J Microbiol Immunol Infect.
2007;40:342-348

Original Article

Factors that affect sputum conversion and treatment outcome in patients with *Mycobacterium avium-intracellulare* complex pulmonary disease

Jung-Jr Ye, Ting-Shu Wu, Ping-Cherng Chiang, Ming-Hsun Lee

Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Taoyuan, Taiwan

Received: April 13, 2006 Revised: July 5, 2006 Accepted: July 20, 2006

Background and Purpose: To investigate factors that might affect the sputum conversion and treatment outcome of *Mycobacterium avium-intracellulare* complex (MAC) pulmonary disease.

Methods: This retrospective study reviewed 46 patients diagnosed with MAC pulmonary disease at the Chang Gung Memorial Hospital at Linkou between July 1998 and February 2005. The diagnosis was based on the American Thoracic Society criteria for diagnosis of disease due to non-tuberculous mycobacteria of 1997.

Results: Of the 46 patients reviewed, 30 were men and 16 women, with a mean age of 64.39 years (range, 28-87 years). Thirty one patients had preexisting lung diseases, including history of pulmonary tuberculosis in 23 patients. Follow-up of sputum cultures could be traced in 28 patients, and sputum conversion was found in 17 patients. Of the 28 patients, 9 were treated with anti-MAC drugs for <5 months or with a regimen not containing at least 2 anti-MAC drugs. These treatment regimens were significantly associated with failure of sputum conversion to culture negativity (adjusted odds ratio [OR], 16.83; 95% confidence interval [CI], 1.16-245.06; p=0.039). Eleven of the remaining 19 patients were treated with an anti-MAC regimen containing clarithromycin for >5 months. However, there was no statistically significant association between sputum conversion and clarithromycin-containing anti-MAC regimens (OR, 0.42; 95% CI, 0.08-2.16; p=0.435).

Conclusions: MAC pulmonary disease often occurs in the context of preexisting lung disease, especially pulmonary tuberculosis. Patients tend to be older. Inappropriate treatment might lead to failure of sputum conversion. Treatment with rational combination regimens for at least 5 months could be necessary for sputum conversion.

Key words: Lung diseases; *Mycobacterium avium* complex; *Mycobacterium avium-intracellulare* infection

Introduction

Mycobacterium avium-intracellulare complex (MAC) has become an increasingly important causal agent of pulmonary disease [1]. In human immunodeficiency virus (HIV)-infected patients, MAC infection usually presents as a disseminated disease, although localized forms of MAC are being reported with the widespread use of more effective antiretroviral therapies [2,3]. Diseases caused by MAC in HIV-negative patients are less common. Manifestations of MAC infections in HIV-negative patients are mainly in the lungs [1]. It often occurs in the context of preexisting lung disease, and patients tend to be older, with a predominantly male demographic [4]. The American Thoracic Society (ATS) has established specific criteria for the diagnosis of pulmonary diseases caused by non-tuberculous mycobacteria (NTM) [5]. All 3 criteria (clinical, radiographic, and microbiological) need to be satisfied for the diagnosis of MAC pulmonary disease. Because the clinical and radiographic presentations of MAC pulmonary disease are often indistinguishable from that of pulmonary tuberculosis (TB) and the results of mycobacterial cultures take considerable time, most patients were treated for pulmonary TB at first following positive acid-fast bacilli (AFB) smears.

Corresponding author: Dr. Ming-Hsun Lee, Division of Infectious Diseases, Department of Internal Medicine, Chang Gung Memorial Hospital, 5 Fu-Shin St, Kweishan 333, Taoyuan, Taiwan.
E-mail: lmh1016@adm.cgmh.org.tw

In the past, sputum conversion rates in MAC lung diseases have ranged between 50-80%, despite the combined use of 3 to 5 antituberculous agents, with a long-term relapse rate of 20% [4,6,7]. However, in a recent study, newer macrolides were found to have a tremendous impact on the treatment of this disease [8,9]. Rifabutin has also been reported to be more active in vitro than rifampin against this organism [10]. However, intolerance to the treatments of MAC pulmonary disease, including clarithromycin and rifabutin, is common [11,12].

Diagnosis of MAC pulmonary disease can be a confusing issue for doctors, and the long-term treatment and follow-up for this patient group is difficult due to poor compliance and treatment intolerance. Thus, we retrospectively studied the factors that might affect sputum conversion and treatment outcomes in patients with MAC pulmonary disease over a 6.6-year period.

