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MAJOR ARTICLE

Clinical Implications of Size of Cavities in Patients With Nontuberculous Mycobacterial Pulmonary Disease: A Single-Center Cohort Study

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Background. The presence of cavities is associated with unfavorable prognosis in patients with nontuberculous mycobacterial pulmonary disease (NTM-PD). However, little is known about the characteristics of such cavities and their impact on clinical outcomes. The aim of this study was to investigate the size of cavities and their implications on treatment outcomes and mortality in patients with NTM-PD.

Methods. We included patients diagnosed with NTM-PD at Seoul National University Hospital between January 1, 2007, and December 31, 2018. We measured the size of cavities on chest computed tomography scans performed at the time of diagnosis and used multivariable logistic regression and Cox proportional hazards regression analysis to investigate the impact of these measurements on treatment outcomes and mortality.

Results. The study cohort comprised 421 patients (noncavitary, n = 329; cavitary, n = 92) with NTM-PD. During a median follow-up period of 49 months, 118 (35.9%) of the 329 patients with noncavitary and 64 (69.6%) of the 92 patients with cavitary NTM-PD received antibiotic treatment. Cavities >2 cm were associated with worse treatment outcomes (adjusted odds ratio, 0.41; 95% CI, 0.17–0.96) and higher mortality (adjusted hazard ratio, 2.52; 95% CI, 1.09–5.84), while there was no difference in treatment outcomes or mortality between patients with cavities ≤2 cm and patients with noncavitary NTM-PD.

Conclusions. Clinical outcomes are different according to the size of cavities in patients with cavitary NTM-PD; thus, the measurement of the size of cavities could help in making clinical decisions.

Keywords. cavity; mortality; nontuberculous mycobacteria; outcome.

Nontuberculous mycobacteria (NTM) are ubiquitous microorganisms that can be isolated from the environment, including soil and water [1]. The most common clinical manifestation of human NTM infection is pulmonary disease (PD) [2]. The burden of NTM-PD is currently increasing globally. Between 2008 and 2016, the annual incidence of NTM infection increased from 6.0 cases/100 000 person-years to 19.0 cases/100 000 person-years in South Korea [3]. Similar increases in incidence have also been reported in Japan [4], the United States [5], and Europe [6].

NTM-PD can be classified into clinical phenotypes according to radiographic presentations: nodular bronchiectatic (NB) and fibrocavitary (FC). NB types can be subclassified into noncavitary and cavitary NB [7, 8]. The presence of cavities is reportedly associated with a worse prognosis [9]. The mortality risk is highest for the FC form, followed by cavitary NB and noncavitary NB forms. Similarly, the responses of cavitary NB and FC forms to antibiotic treatment are worse than those of noncavitary NB forms [7, 8].

Because of their prognostic impact, it is recommended that patients with cavities commence antibiotic treatment, rather than be managed by watchful waiting [2]. Furthermore, more aggressive treatment, including parenteral agents, is also recommended for such patients [10, 11]. The presence of cavities in itself has been considered an important prognostic factor; however, the clinical course may vary according to the radiographic features of the cavities [12]. Nevertheless, the impact on treatment outcomes and mortality of radiographic features such as size of cavities has rarely been reported. In this study, we elucidate the relationships between the size of cavities and treatment outcomes and mortality in patients with NTM-PD.

METHODS

Study Design and Subjects

This retrospective study included patients diagnosed with NTM-PD between January 1, 2007, and December 31, 2018, at Seoul National University Hospital. The diagnostic criteria for

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NTM-PD were as proposed in the American Thoracic Society/European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America clinical practice guidelines [2]. Patients who were at least 18 years old and had chest computed tomography (CT) scans at the time of diagnosis were included. Patients who were lost to follow-up within a year after NTM-PD diagnosis were excluded from the analysis. Some of the patients were included in a previously reported prospective study that was launched on July 1, 2011, (NCT01616745) [13, 14]. This study was conducted in accordance with the tenets of the amended Declaration of Helsinki; the Institutional Review Board of Seoul National University Hospital approved the study protocol (IRB No. 2001-047-1092).

