Mortality after Respiratory Isolation of Nontuberculous Mycobacteria

A Comparison of Patients Who Did and Did Not Meet Disease Criteria

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Abstract

Rationale: The mortality of patients with respiratory tract isolates of nontuberculous mycobacteria (NTM) and their risk factors for death are not well described.

Objectives: To determine age-adjusted mortality rates for patients with respiratory NTM isolates and their causes of death and to examine whether American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) diagnostic criteria identify those at higher risk of death after NTM isolation.

Methods: We linked vital records registries with a previously identified Oregon population-based cohort of patients with NTM respiratory isolation. We excluded patients with *Mycobacterium gordonae* (n = 33) and those who died (n = 21) at the time of first isolation. We calculated 5-year age-adjusted mortality rates. We used Kaplan-Meier and Cox proportional hazards analysis to examine the association of ATS/IDSA criteria and other risk factors with death.

Results: Of 368 subjects with respiratory NTM isolates in 2005–2006, 316 were included in the survival analysis. Most (84%) of their cultures isolated *Mycobacterium avium* complex. 35.1% died in the 5 years following respiratory isolation. Five-year age-adjusted mortality rates were slightly higher for those meeting (28.7/1,000) versus not meeting (23.4/1,000) ATS/IDSA criteria. In multivariate analysis, older age (adjusted hazard ratio [aHR], 1.06; 95% confidence interval [CI], 1.04–1.07) and lung cancer (aHR, 2.77; 95% CI, 1.51–5.07) were associated with an increased risk of death. A trend was noted between meeting ATS/IDSA criteria and subsequent death (aHR, 1.37; 95% CI, 0.95–1.97). Among cases, male sex, older age, and immunosuppressive therapy use were independent risk factors for death.

Conclusions: In the State of Oregon, patients with NTM respiratory isolates have high mortality, regardless of whether they meet ATS/IDSA criteria for pulmonary NTM disease. Most patients die as a result of causes other than NTM infection.

Keywords: nontuberculous mycobacteria; natural history; mortality

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Pulmonary nontuberculous mycobacterial disease is increasingly common, particularly in those over age 65 years (1). Growth of nontuberculous mycobacteria (NTM) in a respiratory culture can reflect not only clinical disease but also colonization, early airway infection, or specimen contamination. Diagnosis of clinical disease is made using criteria developed by the American Thoracic Society (ATS) and the Infectious Diseases Society of America (IDSA) that are based largely on expert opinion (2). These criteria mandate that patients have characteristic radiologic and microbiologic evidence of NTM, including either (1) one isolate from a bronchoalveolar lavage or pulmonary tissue or (2) at least two sputum isolates.

It is unclear if patients who do or do not meet disease criteria have different clinical outcomes, because the natural history of NTM disease has been described in only a few population-based studies to date (3–7). The risk factors for death after respiratory NTM isolation are not well understood. Descriptions of mortality in patients with NTM disease have been limited largely to single-center studies (8–11). A small number of population-based studies have suggested that mortality may be increased (1, 12, 13). However, the researchers in these studies lacked access to clinical and/or microbiologic records for all participants.

In 2009, we conducted a public health surveillance project using statewide laboratory data to identify a population-based cohort of individuals with respiratory isolation of NTM during 2005–2006 (5, 14). We observed that approximately 50% of patients with at least one respiratory isolate failed to meet the ATS/IDSA case definition in those 2 years. Further, we identified that those meeting and those not meeting disease criteria were similar with regard to age and medical comorbidities such as chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, and lung cancer (14).

Given the lack of population-based data on the natural history of respiratory NTM isolation, including mortality and risk factors for subsequent death, we undertook a retrospective natural history study using our previously identified population-based cohort of patients. We evaluated overall mortality rates and whether the ATS/IDSA disease criteria were predictive of greater mortality among those with respiratory

NTM isolation (15, 16). We have described long-term management and other outcomes in a separate publication (17).