Methods

Patient selection

All the mycobacterial smears and cultures of patients who visited or were admitted to the Chang Gung Memorial Hospital at Linkou between July 1998 and February 2005 were reviewed from the database at the microbiology laboratory. All enrolled patients were over 18 years of age. The diagnosis of MAC pulmonary disease was made based on the ATS criteria for diagnosis of disease due to NTM of 1997 [5], according to which patients must be symptomatic, have abnormalities on chest radiographs or computed tomography (CT) scans consistent with mycobacterial lung disease, and have one of the following features: 1) any growth from bronchopulmonary tissue specimen; 2) three positive sputum/bronchial wash cultures without positive smears; 3) two positive sputum/bronchial wash cultures with 1 positive smear; 4) a bronchial wash culture with a 2+ or greater smear; 5) a bronchial wash culture with a 2+ or greater growth on culture; and 6) granuloma and/or AFB on lung biopsy with one or more positive cultures from sputum/bronchial wash.

Chart review

Medical records of the enrolled patients were reviewed for demographic information, history of pulmonary disease, history of prior treatment for TB, records of previous mycobacterial smears and cultures, clinical symptoms, chest radiographs and CT scans, pulmonary specimens of positive MAC cultures, treatment regimens and duration, length of the follow-up period, time of MAC culture conversion to negativity, and radiographic evolution.

Identification of MAC

Generally, sputum or bronchial washing specimens were digested and decontaminated with 5% oxalic acid and 4% sodium hydroxide by routine methods [13]. Semiquantitative AFB smears (fluorochrome method) were performed at a magnification of × 200, as described elsewhere [12]. Specimens were plated on Middlebrook 7H11 agar and onto Lowenstein-Jensen (L-J) slants. Colonies grown on media were stained by AFB smear. Colonies that grew after 7 days of incubation with positive AFB smears were screened for *M. tuberculosis* by TB-polymerase chain reaction (PCR) based on the insertion sequence IS*6110* [14]. Once the TB-PCR showed negative for *M. tuberculosis* twice, microorganisms were identified as MAC by use of mycobacteria other than *M. tuberculosis* PCR-restriction fragment length polymorphism, as described by Telenti et al [15].

Therapy

Appropriate treatment regimen was defined as a minimum 2-drug regimen consisting of any two of clarithromycin, rifabutin (or rifampin), and ethambutol, for at least 5 months [5]. Other treatment regimens were defined as inappropriate treatment.

Definition of sputum conversion and criteria of outcome study

Sputum conversion was defined as: 1) at least 2 consecutive cultures negative for MAC (in both Middlebrook 7H11 agar and L-J slants), with the time of conversion considered to be the date of the first of the 2 or more negative sputum cultures, or 2) 1 negative culture for MAC after a minimum of 1-month follow-up with improvement in clinical symptoms or radiographic findings. Failure of sputum conversion was defined as persistently positive MAC cultures (failure to convert cultures to negative) through the whole course of follow-up [9]. For patients included in the outcome study, failure or success in sputum conversion was based on the above definition criteria with a minimum follow-up of 5 months.

Statistical analysis

Bivariate analysis was conducted to determine the association between potential risk factors and the

failure of sputum conversion. Of primary interest was the association between inappropriate treatment and failure of sputum conversion. Categorical variables were compared using Fisher's exact test. An odds ratio (OR) and 95% confidence interval (CI) were calculated to evaluate the strength of any association, as well as the precision of the estimate of the effect. Continuous variables were compared by the Student's *t* test [16]. Adjusted ORs were calculated using multiple logistic regression analyses, with overall sputum conversion as the dependent outcome [17].

The model for sputum conversion failure began with inclusion of the primary risk factor of interest (i.e., inappropriate treatment), which was based on our prior hypothesis of an association between inappropriate treament and the failure of sputum conversion. Other variables were considered for inclusion in a multivariate model if they were found to be associated with failure of sputum conversion on bivariate analysis ($p<0.2$) or if they were involved in confounding on stratified analysis [18]. A 2-tailed p value of <0.05 was considered to be statistically significant. All statistical calculations were done with standard programs using the Statistical Package for the Social Sciences (SPSS) for Windows (Version 12.0; SPSS Chicago, IL, USA).