Baseline and Follow-up Data Collection

The clinical and laboratory data at the time of NTM-PD diagnosis, including age, sex, body mass index (BMI), smoking history, spirometry data, comorbidities (chronic obstructive pulmonary disease, diabetes mellitus, and malignancy), sputum smear results, the species of causative organisms, and the susceptibility to macrolides, were collected for all patients. The species were identified by 16S rRNA and *rpo*B gene sequencing analysis [15–17]. Radiographic findings (presence of cavities and their size) were interpreted by 3 reviewers (1 chest radiologist and 2 pulmonologists). The presence of a cavity was defined as a gas-filled space presenting as a lucent or low-attenuated space within pulmonary consolidation [18]. Cavity size was determined by measuring the longest diameter on axial images. Three measurements were made, and the average values were used for analysis. Any discrepancies between the reviewers were resolved by discussion. The patients were classified according to the presence and size of cavities.

After diagnosis with NTM-PD, the patients were followed up every 3–6 months. At each follow-up visit, the patient submitted a sputum specimen for an acid-fast bacilli smear test and mycobacterial culture. Chest CT scans were usually performed at intervals of 2 years in patients being managed by watchful waiting and intervals of 6 months for patients on antibiotic treatment. Timing of initiation of antimycobacterial treatment was decided at the discretion of the on-duty physician on the basis of symptoms and radiographic changes. Patients infected with *Mycobacterium avium* complex [MAC] were treated with macrolide-based regimens (azithromycin [or clarithromycin] with ethambutol and rifampicin). Intravenous amikacin was administered according to the severity of disease. In cases of *Mycobacterium abscessus* complex infection, oral macrolides with at least 2 parenteral drugs (amikacin and imipenem [or cefoxitin]) were administered until culture conversion; thereafter, the treatment regimens were adjusted according to the clinical response, drug susceptibility patterns, and adverse events. Clofazimine, tigecycline, and linezolid were also considered as an initial or salvage regimen. After initiation of treatment, patients were followed up every 4–8 weeks.

Clinical Outcomes

Clinical outcomes were assessed according to the criteria suggested by an NTM-NET consensus statement [19]. Culture conversion was defined as at least 3 consecutive negative mycobacterial cultures from sputum samples collected at least 4 weeks apart. Microbiological cure was defined as maintenance of multiple consecutive negative cultures of respiratory samples from after culture conversion until the end of antimycobacterial treatment. Patient death was confirmed using the database of the Ministry of the Interior and Safety, South Korea.

Statistical Analysis

Data are presented as median values with interquartile ranges (IQRs) for continuous variables and as proportions for categorical variables. The Kruskal-Wallis test and Fisher exact test were used to compare continuous and categorical variables. Multivariate logistic regression analysis was used to identify factors associated with the presence of cavities in patients with NTM-PD. Kaplan-Meier analysis with log-rank test and Cox proportional hazards regression were performed to analyze survival data. Variables with a P value <.2 in univariate analysis were used in the multivariate analysis. A P value <.05 was considered to denote statistical significance. All statistical analyses were performed with STATA 13.1 (College Station, TX, USA).

RESULTS

Baseline Characteristics of Patients With NTM-PD

The study cohort comprised 421 patients with NTM-PD. Their median age (IQR) was 64 (57–73) years, and 271 (64.4%) were women. Noncavitary NTM-PD was diagnosed in 329 patients, with the remaining 92 having at least 1 cavity at the time of diagnosis. The median diameter of the cavities (IQR) was 1.8 (1.2–2.8) cm; 53 patients (57.6%) had a single cavity. The median size (rounded up to 2 cm) was used for further analysis, and 44 out of 92 patients had cavities >2 cm.