Methods

Primary Analysis

Study population and time period. The Oregon Health Authority conducted a statewide laboratory surveillance project that identified 807 Oregon residents with a positive respiratory NTM culture in 2005–2006 (5). For a subsequent project, a geographic subset was identified that comprised those residing in the Portland, Oregon, tricity region ($n = 407$) and receiving medical care in the tricity region ($n = 58$) or residing in Marion County (Salem, OR [$n = 30$]). A total of 371 (75%) individuals in this subset had medical records from the major healthcare

systems in the region available for review during the baseline period, defined as the date of isolation to December 31, 2006 (Figure 1) (14). For the present study, we excluded 3 individuals who were younger than 18 years of age at the time of first pulmonary respiratory isolate, leaving 368 eligible for inclusion.

Clinical data. All clinical records from the 2005–2006 baseline period were previously reviewed and described (14). Abstracted data included date of birth, sex, race, comorbid conditions, and immunosuppressive medication use (methotrexate, tacrolimus, cyclosporine, azathioprine, anticancer chemotherapy, biologic therapies, or oral corticosteroids). NTM disease characteristics included radiographic findings as reported by the radiologist based on x-rays or computed tomographic scans (72% had computed tomographic scan reports available for

Figure 1. Oregon nontuberculous mycobacteria (NTM) cohort identification and study population flow diagram.

review), treatment start date and antibiotic type, and all microbiologic acid-fast bacilli culture results and dates from the baseline period.

Disease classification. We previously categorized subjects as meeting or not meeting the ATS/IDSA criteria during the baseline period. To meet the criteria, there must have been radiographic findings (i.e., infiltrate, nodule, or cavity), two sputum or a single bronchoalveolar lavage or bronchoscopy culture, and symptoms consistent with disease (2).

Covariates. We calculated age at the time of first isolation. We identified other variables of interest for our model *a priori* on the basis of known and potential risk factors for NTM isolation and/or death and included comorbidities such as COPD and lung cancer as well as use of immunosuppressive medications. NTM species were categorized as *Mycobacterium gordonae*, *Mycobacterium avium complex* (MAC), or “other,” which included *Mycobacterium abscessus* and *Mycobacterium fortuitum*, species for which there are only one or two identified, as well as those not identified to the species level. Treatment was categorized as “yes” if treatment was started prior to the end of the baseline period. We defined treatment initiation as a macrolide plus at least one other antibiotic (i.e., ethambutol, a rifamycin, or a fluoroquinolone). Treatment for MAC per ATS/IDSA 2007 criteria was defined as starting a macrolide plus ethambutol and a rifamycin (2).

Outcome. We used the Link Plus program (Centers for Disease Control and Prevention National Program of Cancer Registries, Atlanta, GA) to perform probabilistic matching of the cohort with the Oregon state vital records through December 31, 2012, using name and birth date (18). Vital records data included the date of death and the primary cause of death as well as up to six contributing causes of death. We searched online for deaths outside Oregon and identified additional deaths reported by family members during follow-up contact attempts. An additional search for any cohort members who died was performed using LexisNexis Accurint (RELX Group, New York, NY), which enables searches of publicly available records, including obituaries. If no record of death was found, we assumed the individual was still alive at

the end of our follow-up period. For deaths outside Oregon, we did not have access to state vital records registries to determine cause of death.

Statistical Analysis

We excluded those who died at the time (≤ 30 d) of their first NTM isolation. None of these had a reported cause of death due to NTM disease. We also excluded those who isolated only nonpathogenic NTM (*M. gordonae*). We then used the 2000 U.S. standard to calculate 5-year age-adjusted mortality rates (19). We calculated the expected 5-year cumulative probability of death for the cohort using the National Center for Health Statistics 1-year probabilities of death in 2005 for a hypothetical cohort of the general population with the same age and sex distribution (20).