Results

A total of 153 patients had at least 1 positive culture for MAC from any pulmonary specimen. Forty six of these patients fulfilled inclusion criteria for MAC pulmonary disease. For the remaining 107 patients, information contained in medical records was insufficient for review for 5 patients, 2 had concurrent lung cancer, and 100 patients did not fulfill the current ATS criteria for active diseases.

Patient characteristics and coexisting diseases

A total of 46 patients (30 men and 16 women) were enrolled in this study. The median and mean ages at diagnosis of MAC pulmonary disease were 71, and 64.39 ± 15.46 years (range, 28-87 years), respectively. Smoking history could be traced in 17 patients (Table 1). Of the 31 patients with preexisting lung disease, 23 had old pulmonary TB, 13 showed chronic obstructive pulmonary disease, 4 had previous pulmonary infections caused by NTM other than MAC, and 3 showed interstitial fibrosis.

Among the 46 patients enrolled, there were 7 adrenal insufficiencies, 5 HCV infections, 3 diabetes mellitus, 2 malignancies (endometrial cancer and prostate cancer, respectively), 2 HIV infections (HIV antibody test was done in 13 patients), 2 congestive heart failures, 1 end-stage renal disease, and 1 HBV infection.

Symptoms

Forty four patients had pulmonary symptoms, including chronic cough (84.8%), dyspnea (43.5%), and hemoptysis (34.8%). Nineteen patients had constitutional symptoms, including body weight loss (26.1%), fever (26.1%), fatigue (15.2%), and night sweats (4.3%). Nine patients had chest tightness or atypical chest pain, and 2 had lymphadenopathy, including 1 with HIV infection (Table 1). The interval between onset of symptoms and MAC culture positivity for diagnosis could be assessed in 31 patients, and the mean value was 2.77 ± 1.26 months (range, 1.0-6.5 months).

Specimen source of positive MAC cultures

Forty patients had positive sputum cultures for MAC, including 37 with positive AFB smears. Five had positive MAC cultures from bronchial wash fluid and 1 had a positive culture from transbronchial biopsied tissue. Mean interval from positive smear to positive culture was 41.74 ± 14.91 days (range, 23-110 days). Isolates were identified as *M. intracellulare* in 38 patients, *M. avium* in 6, and *M. avium-intracellulare* complex in 2.

Radiographic findings

Forty four patients had chronic pulmonary infiltration on their chest films, including 19 with reticulonodular

Table 1. Demographics, and clinical symptoms and signs of patients with *Mycobacterium avium-intracellulare* complex pulmonary disease (n = 46)

Variable	No. of patients (%)
Age (mean ± SD; range) [years]	64.39 ± 15.46 (28-87)
Gender (male/female)	30/16
History of smoking[a]	17
Clinical symptoms/signs	
Chronic cough	39 (84.8)
Dyspnea	20 (43.5)
Hemoptysis	16 (34.8)
Body weight loss	12 (26.1)
Fever	12 (26.1)
Chest tightness	9 (19.6)
Fatigue	7 (15.2)
Night sweats	2 (4.3)
Lymphadenopathy	2 (4.3)

Abbreviation: SD = standard deviation

[a]40 patients with available history of smoking.