A higher proportion of patients with >2-cm-sized cavities (56.8%) had a history of pulmonary tuberculosis (TB), compared with those with ≤2-cm-sized cavities (45.8%) or no cavities (36.2%). Chronic obstructive pulmonary disease was also most common in patients with >2-cm-sized cavities (18.2%). Eleven out of 48 patients with ≤2-cm-sized cavities (22.9%) and 32 out of 44 patients with >2-cm-sized cavities (72.7%) were classified as FC form.

While sputum smear positivity was 17.3% and 18.8% in patients without cavities and with ≤2-cm-sized cavities, respectively, 40.9% with >2-cm-sized cavities had positive sputum smears (P = .002). Erythrocyte sedimentation rate was also highest in the patients with >2-cm-sized cavities (36 mm/h),

followed by patients with ≤2-cm-sized cavities (25 mm/h) and those without cavities (19 mm/h), respectively. Further, the initial lung function and the distribution of NTM species and macrolide susceptibility did not differ between these 3 groups (Table 1).

Clinical Course of NTM-PD According to the Size of Cavities

During a median follow-up (IQR) of 49 (31–70) months, 239 patients (211 with noncavitary and 28 with cavitary NTM-PD) were managed by watchful waiting and required no treatment. Of these patients, a higher proportion had noncavitary (64.1%) than cavitary NTM-PD (30.4%; $P < .001$). Sixty-six of the 211 (31.3%) patients with noncavitary NTM-PD being managed by watchful waiting achieved culture conversion without treatment, as did 12 of the 28 (42.9%) patients with cavitary NTM-PD (8 patients with cavities ≤2 cm and 4 patients with cavities >2 cm; $P = .396$) (Table 2).

During the study period, 118 (35.9%) of the 329 patients with noncavitary NTM-PD and 64 (69.6%) of the 92 with cavitary NTM-PD received antibiotic treatment. When patients were classified according to cavity size, those with cavities >2 cm (75.0%) were the most likely to require antibiotic treatment, followed by patients with cavities ≤2 cm (64.6%) and patients without cavities (35.9%; $P < .001$). Clinical courses according to NTM species (MAC and *M. abscessus* complex) are provided in Supplementary Table 1.

The proportion of patients who achieved microbiological cure was the lowest among patients with cavities >2 cm (36.4%), followed by those with cavities ≤2 cm (48.4%) and those without cavities (60.2%; $P = .045$). Finally, cavities >2 cm (adjusted odds ratio, 0.41; 95% CI, 0.17–0.96) were inversely associated with microbiological cure according to multivariable logistic regression. However, small cavities (≤2 cm) ($P = .265$) did not affect treatment outcomes (Table 3). The complete results are shown in Supplementary Table 2. Factors associated with the microbiological cure according to NTM species (MAC and *M. abscessus* complex) are provided in Supplementary Table 3 and Supplementary Table 4.

Factors Associated With Mortality in Patients With NTM-PD

During the study period, 32 of 421 (7.6%) patients died, comprising 21 of 329 (6.4%) with noncavitary and 11 of 92 (12.0%) with cavitary NTM-PD. According to the log-rank test, there was a significant difference in mortality between patients with cavities >2 cm and patients with noncavitary NTM-PD ($P = .003$). However, there was no difference in mortality between patients with cavities ≤2 cm and patients with noncavitary NTM-PD ($P = .897$) (Figure 1). According to multivariable Cox proportional hazards regression analysis, patients with cavities >2 cm had a higher risk of death (adjusted hazard ratio, 2.52; 95% CI, 1.09–5.84) than did patients with noncavitary NTM-PD (Table 4). The complete results are shown in Supplementary

Table 1. Baseline Characteristics of 421 Patients With Nontuberculous Mycobacterial Pulmonary Disease According to the Presence of a Cavity

