consist of mycobacterial species other than those of the *Mycobacterium tuberculosis* complex and *Mycobacterium leprae*. These organisms are ubiquitous in the environment and are found in natural aqueous reservoirs, soil, and potable water. Human-to-human transmission has not been proven to occur with NTM. Because they are so widespread in the environment, isolation of these organisms in the laboratory does not necessarily signify clinical disease. However, given the appropriate host setting (eg, immunosuppression or underlying pulmonary disease), disease can occur with NTM infection. Clinical disease due to NTM infection covers a broad spectrum of manifestations, including pulmonary disease, lymphadenitis, skin and soft tissue infection, and even dissemination in immunocompromised hosts. However, the most common disease manifestation of NTM infection is pulmonary involvement.

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Epidemiology of Pulmonary NTM Disease

Pulmonary disease due to NTM is becoming more common in the clinical setting. A US Centers for Disease Control and Prevention report in the mid-1990s found that the most common species of NTM encountered in the United States were the *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium fortuitum* [1••]. It has been recognized that as the prevalence of tuberculosis in the United States has decreased, that of pulmonary NTM has increased. A retrospective analysis of pulmonary NTM in Canada demonstrated that the prevalence increased from 9.1 cases per 100,000 in 1997 to 14.1 cases per 100,000 in 2003. There was a mean annual increase of 8.4% for the most common species of NTM [2]. Analysis of skin sensitization to NTM, an arguably more objective parameter to examine exposure to NTM, has also shown an increase in NTM prevalence. In the United States, the prevalence of skin sensitization to *Mycobacterium intracellulare*, the most common species of MAC, was 11.2% in 1971-1972. This prevalence increased to 16.6% in 1999–2000 [3]. Not only has the prevalence of NTM infection increased over time, but studies have also shown that NTM prevalence appears to increase with the patient's age. A review of hospital discharge data for patients with the diagnosis of pulmonary NTM revealed that the relative prevalence for persons 70 to 79 years of age versus those of 40 to 49 years of age was 15-fold higher for women and ninefold higher for men [4]. There also seems to be geographic variability in the prevalence of NTM, with a preference for southeastern and Gulf Coast states. A study in the 1960s of skin reactivity to a unique antigen common to NTM revealed increased prevalence in the Southeast [5]. Similarly, a study of environmental isolates of NTM revealed a predilection for acidic soil along the southeastern coastal plain [6].

Susceptibility to Nontuberculous Mycobacterial Infection

Pulmonary disease due to nontuberculous mycobacteria was first described in elderly male smokers with emphysema. Radiologic images from these patients revealed fibrocavitary lesions. It is postulated that the underlying emphysematous pulmonary disease in these cases alters the lung architecture and host immunity to such an extent that the relatively low-virulent NTM cause disease [7]. Other syndromes characterized by underlying lung disease have also been associated with pulmonary NTM. Nontuberculous mycobacteria have been seen in relatively high frequency in primary ciliary dyskinesia, a disorder of mucociliary clearance. In one study of patients with primary ciliary dyskinesia, more than 15% were found to have at least one positive sputum culture for NTM [8]. Cystic fibrosis, an autosomal recessive disease due to mutations in the cystic fibrosis transmembrane conductance regulator (CFTR), is characterized by bronchiectatic lung disease, intestinal malabsorption, and infertility. NTM were recently recognized as common pathogens isolated from the lungs of patients with cystic fibrosis. A multicenter study of the prevalence of NTM in patients with cystic fibrosis revealed a prevalence of 13% for the isolation of NTM from sputum cultures of CF patients older than 10 years of age [9]. Although most patients had either MAC or *Mycobacterium abscessus*, the vast majority of the organism strains were molecularly unique, indicating that person-to-person and nosocomial transmission were unlikely. Just as patients with cystic fibrosis have a predilection for pulmonary NTM, patients with pulmonary NTM without known underlying lung disease have been found to have an increased prevalence of mutations in the CFTR gene unassociated with a diagnosis of CF [10]. Patients with the hyper-IgE syndrome, who have autosomal dominant deficiency of the signal transducer and activator of transcription 3 (*STAT3*), are prone to recurrent bacterial pneumonias. They subsequently develop pneumatoceles and bronchiectasis. In a cohort of 32 patients with *STAT3* deficiency at the National Institutes of Health (NIH), nine (28%) were found to have pulmonary NTM in at least one sputum culture [11]. Finally, although AIDS is associated with disseminated