To evaluate risk factors for death, we used univariate and multivariate Cox proportional hazards regression analysis and examined Kaplan-Meier survival curves. All covariates with a *P* value less than 0.20 were included in the multivariate model. In addition, we chose *a priori* to include age and sex in all multivariate models, given their likely strong influence upon survival. Meeting ATS/IDSA criteria or not was included in all models because our primary aim was to explore the association between these criteria and risk of death. The proportional hazards assumption was tested using graphical inspection and Schoenfeld residuals. Tests were considered statistically significant at a two-sided *P* value less than 0.05. Statistical analyses were performed using Stata 13 software (StataCorp, College Station, TX). We did not control for race, given the large number of subjects with missing information. This study was approved by the institutional review boards of the Oregon Health Authority, the University of Rochester, and Oregon Health & Science University, as well as by the sponsor (the National Institute of Allergy and Infectious Diseases).

Sensitivity Analyses

We performed a sensitivity analysis in a subset of individuals, specifically those who isolated MAC only. Although this comprised the majority of patients, we evaluated survival and risk factors for death in this subgroup to evaluate whether

they were similar to the cohort as a whole. In addition, we performed our analysis in a subset that did not have cancer as a cause of death.

Results

In 2005–2006, 368 adults isolated NTM in at least one respiratory specimen. Their average age was 64.6 (SD, ± 15.7) years (Table 1). Slightly more than half were female. One hundred eighty-nine (51%) met ATS/IDSA criteria. Forty-four percent were current or former smokers. The most common NTM species isolated was MAC ($n = 282$ [77%]). Exclusion of subjects who survived less than 1 month ($n = 21$) or isolated *M. gordonae* ($n = 33$) did not change the frequency of comorbidities and other cohort characteristics.

More females than males met ATS/IDSA criteria in the baseline period, but frequencies of comorbidities such as COPD and use of immunosuppressive medications were similar (Table 1). Thirty-one percent of those who met ATS/IDSA criteria initiated therapy in the baseline period, whereas only eight (6%) individuals who lacked criteria initiated therapy. Among 56 patients with MAC who started treatment, 53 (94.6%) were treated according to the 2007 ATS/IDSA guidelines (2). Imaging findings such as bronchiectasis or cavitary disease were more common among those who met the ATS/IDSA criteria. Among those who failed to meet the criteria, 57% failed to meet the microbiologic criteria only and 10% failed to meet the radiologic criteria only, whereas 26% failed to meet both.

Mortality Rates and Causes of Death

The expected cumulative 5-year mortality for this cohort based on age and sex was estimated to be 16.8%. Twenty-one died within 30 days of isolation. In the remaining cohort, the actual mortality was 35.1% (111 of 316) at 5 years of follow-up. Thirty-seven percent (65 of 178) and 33.3% (46 of 138) of those who did and did not meet ATS/IDSA criteria, respectively, were dead within 5 years of follow-up. The 5-year age-adjusted mortality rate was 24.8 per 1,000 population (95% confidence interval [CI], 15.8–33.8/1,000). The mortality rates were similar for those who met the disease criteria versus those who did not, with 5-year age-adjusted

Table 1. Characteristics of patients who isolated nontuberculous mycobacteria from respiratory specimens, northwestern Oregon, 2005–2006