	Patients Without Cavities (n = 329)	Patients With ≤2-cm-Sized Cavities (n = 48)[a]	Patients With >2-cm-Sized Cavities (n = 44)	*P* Value
Age, median (IQR), y	65 (58–73)	66 (55–72)	62 (53–71)	.114
Sex, female, No. (%)	216 (65.7)	35 (72.9)	20 (45.5)	.016
BMI, median (IQR), kg/m^2	21.1 (19.6–22.6)	20.0 (18.6–21.9)	20.1 (18.6–21.6)	.006
Former or current smoker, No. (%)	79 (24.0)	20 (20.9)	12 (27.3)	.774
History of pulmonary tuberculosis, No. (%)	119 (36.2)	22 (45.8)	25 (56.8)	.021
ESR, median (IQR), mm/h	19 (11–31)	25 (16–42)	36 (19–49)	<.001
Spirometry				
FEV1, median (IQR), L	2.17 (1.84–2.54)	1.99 (1.75–2.28)	2.14 (1.74–2.47)	.062
FVC, median (IQR), L	2.88 (2.44–3.37)	2.65 (2.32–3.21)	2.86 (2.37–3.39)	.154
FEV1/FVC, median (IQR), %	76 (71–82)	77 (71–80)	78 (70–82)	.880
Comorbidities, No. (%)				
Diabetes mellitus	21 (6.4)	4 (8.3)	7 (15.9)	.089
COPD	24 (7.3)	2 (4.2)	8 (18.2)	.039
Malignancy	18 (5.5)	4 (8.3)	2 (4.5)	.653
Sputum smear positivity, No. (%)	57 (17.3)	9 (18.8)	18 (40.9)	.002
Causative organism, No. (%)				.295
M. avium complex	237 (72.0)	30 (62.5)	32 (72.7)	
M. abscessus complex	60 (18.2)	15 (31.3)	7 (15.9)	
Others	32 (9.8)	3 (6.2)	5 (11.4)	
Macrolide susceptibility				.386
Susceptible	299 (90.9)	41 (85.4)	41 (93.2)	
Resistant/inducible resistant	30 (9.1)	7 (14.6)	3 (6.8)	

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range.

[a]The median diameter of the cavities (IQR) was 1.8 (1.2–2.8) cm, and 53 patients (57.6%) had a single cavity. The median size (rounded up to 2 cm) was used for the comparison.

Table 2. Clinical Outcomes of 421 Patients With Nontuberculous Mycobacterial Pulmonary Disease

	Patients Without Cavity (n = 329)	Patients With ≤2-cm-Sized Cavities (n = 48)	Patients With >2-cm-Sized Cavities (n = 44)	*P* Value
Follow-up duration, median (IQR), mo	49 (31–71)	41 (24–62)	51 (34–76)	.212
Observed without treatment, No. (%)	211/329 (64.1)	17/48 (35.4)	11/44 (25.0)	<.001
Spontaneous conversion in patients without treatment, No. (%)[a]	66/211 (31.3)	8/17 (47.1)	4/11 (36.4)	.396
Treated with antibiotics, No. (%)	118/329 (35.9)	31/48 (64.6)	33/44 (75.0)	<.001
Microbiological cure, No. (%)[b]	71/118 (60.2)	15/31 (48.4)	12/33 (36.4)	.045

Abbreviation: IQR, interquartile range.

The denominators were patients who were observed without treatment[a] and patients who were treated with antibiotics,[b] respectively.

Table 5. Factors associated with mortality according to NTM species (MAC and *M. abscessus* complex) are provided in Supplementary Tables 6 and 7.

DISCUSSION

In this study, we analyzed the clinical course of 421 patients with NTM-PD according to the size of cavities at the time of diagnosis. We found that patients with cavities >2 cm had worse treatment outcomes than did patients with noncavitary NTM-PD. In contrast, patients with cavities ≤2 cm had treatment outcomes that were comparable to those of patients with noncavitary NTM-PD. Our results support the need for planning treatment according to the radiographic features of cavities in patients with NTM-PD.