mycobacterial disease (eg, tuberculosis or NTM), pulmonary disease due to NTM is not seen in increased frequency in these patients.

It has become increasingly recognized that pulmonary NTM may occur in patients without underlying lung disease. This condition was first described in the early 1990s in a cohort of postmenopausal women who had no predisposing lung disease. They had evidence of lingular or right middle lobe infiltrates on chest imaging. It was postulated that voluntary cough suppression led to pulmonary inflammation in those anatomic regions of the lung. The name “Lady Windermere syndrome” was given to these elderly women with NTM and no underlying lung disease [12,13]. Although it is unclear that voluntary cough suppression explains the pathogenesis of NTM pulmonary disease in this cohort of patients, a genetic explanation may exist for their disease. A study of 63 patients with pulmonary nontuberculous mycobacterial disease followed at the NIH was recently published [14•]. The most common organisms isolated were the MAC and the rapid grower mycobacteria. This study found that more than 90% of the patients were Caucasian women. The women were compared with age-and ethnicity-matched controls in the National Health and Nutrition Examination Survey (NHANES) database and were found to be significantly taller and thinner than the controls. Interestingly, scoliosis, pectus excavatum, and mitral valve prolapse were all found in greater prevalence in the women with pulmonary NTM than in the general population. As mentioned above, alterations in the *CFTR* gene were commonly seen in these patients; 36% of them were found to have mutations. These patients were not found to be immunodeficient and did not have increased environmental exposures compared to controls. In addition, there did not seem to be a history of voluntary cough suppression. Thus, it seems that a multifactorial genetic cause predisposes these patients to pulmonary NTM. More recently, a study of familial cases of pulmonary NTM was undertaken [15]. Six families in which at least two members had pulmonary NTM were studied. Most of the patients were Caucasian women, and they were taller and thinner than the general population. The most common cases were sibling pairs, but a couple of cases of mother and child disease were found. None of the family members were infected with the same NTM species, indicating that person-to-person transmission or a unique environmental exposure was unlikely. This study points to the likelihood of a heritable cause of susceptibility to pulmonary NTM.

Pulmonary NTM has been seen recently in children with otherwise normal immune systems [16]. NTM usually present as cervical lymphadenitis in immunocompetent children. Rarely, however, it may be isolated to the lungs. Pulmonary disease usually presents as an endobronchial lesion or hilar adenopathy in immunocompetent children. There has been no link to any significant mutations in the *CFTR* gene in these patients.

Diagnosis

Because NTM are so ubiquitous in the environment, the clinician must determine whether NTM isolated on sputum culture represents true disease. The American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) have jointly issued an updated set of guidelines for the diagnosis and treatment of NTM disease [1••]. Patients suspected of having NTM pulmonary disease should meet clinical, radiographic, and microbiologic criteria for diagnosis. In addition, the diagnosis of tuberculosis should be excluded. As described above, findings on imaging that are suggestive of pulmonary NTM disease include nodular bronchiectasis as well as fibrocavitary lesions. To minimize the possibility of environmental contamination, at least two positive sputum cultures are necessary for diagnosis. Alternatively, one positive culture from bronchial wash or lavage will suffice, because of the lessened probability of obtaining a contaminant using this diagnostic method [17••].