	Original Cohort (n = 368), n (%)	Primary Analytic Cohort* (n = 316), n (%)	Does Not Meet ATS/IDSA Criteria* (n = 138), n (%)	Meets ATS/IDSA Criteria* (n = 178), n (%)	MAC Isolation† (n = 266), n (%)
Age at isolation‡, yr, mean (SD)	64.6 (15.7)	64.5 (15.9)	62.4 (17.3)	66.1 (14.6)	64.7 (16.0)
Sex					
Female	194 (53)	178 (56)	71 (51)	107 (60)	146 (55)
Male	174 (47)	138 (44)	67 (49)	71 (40)	120 (45)
Race‡					
White	172 (47)	156 (49)	56 (41)	100 (56)	133 (50)
Black	5 (1)	5 (2)	4 (3)	1 (1)	5 (2)
Other§	12 (3)	12 (4)	4 (3)	8 (4)	9 (3)
Unknown	179 (49)	143 (45)	74 (54)	69 (39)	119 (45)
Smoker (current or former)	162 (44)	141 (45)	67 (49)	74 (42)	119 (45)
COPD	105 (29)	91 (29)	38 (28)	53 (30)	73 (27)
Diabetes	29 (8)	24 (8)	11 (8)	13 (7)	17 (6)
HIV/AIDS	13 (4)	10 (3)	5 (4)	5 (3)	9 (3)
Cystic fibrosis	4 (1)	4 (1)	3 (2)	1 (1)	2 (1)
Bronchiectasis‡	100 (27)	93 (29)	29 (21)	64 (36)	76 (29)
Lung cancer	26 (7)	17 (5)	9 (7)	8 (4)	12 (5)
Hemoptysis	69 (19)	58 (18)	22 (16)	36 (20)	50 (19)
Cavity‡	63 (17)	57 (18)	12 (9)	45 (25)	50 (19)
Immunosuppressive medications	73 (20)	68 (22)	29 (21)	39 (22)	55 (21)
Species‡					
<i>Mycobacterium gordonae</i>	33 (9)	N/A	N/A	N/A	N/A
MAC	282 (77)	266 (84)	107 (78)	159 (89)	N/A
<i>Mycobacterium abscessus</i>	11 (3)	9 (3)	3 (2)	6 (3)	N/A
Other	42 (11)	41 (13)	28 (20)	13 (7)	N/A
ATS/IDSA disease criteria					
Yes	189 (51)	178 (56)	N/A	N/A	159 (60)
No	146 (40)	138 (44)			107 (40)
<i>Mycobacterium gordonae</i>	33 (9)	N/A			N/A
Treated††	64 (17)	64 (20)	8 (6)	56 (31)	56 (21)
Died during follow-up (through December 31, 2012)	170 (46)	136 (43)	56 (41)	80 (45)	113 (42)

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; COPD = chronic obstructive pulmonary disease; MAC = *Mycobacterium avium* complex; N/A = not applicable.

*Excludes *Mycobacterium gordonae* isolation only (n = 33) and those who died within 30 days (n = 21).

†Excludes subjects who died within 30 days (n = 21).

‡Significant difference ($P < 0.05$) between those who did and did not meet ATS/IDSA criteria. Chi-square, Fisher's exact, and t tests were used as appropriate.

§Asian and American Indian.

||Includes methotrexate, tacrolimus, cyclosporine, azathioprine, anticancer chemotherapy, biologic therapies, and oral corticosteroids.

¶Other species: *Mycobacterium fortuitum* (n = 7) and n = 1–2 each of *Mycobacterium goodii*, *Mycobacterium kansasii*, *Mycobacterium mucogenicum*, *Mycobacterium simiae* complex, and *Mycobacterium xenopi*, as well as those not identified to the species level.

††Treatment started prior to 2007.

rates of 28.7 per 1,000 population (95% CI, 11.0–46.5/1,000) versus 23.4 per 1,000 population (95% CI, 14.0–32.8/1,000), respectively. The median life expectancies were also similar: 2.0 years (interquartile range [IQR], 0.61–3.92) in those who met the criteria versus 2.6 years (IQR, 0.66–4.22) in those who did not meet the criteria.

Cause of death was available for the 127 deceased patients matched to the Oregon vital records registry. When stratified by ATS/IDSA criteria, cancer

(from all sites) was the most commonly reported primary cause of death in both groups. However, COPD was more commonly reported as a cause of death among those who did not meet the criteria, whereas other lung diseases, such as interstitial lung disease and bronchiectasis, were more commonly reported in those meeting the criteria. All patients who had mycobacterial disease listed as a primary cause of death (n = 5 [4%]) met ATS/IDSA disease criteria (Table 2).

