PREDICTORS OF DEATH AT ISOLATION OF NONTUBERCULOUS MYCOBACTERIA IN RESPIRATORY SPECIMENS

By

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CERTIFICATE OF APPROVAL

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Abstract

Context: Clinicians encounter patients who have isolated nontuberculous mycobacteria (NTM) in respiratory cultures more frequently than in prior years. Isolation in a culture can reflect clinical disease (defined by the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) disease criteria) or simply colonization or contamination. Based on current knowledge and guidelines it is sometimes unclear which patients benefit from therapy with antibiotics and how aggressively to treat NTM pulmonary disease. This is in part due to lack of knowledge regarding the long-term morbidity and mortality associated with NTM isolation and/or disease.

Objective: Evaluate whether meeting ATS/IDSA disease criteria for NTM pulmonary disease is associated with death and identify any factors that may modify this association.

Study population: Adults greater than or equal to 18 years who isolated NTM in respiratory specimens during 2005-2006.

Methods: This retrospective cohort study utilized existing data from 367 Oregonians who isolated NTM in 2005-2006. Probabilistic matching was used to determine which cohort members had died between isolation of NTM and December 31, 2012. The primary exposure of interest was ATS/IDSA disease criteria. Primary and contributing causes of death were abstracted from the vital records registry and summarized. Age-adjusted mortality rates were calculated. Logistic regression was used to determine if meeting ATS/IDSA disease criteria was associated with death and also investigated other factors that might have modified

this association including species of NTM, age, comorbidities, and treatment for NTM disease.

Results: Meeting ATS/IDSA disease criteria is not associated with an increased odds of death (OR=1.04, 95% CI: 0.66, 1.66). The most common causes of death in this cohort were pulmonary diseases. Age-adjusted mortality rates were higher in this cohort than published rates for other well-studied pulmonary diseases.

Conclusions: People who isolate NTM in respiratory specimens appear to have higher rates of death than those with other pulmonary diseases. Further studies to evaluate whether NTM therapy decreases morbidity and mortality are needed. ATS/IDSA disease criteria may need to be modified to better predict which patients are at higher risk of adverse events after isolation of NTM and better categorize those who may benefit from treatment.

Background

Nontuberculous mycobacteria

Nontuberculous mycobacteria (NTM) are a group of bacteria that are widely dispersed in the environment. Infection is thought to be acquired from the environment rather than from person-to-person spread (1). Many studies have found NTM in water sources including hot tubs, showerheads, and soil (2-4). NTM are commonly found in municipal water supplies and thus exposure is likely widespread. However the exact mechanisms of environmental transmission have not been elucidated. NTM can cause a variety of disease ranging from skin and soft tissue to pulmonary disease.

NTM disease is being diagnosed more frequently with pulmonary disease the most common manifestation (5-7). A review of Medicare databases that identified NTM disease using ICD-9 codes found between 1997 and 2007, the overall annual prevalence of pulmonary NTM disease increased from 20 to 47 cases/100,000 persons in those over 65 years old (8). Increases were observed in all regions, with the highest rates of disease in the West and Southeast.

There are over 140 different species of NTM (9). Several different species are associated with pulmonary disease including *Mycobacterium (M) kansasii, M xenopi,* Mycobacterium avium-complex (MAC), *M fortuitum*, and *M abscessus*. MAC and *M abscessus* are the most frequently encountered organisms in patients with pulmonary disease in the United States (1, 10, 11). Others such as *M gordonae* are

frequently isolated from respiratory specimens but are not currently thought to be associated with pulmonary disease (12). NTM species are divided into rapid and slow growers based on their growth characteristics in culture media (i.e. growth of colonies in less than or equal to seven days) (13). The most common cause of pulmonary disease, MAC is a slow grower while *M abscessus* is a rapid grower. NTM disease causes a variety of changes in the lung parenchyma ranging from bronchiectasis (destruction and widening of airways) and pulmonary nodules to destructive cavitary disease. *M abscessus* likely causes more severe disease with greater destruction of underlying lung parenchyma (14). Patients infected with *M abscessus* are often younger with more baseline lung disease (15, 16). Some studies have suggested that those infected with MAC have better outcomes (17). Given the different spectrum of disease caused by these organisms as well as the different background characteristics of those infected, it is possible that outcomes are different between species (18).

ATS/IDSA disease criteria

Growth of NTM in a culture may reflect clinical disease but NTM is often a colonizer or contaminant; the bacteria may be present in the lungs or airways but don't cause clinical consequences or symptoms. Thus, the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have developed criteria to help define who actually has NTM pulmonary disease both to aid in treatment and in studying the epidemiology of NTM disease (12). The criteria have 3 components:

1. Pulmonary symptoms typical of NTM disease and exclusion of other diagnoses

2. Chest imaging with cavities, nodules, or infiltrates

3. Culture growth of NTM from one bronchoalveolar lavage, two sputum samples, or one respiratory sample in the setting of granulomatous histopathology from tissue

Factors associated with disease

It is thought that thin, elderly, females with few comorbidities are most commonly infected with NTM. This group often has specific anatomical defects such as chest wall deformities, and it has been speculated that there is some genetic predisposition or immune dysfunction that predisposes this group to developing disease (15, 19-21). Other studies have identified additional factors associated with NTM disease including underlying pulmonary disease such as emphysema, cystic fibrosis, and prior tuberculosis (16, 22). Males have also been shown to develop NTM disease, in particular former smokers with chronic obstructive pulmonary disease (COPD) (23). These males may have a more rapidly progressive disease with cavitary findings on imaging. People who are immunosuppressed are at higher risk of developing NTM disease (24). Studies have consistently shown that older patients more frequently develop NTM disease (6).