When processing specimens for isolation of mycobacteria, decontamination with N-acetyl-L-cysteine-sodium hydroxide (NALC/NaOH) is necessary to preclude the growth of other bacteria. Patients with cystic fibrosis represent a special population, because their sputum often contains large numbers of aerobic gram-negative rods (eg, *Pseudomonas aeruginosa*). In this case, an additional decontamination step with oxalic acid reduces the overgrowth and increases the yield of NTM on culture [18]. The fluorochrome method is the recommended technique for staining specimens for mycobacteria, because it is more sensitive than the Ziehl-Neelsen and Kinyoun methods. It is recommended that mycobacteria be cultured on solid media and broth. Broth systems (eg, the mycobacteria growth indicator tube) have the advantage of more rapid growth and higher culture yield than solid media. The two most commonly used solid media for growth of mycobacteria are Löwenstein-Jensen (an egg-based medium) and Middlebrook media (an agar-based medium). The advantages of solid media over broth are that colony morphology, quantity, and the presence or absence of other organisms can be determined [1••]. Most NTM organisms grow best on culture when incubated at temperatures between 28°C to 37°C; they usually grow within 2 to 3 weeks. Rapidly growing mycobacteria, such as *M. abscessus*, *M. fortuitum*, and *Mycobacterium chelonae*, grow within 7 days. In addition, they grow best when incubated at temperatures of 28°C to 30°C.

It is necessary to speciate NTM to determine appropriate antibiotic therapy, because NTM species differ widely with regard to antimicrobial susceptibility. In the past, NTM was identified on the basis of growth rate, colony pigmentation, and other biochemical tests, but more rapid tests are now available for speciation. Current rapid techniques for identification of NTM include high-performance liquid chromatography (HPLC), probes, and other molecular techniques [1••]. HPLC identifies mycobacteria on the basis of differences in mycolic acids, the long-chain fatty acids found in the cell wall of mycobacteria. Molecular DNA probes have now been developed for MAC, *M. kansasii*, and *M. gordonae*; however, probes are not available for all species of mycobacteria. Polymerase chain reaction restriction fragment length polymorphism analysis is another molecular technique for identifying mycobacteria on the basis of differences in restriction fragments of the 65-kD heat-shock protein. Sequence analysis of 16 S ribosomal RNA and the *rpo*B gene also has been developed recently as another method for speciation of NTM. In the future, serodiagnosis of pulmonary NTM infection may be possible. A recent study described the diagnostic utility of antibodies specific to lipid antigens found in NTM [19].

Broth-based macrodilution and microdilution techniques are recommended by the Clinical and Laboratory Standards Institute for select NTM species. In vitro susceptibility does not always correlate with clinical response to treatment for NTM pulmonary disease [1••,17••]. For MAC, the most common cause of pulmonary NTM disease, clinical response correlates only with in vitro susceptibility to macrolides. Thus, it is recommended that MAC isolates undergo susceptibility testing only for macrolides [1••]. Because rifampin appears to be necessary for successful treatment of *M. kansasii* pulmonary disease, *M. kansasii* isolates should be tested for rifampin susceptibility [1••]. Pulmonary infections due to *M. abscessus* are difficult to treat successfully and are associated with variable in vitro drug susceptibilities. It is recommended that *M. abscessus* undergo susceptibility testing to amikacin, doxycycline, fluoroquinolones, sulfonamides, cefoxitin, clarithromycin, and linezolid [1••,17••]. There is a dearth of data regarding routine susceptibility testing for other species of NTM.