Association between ATS/IDSA Criteria and Survival

In univariate analysis, age at isolation, current or former smoking history, lung cancer, COPD, and immunosuppressive medications were significantly associated with death (Table 3). Meeting ATS/IDSA criteria (Figure 2) in the baseline period was not statistically significantly associated with death. A diagnosis of bronchiectasis in patients with NTM infection was associated with better survival but was not significant. In multivariate analysis (Table 3)

Table 2. Reported causes of death in patients with isolated nontuberculous mycobacteria from respiratory specimens, northwestern Oregon, 2005–2006 (n = 127)

Primary Cause of Death	Does Not Meet ATS/IDSA Criteria (n = 51), n (%)	Meets ATS/IDSA Criteria (n = 76), n (%)
COPD/emphysema	11 (22)	10 (13)
Cancer (nonlung)	8 (16)	12 (16)
Other lung diseases	4 (8)	14 (18)
Cardiovascular/vascular	6 (12)	10 (13)
Lung cancer	6 (12)	8 (11)
Infections (nonpulmonary)	3 (6)	4 (5)
Autoimmune	1 (2)	5 (6)
Lung infections	2 (4)	4 (5)
Mycobacterial	0	5 (6)
Endocrine/nutrition	4 (8)	0
Neurologic/psychiatric	3 (6)	1 (1)
Other	1 (2)	2 (3)
Renal	1 (2)	1 (1)
Gastrointestinal	1 (2)	0

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; COPD = chronic obstructive pulmonary disease.

Excludes *Mycobacterium gordonae* isolation only and those who died within 30 days. Total number is 136, but cause of death was known in 127.

controlling for these factors, there was a trend toward meeting ATS/IDSA disease criteria and subsequent death (adjusted hazard ratio [aHR], 1.37; 95% CI, 0.95–1.97).

Risk Factors for Death among Those Meeting ATS/IDSA Criteria for Pulmonary NTM

We performed a subgroup analysis among those meeting the disease criteria. Among cases, males were more likely to die than females even after controlling for age, COPD, and other factors. In addition, those using immunosuppressive therapy also had a higher risk of death (Table 4).

Sensitivity Analyses

We also performed a survival analysis restricted to only those who isolated MAC (the majority of the cohort) as well as those with a cause of death other than cancer. In these subgroups, we obtained similar findings (data not shown).

Discussion

We followed a population-based cohort of patients with respiratory NTM isolates. Importantly, we observed high rates of death, regardless of whether patients met ATS/IDSA criteria for pulmonary NTM disease. Cancer and chronic underlying pulmonary diseases were the most common causes of death. The ATS/IDSA

disease criteria were associated with a greater likelihood of death; however, this trend was not statistically significant.

Among cases, significant risk factors for death included older age at time of NTM isolation, male sex, and use of immunosuppressive therapy.

Over one-third of patients died in the 5 years post respiratory isolation compared with our calculated expected mortality of 16.8% in a general population of similar age and sex. Comparison with published data of patients with chronic underlying lung disease who lack NTM suggests that our cohort died at similar or higher rates. A study of 245 non-cystic fibrosis bronchiectasis patients from Belgium with a median age of 68 years (IQR, 56–78) demonstrated an overall crude mortality of 20.4% with a median follow-up of 5.18 years (21). In a review, Nishimura and colleagues reported 5-year mortality rates ranging from 40 to 70% with increasing disease severity in studies of patients with COPD (22). The Intermittent Positive Pressure Breathing Trial Group reported a crude 3-year mortality rate of 23% in 985 patient with COPD with an average age of 61 years (± 7.7) (23). Burrows and colleagues found a mortality rate of 34% at 5 years in a group of patients with COPD with an average age of 64.6 years (± 6.7) (24). It is unclear whether isolating NTM or even meeting disease criteria is associated with decreased survival directly or

indirectly as a marker for more severe underlying lung disease.