The presence of cavities in patients with NTM-PD has been recognized as an indicator of poor prognosis [9]. Cavities are associated with unfavorable treatment outcomes, including higher mortality [20, 21]. Cavity formation has been found to be more common in patients who do not respond to treatment than in those with culture conversion [21]. Additionally, the presence of a cavity increases the risk of all-cause mortality in patients with *Mycobacterium avium* complex pulmonary disease (MAC-PD) [20]. Moreover, large cavities are strongly associated with disease progression [12]. However, the impact of detailed differentiation based on radiographic findings has not been reported.

Table 3. Factors Associated With Microbiological Cure in Patients With Nontuberculous Mycobacterial Pulmonary Disease

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
Age, y	0.98 (0.95–1.00)	.162	0.97 (0.03–0.99)	.037
FEV1, L	0.62 (0.35–1.11)	.107	0.06 (0.01–2.89)	.152
Sputum smear positivity	0.43 (0.22–0.85))	.014	0.42 (0.21–0.85)	.016
Size of cavity				
Absence of cavity	Reference			
≤2 cm sized	0.62 (0.28–1.37)	.240	0.61 (0.27–1.44)	.265
>2 cm sized	0.38 (0.17–0.84)	.017	0.41 (0.17–0.96)	.040

Abbreviations: FEV1, forced expiratory volume in 1 second; OR, odds ratio.

NTM-PD has been classified into NB and FC types [10]. However, it is sometimes difficult to clearly differentiate between these types. Bronchiectasis coexists with cavities in most patients with NTM-PD [22]. Moreover, centrilobular nodules have been observed in most patients with cavitary NTM-PD [23]. Pathologic findings on examination of specimens from patients with NTM-PD has suggested that peri-bronchial nodules evolve into cavities [22]. Another cohort study found that cavities develop over time, even in the NB form of MAC-PD [24]. If we assume that bronchiectasis and cavities are on the same disease spectrum, NTM-PD could be differentiated initially by the presence of 1 or more cavities and the extent of those cavities. In our study, we classified NTM-PD according to the presence and size of cavities.

Patients with cavitary NTM-PD more frequently received antibiotic treatment than those without cavities. When the cavity was >2 cm in diameter, the treatment outcome was unfavorable. The mortality rate was also higher in patients with cavities >2 cm. However, the cavities ≤2 cm did not affect clinical outcomes. In our study, cavities only had an impact on the prognosis of patients with NTM-PD when they were >2 cm.

Cavitation in the lung results from a number of pathological processes, including suppurative, caseous, and ischemic necrosis

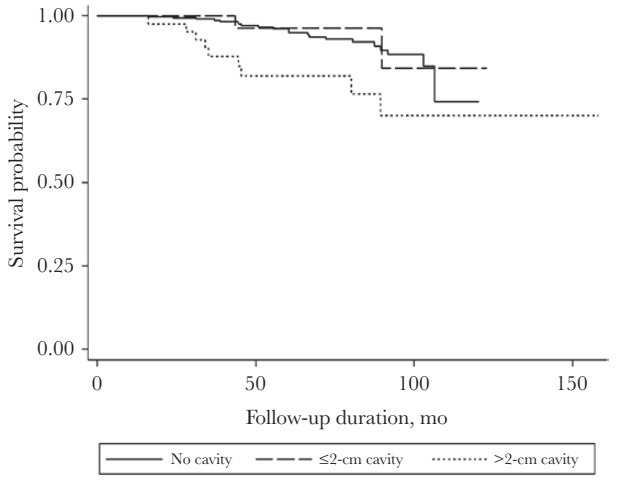

Figure 1. Kaplan-Meier curve according to the presence and size of cavities.