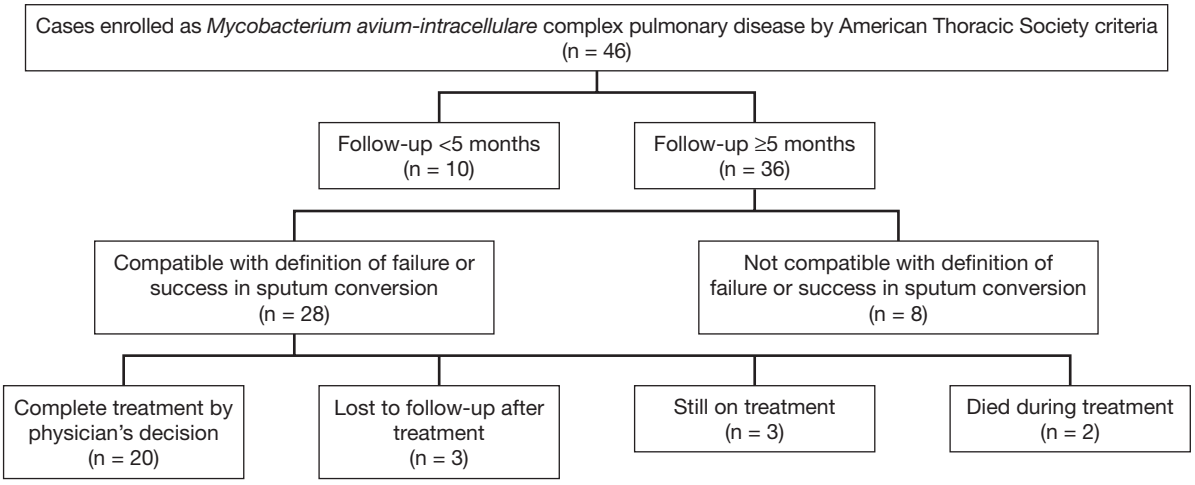

Fig. 1. Flow chart of patient selection for outcome analysis.

patterns of infiltration. Twenty nine patients had destructive lungs or fibrotic scar, 11 cavitations, 4 bronchiectasis, 3 mass-like lesions, and 1 pleural effusion.

Treatment and outcome

Of the 46 patients enrolled, 10 were lost to follow-up within 5 months, including 8 at around one month, 1 at two months, and 1 at three months. The other 36 patients received outpatient clinic and sputum culture follow-up for at least 5 months, of whom only 28 had follow-up sputum cultures compatible with the definition of failure or success in sputum conversion. Thus, a total of 28 patients were included in the outcome analysis (Fig. 1).

Of the 28 patients, 11 failed in sputum conversion, and the mean interval between the first and the last positive sputum culture was 13.82 ± 6.63 months (range, 5-29 months). Seventeen patients had sputum conversion, with mean treatment duration of 12.41 ± 4.95 months (range, 7-22 months). The mean interval of sputum conversion in 16 patients with available data was 6.06 ± 4.27 months (range, 1-18 months). One patient was excluded for sputum conversion time analysis because the timing of sputum conversion was uncertain.

Nine of 28 patients were treated inappropriately, including 2 treated with a regimen involving clarithromycin for <5 months. Nineteen were treated appropriately, including 11 with clarithromycin-based regimens (clarithromycin, ethambutol, and either rifabutin or rifampin).

Risk factors for failure of sputum conversion

Eleven patients had no sputum conversion, and 6 of them were treated inappropriately. In comparison with the 17 patients with sputum conversion, 3 were treated inappropriately (OR, 5.60; 95% CI, 1.00-31.32; p=0.095). Variables potentially associated with failure of sputum conversion are shown in Table 2. On multivariate analysis, inappropriate treatment was found to be significantly associated with the failure of sputum conversion (adjusted OR, 16.83; 95% CI, 1.16-245.06; p=0.039) [Table 3]. Association between sputum conversion and clarithromycin-based regimens was not statistically significant (OR, 0.42; 95% CI, 0.08-2.16; p=0.435).

Discussion

In this study, patients with MAC pulmonary disease were usually elderly men. Most of the patients (31, 67.4%) had preexisting lung diseases, such as pulmonary TB, chronic obstructive pulmonary disease, and interstitial lung fibrosis. Pulmonary TB was the most common (23, 50%). Histories of previous pulmonary TB were confirmed either based on information from the patients themselves (n = 17) who had been diagnosed and treated at other hospitals several years ago, or from sputum cultures of *M. tuberculosis* in our laboratory (n = 6). MAC pulmonary disease was found in 2 patients with pulmonary TB, who had received anti-TB therapy with sputum conversion to negative for *M. tuberculosis* within 1 year. No patient was diagnosed to have MAC pulmonary disease and active pulmonary TB at the same time. The clinical manifestations of MAC pulmonary disease are insidious and often similar to those of underlying diseases, such as pulmonary TB.

Radiographic findings of MAC pulmonary disease are often indistinguishable from that of preexisting lung