The most common causes of death in our analysis were cancer and pulmonary diseases in both those who did and did not meet ATS/IDSA criteria. NTM disease was documented as the primary or contributing cause of death in only 5% of patients. The National Center for Health Statistics reported NTM disease as an immediate cause of death from 1999 to 2010 in 2,990 people in the United States. There was a significant increase in NTM-related deaths from 1999 to 2010 ($P < 0.0001$), but after adjustment for age, this increase was not significant (25). Given that our analysis relied on administrative death codes, it is possible that NTM are a contributing cause of death in a larger number of individuals than is readily apparent.

Researchers in other studies have attempted to evaluate whether having pulmonary NTM increases one's risk of death. We frequently discuss with our patients that this disease will potentially decrease their quality of life but is unlikely to shorten life (2). In prior investigations, researchers have evaluated smaller cohorts of patients with NTM disease, groups with specific underlying disease such as HIV, those with lung transplants, and hospitalized patients (8–11) and have not found a significant association with mortality. In a study of 120 patients with positive NTM cultures between 1990 and 1998, there was a nonsignificant difference in median survival time between those who did and did not meet ATS criteria (7.4 yr; 95% CI, 0.2–14.6; vs. 5.3 yr; 95% CI, 3.0–7.6) (11).

Recent evidence derived from a large population-based study in Ontario suggests that NTM isolation or disease increases the risk of death compared with propensity score-matched controls (HR, 1.47; 95% CI, 1.42–1.51) and that NTM disease increases the risk of death compared with those isolating NTM (aHR, 1.23; 95% CI, 1.17–1.28) (13). The main limitation of the Ontario study was the use of microbiologic criteria alone to define NTM disease, which may have lowered the HR because some patients not meeting clinical criteria were included in the “disease” group. In another population-based study, Andréjak and colleagues used hospital discharge data (again lacking detailed clinical and radiologic records) to classify patients as colonized with definite and probable NTM

Table 3. Analysis of risk factors associated with death in patients with isolated nontuberculous mycobacteria from respiratory specimens, northwestern Oregon, 2005–2006 (n = 316)

	Univariate HR (95% CI)	Adjusted HR* (95% CI)
Meets ATS/IDSA disease criteria	1.15 (0.82–1.62)	1.37 (0.95–1.97)
Age at isolation	1.05 (1.04–1.07)[†]	1.06 (1.04–1.07)[†]
Sex		
Female	Reference	Reference
Male	1.04 (0.74–1.46)	1.32 (0.89–1.94)
Smoker (current or former)	1.50 (1.07–2.10)[†]	1.15 (0.77–1.74)
COPD	2.52 (1.79–3.54)[†]	1.47 (0.97–2.23)
Bronchiectasis	0.69 (0.47–1.01)	0.68 (0.44–1.04)
Lung cancer	3.85 (2.17–6.86)[†]	2.77 (1.51–5.07)[†]
Hemoptysis	1.19 (0.79–1.81)	N/A
Cavity	1.16 (0.76–1.77)	N/A
Immunosuppressive medications [‡]	1.73 (1.19–2.51)[†]	1.41 (0.95–2.08)
Species		N/A
MAC	Reference	
Non-MAC	1.10 (0.70–1.72)	
Treated [§]	0.73 (0.47–1.14)	0.80 (0.50–1.30)

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MAC = *Mycobacterium avium* complex; N/A = not applicable (not included in model).

Excludes *Mycobacterium gordonae* isolation only and those who died within 30 days.

*Adjusted for ATS/IDSA criteria, age at isolation, sex, smoking status, COPD, bronchiectasis, lung cancer, immunosuppressive medications, and treatment.

[†]Significant ($P < 0.05$) in boldface type.

[‡]Includes methotrexate, tacrolimus, cyclosporine, azathioprine, anticancer chemotherapy, biologic therapies, and oral corticosteroids.