Table 4. Factors Associated With Mortality in Patients With Nontuberculous Mycobacterial Pulmonary Disease

	Univariate Analysis		Multivariate Analysis	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age, y	1.06 (1.02–1.10)	.001	1.03 (0.99–1.08)	.112
Sex, male	3.91 (1.80–8.47)	.001	4.12 (1.49–11.4)	.006
BMI, kg/m^2	0.86 (0.75–0.99)	.030	0.88 (0.75–1.03)	.117
ESR, mm/h	1.03 (1.02–1.04)	<.001	1.02 (1.01–1.04)	.034
FEV1, L	0.68 (0.37–1.22)	.196	0.80 (0.35–1.79)	.581
Diabetes mellitus	4.23 (1.89–9.44)	<.001	2.99 (1.15–7.82)	.025
COPD	2.87 (1.33–6.17)	.007	0.63 (0.23–1.76)	.378
Malignancy	2.50 (0.96–6.52)	.062	5.06 (1.66–15.4)	.004
Sputum smear positivity	1.82 (0.84–3.94)	.128	1.87 (0.78–4.49)	.159
Resistance or inducible resistance to macrolide	2.86 (1.24–6.59)	.014	3.26 (1.33–7.99)	.010
Size of cavity				
Absence of cavity	Reference			
≤2 cm sized	0.89 (0.21–3.81)	.879	1.14 (0.26–5.03)	.856
>2 cm sized	3.09 (1.40–6.79)	.005	2.52 (1.09–5.84)	.031

Abbreviations: BMI, body mass index; COPD, chronic obstructive pulmonary disease; ESR, erythrocyte sedimentation rate; FEV1, forced expiratory volume in 1 second; HR, hazard ratio.

[25]. In NTM-PD, cavitation occurs in patients with more extensive disease, and the cavities contain numerous organisms [25, 26]. Drugs penetrate cavities poorly, and subtherapeutic drug concentrations in these lesions can lead to acquired drug resistance [27]. These factors explain the worse outcomes of patients with NTM-PD with cavities >2 cm.

Interestingly, in our study, a small cavity (<2 cm) was not associated with poor prognosis. Large cavities were more prevalent in progressive cavitary NTM-PD [12]. Thus, the favorable outcomes of small cavities in patients with NTM-PD may be attributable to slow disease progression. Another possible explanation is that once such cavities have been detected, more careful monitoring and aggressive treatment are adopted, resulting in favorable outcomes given that such patients respond better to treatment than do those with larger cavities.

Our findings suggest the need for more detailed planning of treatment for cavitary NTM-PD according to the characteristics of the cavities. Recent guidelines recommend initiation of antibiotic treatment for NTM-PD rather than watchful waiting, especially when sputum smears are positive for acid-fast bacilli or when there is evidence of cavitary lung disease [2]. Parenteral agents are recommended for cavitary disease in patients with MAC-PD [2, 11]. Our results suggest a more complex treatment strategy for patients with cavitary NTM-PD. In patients with >2 cm, immediate and intensive treatment is indicated. If the cavity size is ≤2 cm, whether to treat should be decided on the basis of the overall clinical situation, under the premise that watchful follow-up is guaranteed.

Retrospective studies from South Korea have shown that the condition of about 40% of patients with noncavitary NB NTM-PD remains stable when they are observed without treatment [28, 29]. Spontaneous culture conversion occurs in 35%–50% of untreated patients [28, 29]. In our study, spontaneous conversion was achieved in 12 of 28 patients (42.9%) with cavitary NTM-PD who had been undergoing regular monitoring without initiation of treatment. Thus, when an immediate initiation of treatment is not available, watchful waiting might be a valid management option for patients with small cavities, once close monitoring is ensured.

This study has some limitations. First, the causes of the cavities could not be determined. Although the cavities were suggested to be the manifestation of NTM-PD, we could not completely exclude the possibility of combined fungal infection or other chronic infection [30, 31]. Second, we did not use the classical classification of NB or FC forms in our analysis. In fact, cavities frequently coexist with bronchiectasis, and some of cavities develop from bronchiectatic changes [22]. It is difficult to distinguish between noncavitary NB, cavitary NB, and FC types in some patients. In our study, about a quarter of patients with ≤2-cm-sized cavities and >2-cm-sized cavities were interpreted as FC form and cavitary NB form, respectively. A classification based on size may be easier to use.