Treatment

The decision to treat pulmonary NTM should be carefully deliberated and should take into account whether the patient has met the clinical, radiologic, and microbiologic criteria for

NTM disease. The clinician should consider that the treatment regimen for pulmonary NTM involves a prolonged course of multiple antibiotics that have multiple adverse effects. Furthermore, the costs of such prolonged courses of therapy are not trivial. A study of the cost of treatment for NTM pulmonary disease found that, on average, patients underwent 2630 drug-days of treatment with a cost per person of $19,876 [20]. Higher costs and more prolonged treatment intervals were associated with more extensive pulmonary disease and with *M. abscessus* infection. In some instances (eg, *M. abscessus* pulmonary disease), complete cure is not possible; rather, clinical improvement is the goal of therapy. Cure is considered to have occurred when a patient has had at least 12 months of negative sputum cultures while on antimycobacterial therapy [1••]. However, because many of the patients with pulmonary disease likely have a predisposing alteration in mucociliary clearance and given the likely repeated exposure to these ubiquitous environmental organisms, patients may be at risk for reinfection once treatment is discontinued [21].

MAC, the most common cause of pulmonary NTM disease, was initially treated with antituberculous drugs. During that time, results were mixed, and relapses were common. The Research Group of the British Thoracic Society published a study of HIV-negative patients with pulmonary MAC who were treated with rifampicin and ethambutol, with or without isoniazid [22]. Cure was achieved in only 31% of the patients. There was no correlation between clinical failure and in vitro resistance to these antituberculous agents. The advent of newer macrolides (eg, clarithromycin, azithromycin) has drastically improved the clinical outcome of pulmonary NTM disease due to MAC. In one study in the early 1990s, 19 patients with pulmonary MAC were treated with clarithromycin monotherapy for the first 4 months of their treatment regimen. Of these patients, 18 of 19 (95%) had an improvement in sputum cultures, chest radiographs, or both. Relapse in these cases was associated with in vitro resistance to clarithromycin [23]. There appears to be no difference with regard to the use of clarithromycin or azithromycin; another study with azithromycin found similar success as with clarithromycin [24]. Patients with macrolide-resistant isolates are much more difficult to treat and have a significantly worse prognosis [25]. Thus, it is recommended that only susceptibility testing to macrolides be performed for MAC isolates. Macrolide therapy can be given intermittently (eg, three times weekly) to reduce cost and toxicities; however, it should never be given as monotherapy or in combination with only a quinolone [25]. The most recent ATS/IDSA guidelines for treatment of pulmonary MAC recommend combination treatment with clarithromycin or azithromycin, rifampin, and ethambutol, as well as streptomycin or amikacin for cavitary or otherwise advanced disease [1••]. Daily therapy is recommended for more severe disease [26]. Surgical resection in conjunction with antibiotics may be curative in cases of focal pulmonary disease.

M. kansasii, the second most common cause of pulmonary NTM, is treated with antituberculous agents. Prior to the use of rifampin-containing regimens, sputum conversion rates were 80% at best. Since the advent of rifampin, *M. kansasii* has become one of the most treatable causes of pulmonary NTM, with essentially 100% cure rates. A study published in the early 1980s compared treatment of *M. kansasii* pulmonary infection with and without rifampin. Sputum conversion rates were 80% at 6 months in regimens not containing rifampin. Among the patients who received rifampin-containing regimens, all had cure at 6 months. One patient relapsed in this study [27]. Another British study with a longer follow-up interval (at least 5 years) reported success rates of 100% with rifampincontaining regimens [28]. Consequently, it seems that rifampin is essential for successful treatment of *M. kansasii* pulmonary infection. Current recommendations are that *M. kansasii* be treated with isoniazid, rifampin, and ethambutol until sputum cultures have been negative for at least 12 months [1••]. If resistance to rifampin does occur, it is recommended that in vitro susceptibility testing be obtained for secondary agents in order to

formulate an appropriate treatment regimen. Because *M. kansasii* is curable with antibiotics, surgical resection is not indicated.