[§]Treatment started prior to 2007.

disease. Similarly to us, they observed a high 5-year mortality of 40% in patients with definite disease and a small, nonsignificant increase in 5-year mortality compared with colonization (aHR, 1.15; 95% CI, 0.90–1.51) (12).

We also found an increased risk of death in patients with underlying lung disease, though only lung cancer remained significant in multivariable analysis. Similarly, Adjemian and colleagues found that hospitalized patients diagnosed with NTM were more likely to die than patients of similar age lacking a diagnosis and that the odds of death were increased in those with three or more comorbidities (1). Again, this claims-based study lacked access to clinical or microbiologic records, so it is unknown if any patients without the NTM International Classification of Diseases, Ninth Revision, diagnosis code had any respiratory NTM isolates. Further, this study was limited to those who were hospitalized and likely represents patients with more severe or more advanced disease.

Traditionally, two types of NTM disease with potentially different risks of death have been considered: slowly progressive nodular bronchiectatic disease and more rapidly progressive cavitary disease frequently associated with COPD (2, 26–30). Our study appears to support the idea that these subgroups may have different risks of death (Table 3). In multivariate modeling, COPD was associated with higher risk of death, whereas bronchiectasis was associated with a lower risk, although both associations narrowly missed statistical significance. These findings confirm a recent, large, population-based study by Marras and colleagues (13). They reported a lower death rate in patients with pulmonary NTM disease (HR, 0.77; 95% CI, 0.70–0.84) and an increased death rate in patients with COPD (HR, 1.38; 95% CI, 1.29–1.48). In addition, Adjemian and colleagues found in a claims-based study of NTM pulmonary patients older than 65 years of age that those with bronchiectasis were half as likely to die as those without bronchiectasis (odds ratio, 0.5; 95% CI, 0.4–0.6) (1).

It is possible that differences in NTM disease severity could be driving these observed differences. We previously found within this cohort that bronchiectatic patients were less likely to have cavitary pulmonary disease than those with COPD (13). Prior studies have found associations between cavitary disease and mortality, presumably because of a higher burden of NTM organisms and/or structural lung disease (26–28). Researchers in a Japanese study found that cavitary disease was associated with higher mortality in patients with MAC (aHR, 1.82; 95% CI, 1.14–2.89) (26). When we restricted our analysis to those meeting disease criteria in our cohort, we failed to find an association between cavity disease and mortality, although we had a low number of cavitary cases.

Last, among those meeting disease criteria, male sex and the use of immunosuppressive therapy were independent risk factors for death even after controlling for COPD, presence of cavitary disease, age, and other factors. It is possible that the use of immunosuppressive medication promotes progression of NTM or, alternatively, that the use of these therapies could simply be a marker for those with more severe underlying lung disease (31). We have no explanation of why males would die more frequently than females, although this association has also been noted for pulmonary tuberculosis (32) and was seen in prior studies of NTM disease in Denmark and Canada (12, 13).

Limitations

This study has several limitations. It is possible that we missed some deaths in patients who moved out of state; however, such instances would likely be nondifferential in terms of whether such patients met ATS/IDSA criteria. Further, it is unlikely that many deaths were missed, because we used both state vital records and supplemented this with a LexisNexis search to capture deaths, which allowed us to capture deaths that occurred outside Oregon.