CONCLUSIONS

In conclusion, the clinical outcomes of patients with cavitary NTM-PD differ according to the size of cavities. A cavity >2 cm in size in patients with NTM-PD is associated with unfavorable treatment outcomes and higher mortality, whereas cavities ≤2 cm do not affect prognosis. The radiographic features of cavities could help clinicians to decide whether to initiate treatment.

Supplementary Data

Supplementary materials are available at Open Forum Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility

of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. All authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors, agree to be fully responsible for all content, and were involved at all stages of manuscript development. H.R.K. and N.K. designed the study and protocol. H.R.K., E.J.H., and N.K. did the data analysis. H.R.K., J.J.Y., and N.K. wrote the initial draft of the manuscript, and all authors were involved at all stages of critical revision of the manuscript. All the authors read and approved the final manuscript.

Patient consent. Ethics approval was obtained, and consent was waived by the Institutional Review Board of Seoul National University Hospital, which approved the study protocol (IRB No. 2001-047-1092).

References

1. Falkinham JO 3rd. Current epidemiologic trends of the nontuberculous mycobacteria (NTM). Curr Environ Health Rep **2016**; 3:161–7.
2. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: an official ATS/ERS/ESCMID/IDSA clinical practice guideline. Clin Infect Dis **2020**; 71:905–13.
3. Lee H, Myung W, Koh WJ, et al. Epidemiology of nontuberculous mycobacterial infection, South Korea, 2007-2016. Emerg Infect Dis **2019**; 25:569–72.
4. Namkoong H, Kurashima A, Morimoto K, et al. Epidemiology of pulmonary nontuberculous mycobacterial disease, Japan. Emerg Infect Dis **2016**; 22:1116–7.
5. Henkle E, Hedberg K, Schafer S, et al. Population-based incidence of pulmonary nontuberculous mycobacterial disease in Oregon 2007 to 2012. Ann Am Thorac Soc **2015**; 12:642–7.
6. Wagner D, Lipman M, Cooray S, et al. Global epidemiology of NTM disease (except Northern America). In: Griffith DE. *Nontuberculous Mycobacterial Disease*. Cham: Humana Press, Springer; **2019**:163–260.
7. Jhun BW, Moon SM, Jeon K, et al. Prognostic factors associated with long-term mortality in 1445 patients with nontuberculous mycobacterial pulmonary disease: a 15-year follow-up study. Eur Respir J. **2020**; 55: 1900798; doi:10.1183/13993003.00798-2019.
8. Koh W-J, Moon SM, Kim S-Y, et al. Outcomes of *Mycobacterium* avium complex lung disease based on clinical phenotype. Eur Respir J **2017**; 50:1602503.
9. Kim HJ, Kwak N, Hong H, et al. BACES score for predicting mortality in nontuberculous mycobacterial pulmonary disease. Am J Respir Crit Care Med **2021**; 203:230–6.
10. Griffith DE, Aksamit T, Brown-Elliott BA, et al; ATS Mycobacterial Diseases Subcommittee; American Thoracic Society; Infectious Disease Society of America. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med **2007**; 175:367–416.
11. Haworth CS, Banks J, Capstick T, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). Thorax **2017**; 72: ii1–64.
12. Oshitani Y, Kitada S, Edahiro R, et al. Characteristic chest CT findings for progressive cavities in *Mycobacterium avium* complex pulmonary disease: a retrospective cohort study. Respir Res **2020**; 21:10.