Pulmonary disease due to *M. abscessus* is difficult to treat; often the only feasible goal is clinical improvement. Antibiotic susceptibilities should be performed whenever treatment of *M. abscessus* infection is considered, because this species varies widely with regard to in vitro drug susceptibilities [1••,17••]. Amikacin, cefoxitin, glycylcyclines (eg, tigecycline), and the newer macrolides (azithromycin, clarithromycin) have in vitro activity against *M. abscessus*. Of note, a paper was recently published describing inducible macrolide resistance due to expression of the *erm*(41) gene. This finding may explain why macrolide-based therapy for *M. abscessus* may fail despite initially testing susceptible to clarithromycin in vitro [29]. The suggested regimen for treatment of *M. abscessus* pulmonary infection involves combination therapy with oral susceptible agents (eg, clarithromycin, doxycycline) for a prolonged period in addition to parenteral therapy with amikacin and cefoxitin or imipenem for 2 to 4 months [1••,17••]. Limiting factors for such a complex regimen include serious adverse effects, such as nephrotoxicity, ototoxicity, and cytopenias as well as the inconvenience of parenteral treatment. A group in South Korea studied the efficacy of a standardized combination regimen for *M. abscessus* lung disease using clarithromycin, ciprofloxacin, and doxycycline as well as 4 weeks of amikacin and cefoxitin [30]. The cure rate, defined as maintenance of negative sputum cultures for more than 12 months, was only 58%. Clinical improvement, however, was more successful: 83% of the patients had symptomatic improvement, and 74% had improvement of pulmonary lesions on high-resolution CT. Limiting factors during the treatment were related to drug toxicities. Because *M. abscessus* is so difficult treat, surgical resection may be necessary for control of the infection.

Several antibacterial agents not traditionally used in treatment regimens of pulmonary NTM have recently been investigated. One such drug that has gained more attention is linezolid. Linezolid appears to have some activity against several nontuberculous mycobacteria [31]. *M. avium* and rapidly growing mycobacteria other than *M. abscessus* have lower minimum inhibitory concentrations (MICs) to linezolid, whereas *M. abscessus* has higher MICs [32]. Clinicians using linezolid for treatment of pulmonary NTM must be vigilant of the side effects associated with linezolid during prolonged treatment regimens, specifically bone marrow suppression and neuropathy.

Cystic Fibrosis

Patients with cystic fibrosis represent a unique population for the management of pulmonary NTM. As mentioned earlier, NTM are often found in sputum cultures of patients with cystic fibrosis. Because many patients with cystic fibrosis undergo lung transplantation and are subsequently placed on immunosuppressive medications, management of the infection is an important issue. One study found that the overall prevalence of invasive pulmonary NTM after transplantation was relatively low (3.4%); however, pretransplant NTM growth on culture was the strongest predictor for posttransplant invasive disease (OR, 6.13) [33]. Interestingly, the survival of the patients with invasive pulmonary NTM was similar to that of posttransplant patients who did not have NTM. This suggests that sputum culture positivity for NTM before lung transplantation should not preclude transplantation, but rather should be treated in order to minimize the risk for recurrence after transplantation. Special consideration ought to be given to *M. abscessus*. Case reports exist of fatal disseminated infection from *M. abscessus* occurring after lung transplantation [34]. This organism should be treated prior to transplantation.

Conclusions

Treatment of pulmonary disease due to nontuberculous mycobacteria is an intensive process. Success often depends on the identity of the infecting species as well as the extent to which toxicities due to prolonged combination therapy limit completion of treatment. In many cases, multiple regimens may be necessary, or surgical resection may need to be considered. More rapid diagnostic testing as well as newer antimycobacterial agents with minimal toxicities will hopefully allow for more successful cure of pulmonary disease. Finally, future advances in our understanding of the host's predisposition to contract pulmonary infection will aid in the management of this complex disease.