Table 2. Bivariate analysis of risk factors for failure of sputum conversion

Variable	No. of patients (%)			*p*
	No sputum conversion (n = 11)	Sputum conversion (n = 17)	OR (95% CI)	
Demographic parameters				
Average age (years [range])	70.64 (38-82)	59.47 (31-77)		0.050
Male	9/11 (81.8)	11/17 (64.7)	2.46 (0.4-15.25)	0.419
History of smoking	6/9 (66.7)	6/15 (40.0)	3 (0.53-16.90)	0.400
Concomitant diseases				
Previous pulmonary TB	7/11 (63.6)	8/17 (47.1)	1.97 (0.42-9.32)	0.460
Previous NTM lung disease	2/11 (18.2)	1/17 (5.9)	3.56 (0.28-44.88)	0.543
COPD	3/11 (27.3)	5/17 (29.4)	0.90 (0.17-4.87)	1
Idiopathic pulmonary fibrosis	1/11 (9.1)	1/17 (5.9)	1.6 (0.09-28.57)	1
End-stage renal disease	0/11 (0.0)	1/17 (5.9)	0.73 (0.02-23.62)	1
Hepatitis C virus infection	1/11 (5.9)	3/17 (17.6)	0.47 (0.04-5.17)	1
Hepatitis B virus infection	0/11 (0.0)	1/17 (5.9)	0.73 (0.02-23.62)	1
HIV infection	0/3 (0.0)	1/8 (12.5)	1.17 (0.03-45.08)	1
Diabetes mellitus	0/11 (0.0)	2/17 (11.8)	0.34 (0.01-8.32)	0.505
Adrenal insufficiency	3/11 (27.3)	2/17 (11.8)	2.81 (0.39-20.46)	0.353
Radiographic findings				
Destructive lung or fibrosis scar	9/11 (81.8)	9/17 (52.9)	4 (0.66-24.3)	0.226
Infiltration >2 months	11/11 (100.0)	16/17 (94.1)	1.38 (0.04-44.66)	1
Reticulonodular appearance	3/11 (27.3)	7/17 (41.2)	0.54 (0.10-2.77)	0.689
Cavity	2/11 (18.2)	6/17 (35.3)	0.41 (0.07-2.53)	0.419
Bronchiectasis	0/11 (0.0)	2/17 (11.8)	0.34 (0.01-8.32)	0.505
Focal mass-like opacities	0/11 (0.0)	3/17 (17.6)	0.21 (0.01-4.69)	0.258
Bilateral disease	5/11 (45.5)	7/17 (41.2)	1.19 (0.26-5.50)	1
Treatment				
Inappropriate therapy	6/11 (54.5)	3/17 (17.6)	5.6 (1.00-31.32)	0.095
Clarithromycin-based regimen	3/11 (27.3)	8/17 (47.1)	0.42 (0.08-2.16)	0.435

Abbreviations: OR = odds ratio; CI = confidence interval; TB = tuberculosis; NTM = non-tuberculous mycobacterium; COPD = chronic obstructive pulmonary disease; HIV = human immunodeficiency virus

[a]Fisher's exact test for categorical variables and Student's *t* test for continuous variables.

disease or pulmonary TB [19]. In this study, most patients had chronic pulmonary infiltration (>2 months), especially nodular pattern infiltration (19, 41.3%). In previous studies, cavitary disease at the upper lung zones or nodular/bronchiectatic disease was seen in approximately 50% of patients with MAC pulmonary disease [19-21], but such presentation was not common in our cases. Many studies have suggested that high-resolution CT or CT scans of the chest are more sensitive than chest radiographs for the detection of abnormalities associated with MAC pulmonary disease [22-24]. CT or high-resolution CT scans were done for 20 patients in this study, and the procedure did afford useful information. Only 1 patient in this study had a right-sided pleural effusion; he was a case of AIDS with disseminated MAC infection. MAC was identified from the cultures of pleural effusion, sputum, and bone marrow.

The possible presence of MAC pulmonary disease often arises clinically when MAC are identified from the sputum culture of a patient with suspected pulmonary malignancy or TB. The ATS has established specific criteria for diagnosis in an attempt to specifically address the difficulties involved in making a NTM lung disease diagnosis [5]. Accordingly, all 3 criteria (clinical, radiographic, and microbiological) must be satisfied for a positive diagnosis of MAC pulmonary disease. However, the ATS statement does not clearly delineate the role of bronchoscopy in the diagnosis of infection. A recent study of MAC pulmonary infections in HIV-negative patients without preexisting lung disease showed that sputum cultures had a high false-negative rate, as 45% of the patients had non-diagnostic sputum cultures and required bronchoscopy or transbronchial lung biopsies for diagnosis. The issue of whether sputum culture is a sufficiently sensitive method to exclude

Table 3. Multivariate analysis of risk factors for failure of sputum conversion

Variable[a]	Adjusted OR (95% CI)	*p*
Age[b]	1.06 (0.98-1.14)	0.139
Destructive lung or fibrosis scar	10.71 (0.66-173.56)	0.095
Inappropriate treatment	16.83 (1.16-245.06)	0.039
Previous pulmonary tuberculosis	2.13 (0.26-17.56)	0.481

Abbreviations: OR = odds ratio; CI = confidence interval

[a]All variables included in the final multivariable model are shown.