It is possible that some patients had isolated NTM prior to 2005 and that the results do not represent incident NTM isolation. However, during the chart

Table 4. Multivariate Cox proportional hazards analysis evaluating risk factors for death in patients who met ATS/IDSA disease criteria for pulmonary nontuberculous mycobacteria disease, northwestern Oregon, 2005–2006 (n = 178)

	Univariate HR (95% CI)	Adjusted HR (95% CI)*
Age at isolation	1.06 (1.04–1.08)[†]	1.07 (1.05–1.10)[†]
Sex		
Female	Reference	Reference
Male	1.45 (0.93–2.25)	1.99 (1.17–3.39)[†]
Smoker (current or former)	1.62 (1.05–2.51)[†]	1.31 (0.74–2.32)
COPD	2.10 (1.35–3.28)[†]	1.28 (0.75–2.19)
Bronchiectasis	0.65 (0.41–1.06)	0.72 (0.43–1.20)
Lung cancer	3.68 (1.59–8.48)[†]	3.95 (1.64–9.53)[†]
Hemoptysis	1.40 (0.84–2.32)	0.88 (0.52–1.50)
Cavity	1.05 (0.64–1.73)	N/A
Immunosuppressive medications [‡]	1.83 (1.13–2.95)[†]	1.87 (1.13–3.11)[†]
Species		N/A
MAC	Reference	
Non-MAC	1.05 (0.53–2.11)	
Treated [§]	0.75 (0.46–1.22)	N/A

Definition of abbreviations: ATS/IDSA = American Thoracic Society/Infectious Diseases Society of America; CI = confidence interval; COPD = chronic obstructive pulmonary disease; HR = hazard ratio; MAC = *Mycobacterium avium* complex; N/A = not applicable (not included in the model). Excludes *Mycobacterium gordonae* isolation only and those who died within 30 days.

*Adjusted for age at isolation, sex, smoking status, COPD, bronchiectasis, lung cancer, hemoptysis, and immunosuppressive medications.

[†]Significant ($P < 0.05$) in boldface type.

[‡]Includes methotrexate, tacrolimus, cyclosporine, azathioprine, anticancer chemotherapy, biologic therapies, and oral corticosteroids.

[§]Treatment started prior to 2007.

reviews, evidence of NTM isolation prior to 2005 was found in only 16 (5%) of 316 in the primary analytic cohort. It is also possible that some patients isolated NTM after the

end of baseline period and later met disease criteria. However, our follow-up chart reviews described in a separate publication showed that only 4 additional patients

met the criteria during the 5–6 years following the baseline period (17).

We were unable to directly compare death rates within our cohort with a control population of similar age within our study and had to rely on published estimates of death among those with similar chronic underlying lung disease. As described in a separate publication, in an estimated 20% of cases, treatment was started after the baseline period and may have contributed to improved survival (17). We were not able to account for this, although for the majority of patients who initiated treatment within the baseline period, there was no impact on survival.

We relied on physician documentation for diagnosis of comorbidities such as COPD and bronchiectasis, and there may have been some misclassification. This was a retrospective study, and the clinical care of patients was not standardized. We are unable to adjust for an individual physician's clinical judgment and how this might have affected the collection of additional sputum cultures or decisions to start therapy. Last, it is possible that the study was underpowered to evaluate whether ATS disease criteria were associated with death, given that our cohort consisted of only several hundred individuals overall.

Figure 2. Kaplan-Meier survival curves showing probability of survival among those who did and did not meet American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) criteria; includes those subjects who survived at least 1 month and with a respiratory nontuberculous mycobacteria isolate other than *Mycobacterium gordonae* (n = 316). The solid line represents subjects who did not meet ATS/IDSA criteria (n = 138), and the dashed line represents subjects who did meet ATS/IDSA criteria (n = 178; hazard ratio, 1.15; 95% confidence interval, 0.82–1.62).

Conclusions

Mortality after respiratory NTM isolation appears to be high within the general population, at least in Oregon, where we conducted this study. Most patients died as a result of causes other than NTM infection. Mortality was higher than expected for age and sex in comparison to the general population and was similar to or higher than published estimates of similarly aged cohorts with COPD or non-cystic fibrosis bronchiectasis reported in the scientific literature. ATS/IDSA pulmonary NTM disease criteria may distinguish patients at higher risk of death than those with isolation but not meeting disease criteria. Among those meeting disease criteria, our study suggests that males and those using immunosuppressive therapy are at higher risk of death. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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