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References

Papers of particular interest, published recently, have been highlighted as:

• Of importance

•• Of major importance

1••. Griffith DC, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med. 2007; 175:367–416. This article provides the most up-to-date official guidelines for the diagnosis and management of pulmonary infections caused by nontuberculous mycobacteria endorsed by the American Thoracic Society and the Infectious Diseases Society of America. [PubMed: 17277290]

2. Marras TK, Chedore P, Ying AM, et al. Isolation prevalence of pulmonary non-tuberculous mycobacteria in Ontario, 1997–2003. Thorax. 2007; 62:661–666. [PubMed: 17311842]

3. 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; 176:306–313. [PubMed: 17507546]

4. Billinger ME, Olivier KN, Viboud C, et al. Nontuberculous mycobacteria-associated lung disease in hospitalized persons, United States, 1998–2005. Emerging Infect Dis. 2009; 15:1562–1569. [PubMed: 19861046]

5. Edwards LB, Acquaviva FA, Livesay VT, et al. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. Am Rev Respir Dis. 1969; 99(Suppl):1–132. [PubMed: 5767603]

6. Kirschner R, Parker B, Falkinham J. Epidemiology of infection by nontuberculous mycobacteria: *Mycobacterium avium*, *Mycobacterium intracellulare*, and *Mycobacterium scrofulaceum* in acid, brown-water swamps of the Southeastern United States and their association with environmental variables. Am Rev Respir Dis. 1992; 145:271–275. [PubMed: 1736730]

7. Aksamit TR. *Mycobacterium avium* complex pulmonary disease in patients with pre-existing lung disease. Clin Chest Med. 2002; 23:643–653. [PubMed: 12371000]

8. Noone PG, Leigh MW, Sannuti A, et al. Primary ciliary dyskinesia: diagnostic and phenotypic features. Am J Respir Crit Care Med. 2004; 169:459–467. [PubMed: 14656747]

9. Olivier KN, Weber DJ, Wallace RJ, et al. Nontuberculous mycobacteria: 1. Multicenter prevalence study in cystic fibrosis. Am J Respir Crit Care Med. 2003; 167:828–834. [PubMed: 12433668]

10. Ebert DL, Olivier KN. Nontuberculous mycobacteria in the setting of cystic fibrosis. Clin Chest Med. 2002; 23:655–663. [PubMed: 12371001]

11. Melia E, Freeman AF, Shea YR, et al. Pulmonary nontuberculous mycobacterial infections in hyper-IgE syndrome. J Allergy Clin Immunol. 2009; 124:617–618. [PubMed: 19733303]

12. Reich JM, Johnson RE. *Mycobacterium avium* complex pulmonary disease presenting as an isolated lingular or middle lobe pattern: the Lady Windermere syndrome. Chest. 1992; 101:1605–1609. [PubMed: 1600780]

13. Dhillon SS, Watanakunakorn C. Lady Windermere syndrome: middle lobe bronchiectasis and *Mycobacterium avium* complex infection due to voluntary cough suppression. Clin Infect Dis. 2000; 30:572–575. [PubMed: 10722445]

14•. Kim RD, Greenberg DE, Ehrmantraut ME, et al. Pulmonary nontuberculous mycobacterial disease: prospective study of a distinct preexisting syndrome. Am J Respir Crit Care Med. 2008; 178:1066–1074. This article provides an excellent study of the phenotypic characteristics of women without underlying pulmonary disease who develop pulmonary nontuberculous mycobacterial disease. [PubMed: 18703788]

15. Colombo RE, Hill SC, Claypool RJ, et al. Familial clustering of pulmonary nontuberculous mycobacterial disease. Chest. 2009 Epub ahead of print.

16. Freeman AF, Olivier KN, Rubio TT, et al. Intrathoracic non-tuberculous mycobacterial infections in otherwise healthy children. Pediatr Pulmonol. 2009; 44:1051–1056. [PubMed: 19824053]

17••. Colombo RE, Olivier KN. Diagnosis and treatment of infections caused by rapidly growing mycobacteria. Semin Respir Crit Care Med. 2008; 29:577–588. This article provides a review of the spectrum of disease and management of infection due to rapidly growing mycobacteria, especially Mycobacterium abscessus. [PubMed: 18810691]