[b]OR reflects the odds associated with each 1-year increase in age.

active MAC infection has not been systematically addressed or answered by prior studies. An aggressive approach with bronchoscopy for bronchial wash culture or tissue proof may offer useful information for the diagnosis of infection if there is significant clinical suspicion of MAC involvement [25].

Four patients were diagnosed to have MAC pulmonary disease based on radiographic findings and a series of sputum cultures positive for MAC, but lacked a detailed description of symptoms in their medical records. As these 4 patients did not fulfill ATS criteria for MAC pulmonary disease diagnosis, we did not include them in this review; however, one of them did have a lung mass over the right lower lobe. Although there were no correlated symptoms of MAC pulmonary disease, the patient, a woman, received lobectomy under the impression of malignancy. MAC was identified from her sputum, bronchial wash, and lung tissue cultures. She received anti-MAC agents for 10 months after surgery, but no sputum culture follow-ups were done. Her follow-up chest radiographs showed no relapse. This case highlights the possibility of asymptomatic patients being ignored by the ATS criteria, even when lung tissue invasion is apparent. A previous study reported that early cases might be asymptomatic and only discovered by routine screening chest radiographs [24]. Focal mass-like opacities are an uncommon presentation of MAC infection. Typically, these are asymptomatic, and the diagnosis is often made at resection for suspected malignancy [26,27].

Although putatively appropriate regimens and treatment durations should lead to sputum conversion, there were no statistically significant associations found between sputum conversion and treatment with clarithromycin-based combination therapies (OR, 0.42; 95% CI, 0.08-2.16; p=0.435). Three patients receiving clarithromycin-based combination therapies for >6 months showed no sputum conversion, although susceptibility testing of cultures isolates was not done.

Treatment and follow-up protocols varied widely in this study because there are no standardized treatments and follow-up protocols for MAC pulmonary disease. Incomplete follow-ups and a lack of repeat sputum cultures may also be due to poor compliance by some patients or the lack of sputum production following treatment. Also, further analysis of side effects and recurrences could not be done in this study, as most physicians did not record clearly their reasons for deciding on a particular treatment regimen or treatment duration, the compliance and adverse effects shown by patients, or the reasons for inadequate follow-up, such as lack of repeated sputum cultures. Therefore, another exhaustive study with more complete information will be necessary to address these issues.

In summary, although the ATS guidelines offer a good reference for the diagnosis of MAC pulmonary disease, the possibility of asymptomatic cases slipping through undiagnosed cannot be ignored or underestimated. The association of inappropriate treatment and failure of sputum conversion was statistically significant. The appropriate use of antimycobacterial therapy for at least 5 months should be given due consideration with the goal of sputum conversion.

References

1. O'Brien RJ, Geiter LJ, Snider DE. The epidemiology of nontuberculous mycobacterial diseases in the United States: results from a national survey. Am Rev Respir Dis. 1987;135: 1007-14.
2. Karakousis PC, Moore RD, Chaisson RE. *Mycobacterium avium* complex in patients with HIV infection in the era of highly active antiretroviral therapy. Lancet Infect Dis. 2004;4: 557-65.
3. Sungkanuparph S, Vibhagool A, Mootsikapun P, Chetchotisakd P, Tansuphaswaswadikul S, Bowonwatanuwong C. Opportunistic infections after the initiation of highly active antiretroviral therapy in advanced AIDS patients in an area with a high prevalence of tuberculosis. AIDS. 2003;17:2129-31.
4. Rosenzweig DY. Pulmonary mycobacterial infections due to