13. Kwak N, Kim SA, Choi SM, Lee J, Lee C-H, Yim J-J. Longitudinal changes in health-related quality of life according to clinical course among patients with non-tuberculous mycobacterial pulmonary disease: a prospective cohort study. BMC Pulm Med **2020**; 20:126.
14. Park J, Cho J, Lee CH, et al. Progression and treatment outcomes of lung disease caused by *Mycobacterium abscessus* and *Mycobacterium massiliense*. Clin Infect Dis **2017**; 64:301–8.
15. Clinical and Laboratory Standards Institute. Interpretive Criteria for Identification of Bacteria and Fungi by DNA Target Sequencing: Approved Guideline, MM18-A. Wayne, PA: CLSI; **2008**.
16. Kim BJ, Lee SH, Lyu MA, et al. Identification of mycobacterial species by comparative sequence analysis of the RNA polymerase gene (rpoB). J Clin Microbiol **1999**; 37:1714–20.
17. Ben Salah I, Adékambi T, Raoult D, Drancourt M. rpoB sequence-based identification of *Mycobacterium avium* complex species. Microbiology (Reading) **2008**; 154:3715–23.
18. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology **2008**; 246:697–722.
19. van Ingen J, Aksamit T, Andrejak C, et al. Treatment outcome definitions in nontuberculous mycobacterial pulmonary disease: an NTM-NET consensus statement. Eur Respir J **2018**; 51:1800170.
20. Hayashi M, Takayanagi N, Kanauchi T, et al. Prognostic factors of 634 HIV-negative patients with *Mycobacterium avium* complex lung disease. Am J Respir Crit Care Med **2012**; 185:575–83.
21. Kuroishi S, Nakamura Y, Hayakawa H, et al. *Mycobacterium avium* complex disease: prognostic implication of high-resolution computed tomography findings. Eur Respir J **2008**; 32:147–52.
22. Kim TS, Koh WJ, Han J, et al. Hypothesis on the evolution of cavitary lesions in nontuberculous mycobacterial pulmonary infection: thin-section CT and histopathologic correlation. AJR Am J Roentgenol **2005**; 184:1247–52.
23. Kim C, Park SH, Oh SY, et al. Comparison of chest CT findings in nontuberculous mycobacterial diseases vs. *Mycobacterium tuberculosis* lung disease in HIV-negative patients with cavities. PLoS One **2017**; 12:e0174240.
24. Lee G, Lee KS, Moon JW, et al. Nodular bronchiectatic *Mycobacterium avium* complex pulmonary disease. Natural course on serial computed tomographic scans. Ann Am Thorac Soc **2013**; 10:299–306.
25. Gadkowski LB, Stout JE. Cavitary pulmonary disease. Clin Microbiol Rev **2008**; 21:305–33, table of contents.
26. Gafoor K, Patel S, Girvin F, et al. Cavitary lung diseases: a clinical-radiologic algorithmic approach. Chest **2018**; 153:1443–65.
27. Strydom N, Gupta SV, Fox WS, et al. Tuberculosis drugs' distribution and emergence of resistance in patient's lung lesions: a mechanistic model and tool for regimen and dose optimization. PLoS Med **2019**; 16:e1002773.
28. Kwon BS, Lee JH, Koh Y, et al. The natural history of non-cavitary nodular bronchiectatic *Mycobacterium avium* complex lung disease. Respir Med **2019**; 150:45–50.
29. Moon SM, Jhun BW, Baek SY, et al. Long-term natural history of non-cavitary nodular bronchiectatic nontuberculous mycobacterial pulmonary disease. Respir Med **2019**; 151:1–7.
30. Jhun BW, Jeon K, Eom JS, et al. Clinical characteristics and treatment outcomes of chronic pulmonary aspergillosis. Med Mycol **2013**; 51:811–7.
31. Takeda K, Imamura Y, Takazono T, et al. The risk factors for developing of chronic pulmonary aspergillosis in nontuberculous mycobacteria patients and clinical characteristics and outcomes in chronic pulmonary aspergillosis patients coinfected with nontuberculous mycobacteria. Med Mycol **2016**; 54:120–7.