18. Bange FC, Bottger EC. Improved decontamination method for recovering mycobacteria from patients with cystic fibrosis. Eur J Clin Microbiol Infect Dis. 2002; 21:546–548. [PubMed: 12172748]

19. Nishimura T, Hasegawa N, Fujita Y, et al. Serodiagnostic contributions of antibody titers against mycobacterial lipid antigens in *Mycobacterium avium* complex pulmonary disease. Clin Infect Dis. 2009; 49:529–535. [PubMed: 19591595]

20. Ballarino GB, Olivier KN, Claypool RJ, et al. Pulmonary nontuberculous mycobacterial infections: antibiotic treatment and associated costs. Respir Med. 2009; 103:1448–1455. [PubMed: 19467851]

21. Wallace RJ, Zhang Y, Brown BA, et al. Polyclonal Mycobacterium avium complex infections in patients with nodular bronchiectasis. Am J Respir Crit Care Med. 1998; 158:1235–1244. [PubMed: 9769287]

22. 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 standardized treatment. Int J Tuberc Lung Dis. 2002; 6:628–634. [PubMed: 12102303]

23. Wallace RJ Jr, Brown BA, Griffith DE, et al. Initial clarithromycin monotherapy for *Mycobacterium avium-intracellulare* complex lung disease. Am J Respir Crit Care Med. 1994; 149:1335–1341. [PubMed: 8173775]

24. Griffith DE, Brown BA, Girard WM, et al. Azithromycin activity against *Mycobacterium avium* complex lung disease in patients who were not infected with human immunodeficiency virus. Clin Infect Dis. 1996; 23:983–989. [PubMed: 8922790]

25. Griffith DE, Brown-Elliott BA, Longsjoen B, et al. Clinical and molecular analysis of macrolide resistance in *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med. 2006; 174:928–934. [PubMed: 16858014]

26. Lam PK, Griffith DE, Aksamit TR, et al. Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med. 2006; 173:128–1289.

27. Pezzia W, Raleigh JW, Bailey MC, et al. Treatment of pulmonary disease due to *Mycobacterium kansasii*: recent experience with rifampin. Rev Infect Dis. 1981; 3:1035–1039. [PubMed: 7339801]

28. Banks J, Hunter AM, Campbell IA, et al. Pulmonary infection with *Mycobacterium kansasii* in Wales, 1970–79: review of treatment and response. Thorax. 1983; 38:271–274. [PubMed: 6867979]

29. Nash KA, Brown-Elliott BA, Wallace RJ. A novel gene, *erm*(41), confers inducible macrolide resistance to clinical isolates of *Mycobacterium abscessus* but is absent from *Mycobacterium chelonae*. Antimicrob Agents Chemother. 2009; 53:1367–1376. [PubMed: 19171799]

30. Jeon K, Jung Kwon O, Lee NY, et al. Antibiotic treatment of *Mycobacterium abscessus lung disease*: a retrospective analysis of 65 patients. Am J Respir Crit Care Med. 2009; 180:896–902. [PubMed: 19661243]

31. Brown-Elliott BA, Crist CJ, Mann LB, et al. In vitro activity of linezolid against slowly growing nontuberculous mycobacteria. Antimicrob Agents Chemother. 2003; 47:1736–1738. [PubMed: 12709349]

32. Cavusoglu C, Soyler I, Akinci P. Activities of linezolid against nontuberculous mycobacteria. New Microbiol. 2007; 30:411–414. [PubMed: 18080676]

33. Chalermskulrat W, Sood N, Neuringer IP, et al. Non-tuberculous mycobacteria in end stage cystic fibrosis: implications for lung transplantation. Thorax. 2006; 61:507–513. [PubMed: 16601086]

34. Zaidi S, Elidemir O, Heinle JS, et al. *Mycobacterium abscessus* in cystic fibrosis lung transplant recipients: report of 2 cases and risk for recurrence. Transpl Infect Dis. 2009; 11:243–248. [PubMed: 19298240]