Mycobacterium intracellulare-avium complex. Clinical features and course in 100 consecutive cases. Chest. 1979;75:115-9.
5. American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med. 1997;156:S1-25.
6. Ahn CH, Ahn SS, Anderson RA, Murphy DT, Mammo A. A four-drug regimen for initial treatment of cavitary disease caused by *Mycobacterium avium* complex. Am Rev Respir Dis. 1986;134:438-41.
7. Dutt AK, Stead WW. Long-term results of medical treatment in *Mycobacterium intracellulare* infection. Am J Med. 1979; 67:449-53.
8. Wallace RJ, Brown BA, Griffith DE, Girard WM, Murphy DT, Onyi GO, et al. Initial clarithromycin monotherapy for *Mycobacterium avium-intracellulare* complex lung disease. Am J Respir Crit Care Med. 1994;149:1335-41.
9. Wallace RJ, Brown BA, Griffith DE, Girard WM, Murphy DT. Clarithromycin regimens for pulmonary *Mycobacterium avium* complex. Am J Respir Crit Care Med. 1996;153:1766-72.
10. Kunin CM. Antimicrobial activity of rifabutin. Clin Infect Dis. 1996;22(Suppl 1):S3-13.
11. Wallace RJ, Brown BA, Griffith DE. Drug intolerance to high-dose clarithromycin among elderly patients. Diagn Microbiol Infect Dis. 1993;16:215-21.
12. Griffith DE, Brown BA, Girard WM, Wallace RJ. Adverse events associated with high-dose rifabutin in macrolide-containing regimens for the treatment of *Mycobacterium avium* complex lung disease. Clin Infect Dis. 1995;21:594-8.
13. Vincent V, Brown-Elliott BA, Jost KC, Wallace RJ, eds. Mycobacterium: phenotypic and genotypic identification. In: Murray PR, Baron EJ, Jorgensen JH, Pfaller MA, Yolken RH, eds. Mannual of clinical microbiology. 8th ed. Washington: American Society for Microbiology; 2003:560-84.
14. van Embden JD, Cave MD, Crawford JT, Dale JW, Eisenach KD, Gicquel B, et al. Strain identification of *Mycobacterium tuberculosis* by DNA fingerprinting: recommendations for a standardized methodology. J Clin Microbiol. 1993;31:406-9.
15. Telenti A, Marchesi F, Balz M, Bally F, Böttger EC, Bodmer T. Rapid identification of mycobacteria to the species level by polymerase chain reaction and restriction enzyme analysis. J Clin Microbiol. 1993;31:175-8.
16. Kleinbaum DG, Kupper LL, Morgenstern H. Epidemiologic research: principles and quantitative methods. New York: Van Nostrand Reinhold; 1982.
17. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley & Sons; 1989.
18. Sun GW, Shook TL, Kay GL. Inappropriate use of bivariable analysis to screen risk factors for use in multivariable analysis. J Clin Epidemiol. 1996;49:907-16.
19. Christensen EE, Dietz GW, Ahn CH, Chapman JS, Murry RC, Anderson J, et al. Initial roentgenographic manifestations of pulmonary *Mycobacterium tuberculosis*, *M. kansasii*, and *M. intracellularis* infections. Chest. 1981;80:132-6.
20. Woodring JH, Vandiviere HM. Pulmonary disease caused by nontuberculous mycobacteria. J Thorac Imaging. 1990;5: 64-76.
21. Levin, DL. Radiology of pulmonary *Mycobacterium avium-intracellulare* complex. Clin Chest Med. 2002;23:603-12.
22. Lynch DA, Simone PM, Fox MA, Bucher BL, Heinig MJ. CT features of pulmonary *Mycobacterium avium* complex infection. J Comput Assist Tomogr. 1995;19:353-60.
23. Koh WJ, Lee KS, Kwon OJ, Jeong YJ, Kwak SH, Kim TS. Bilateral bronchiectasis and bronchiolitis at thin-section CT: diagnostic implications in nontuberculous mycobacterial pulmonary infection. Radiology. 2005;235:282-8.
24. Kubo K, Yamazaki Y, Hachiya T, Hayasaka M, Honda T, Hasegawa M, et al. *Mycobacterium avium-intracellulare* pulmonary infection in patients without known predisposing lung disease. Lung. 1998;176:381-91.
25. Huang JH, Kao PN, Adi V, Ruoss SJ. *Mycobacterium avium-intracellulare* pulmonary infection in HIV-negative patients without preexisting lung disease: diagnostic and management limitations. Chest. 1999;115:1033-40.
26. Miller WT. Spectrum of pulmonary nontuberculous mycobacterial infection. Radiology. 1994;191:343-50.
27. Gribetz AR, Damsker B, Bottone EJ, Kirschner PA, Teirstein AS. Solitary pulmonary nodules due to nontuberculous mycobacterial infection. Am J Med. 1981;70:39-43.