Treatment

Treatment is not generally recommended unless a person meets the ATS/IDSA disease criteria. Treatment usually involves at least 3 different antibiotics taken on a daily basis for up to 18-24 months. It is often difficult for clinicians to know who benefits from treatment, and clinicians are often hesitant to start therapy given the

length of therapy and risk of side effects. Common side effects include nausea/vomiting and fatigue. Less common but more serious side effects include renal insufficiency and hearing damage. The adverse effects of delayed therapy are not well understood. For some patients this means advancing lung disease and its associated morbidity and mortality. For other patients delaying therapy most likely means decreased quality of life with persistent daily symptoms of cough and fatigue. While for some patients therapy itself may be associated with a decreased quality of life and other adverse events that may lead to worse outcomes (25).

What predicts outcomes?

It is not clear if meeting the ATS/IDSA disease criteria is associated with patient outcomes, i.e. is a person at higher risk of death after meeting these criteria. Small studies have suggested that these criteria are not associated with death (17). A recently published study has suggested that the ATS/IDSA disease criteria do not have prognostic value. In a study of 120 patients with positive NTM cultures, there was no significant difference in mean survival time between those who did and those who didn't meet ATS/IDSA disease criteria, 7.4 years (95% confidence interval (CI): 0.2-14.6) versus 5.3 years (95% CI: 3.0-7.6) (p=0.15). In this group MAC comprised 61% of isolates in the ATS-positive and 47% in the ATS-negative group (26). Some studies have found that certain radiographic findings are associated with worse outcomes, in particular cavitary disease (27) while bronchiectasis is associated with lower mortality (14). A study in Japan found higher mortality in patients with MAC and cavitary lung disease (hazard ratio (HR)

1.82, 95% CI: 1.14, 2.89) (28). Among lung transplant patients median survival was not different between those with transient NTM colonization and those who never isolated NTM (10). Among HIV patients with *M kansasii,* negative smear microscopy and treatment were associated with improved survival (29).

Death and NTM disease

There are few studies evaluating causes of death in those with NTM disease. A recent study examined cause of death data from the National Center for Health Statistics. From 1999 to 2010, NTM disease was reported as an immediate cause of death in 2990 people in the United States. They found a significant increase in NTM related deaths from 1999-2010 ($p<0.0001$) but after adjustment for age this increase was not significant. COPD, bronchiectasis, HIV, interstitial lung diseases (ILD), and tobacco use were significantly more common in those with NTM related deaths compared to tuberculosis related deaths (30).

Research Questions and Specific Aims

This study examined the association between death and meeting ATS/IDSA disease criteria in a cohort of Oregonians who isolated NTM in 2005-2006. In addition, the mortality rate and causes of death in this group were examined. The results from this study furthered the understanding of the prognostic value of the ATS/IDSA disease criteria. This study can inform the design of future studies to learn more about morbidity and mortality associated with NTM disease.

1. What is the death rate and what are the causes of death after isolation of NTM in respiratory specimens?

Specific Aim 1: Categorize each member of the 2005-2006 cohort as currently alive or deceased and document date of death.

Specific Aim 2: Describe cause of death in 2005-2006 cohort using information from vital records registry.

2. What factors are associated with death in adults who isolated NTM in respiratory specimens?

Specific Aim 3: Use descriptive statistics to describe the age, NTM species isolated, comorbidities, sex, smoking status, and ATS /IDSA disease status of each group (alive vs. dead) and perform univariate analysis to analyze relationship between death and each covariate.

Specific Aim 4: Evaluate the association between ATS/IDSA disease criteria and death and identify factors that may modify this association.

Significance

This study is one of the few to evaluate cause of death in individuals who have isolated NTM in respiratory specimens; a prior study looked only at deaths with NTM disease listed as cause of death. It is possible that deaths may be related to underlying NTM disease even if NTM is not identified as a cause of death via death certificate data. Therefore, it is important to look at death in those known to have isolated NTM, not only in those with NTM as an official cause of death. Given that

clinicians often delay treatment or do not treat patients who may benefit from therapy, more knowledge regarding outcomes of patients who isolate NTM is needed to better inform clinicians. This type of analysis is an initial step in better prognosticating NTM isolation. As the population ages, NTM isolation will be more commonly encountered thus it becomes even more important for clinicians to be able to accurately predict prognosis for these patients.

Methods

Overview

This was a retrospective cohort study that utilized secondary data collected during a study of NTM disease in Oregon. The prior study assembled a cohort of Oregonians who isolated NTM in at least one respiratory specimen during 2005-2006 (5, 11). The current study calculated the death rate and summarized reasons for death in this cohort. In addition, this study examined factors associated with an increased risk of death in people who have isolated NTM in respiratory specimens, in particular if meeting ATS/IDSA disease criteria is associated with an increased risk of death.

Original Data

The original study subjects were identified in 2009 as part of a public health surveillance project. The Oregon State Health Department requested that the microbiology laboratories that process Acid-Fast Bacilli (AFB) cultures (culture method used to isolate NTM) provide information on Oregon residents who isolated

NTM in respiratory specimens during 2005-2006. Information released included name, sex, age at isolation, and species of NTM isolated. All labs provided the requested information. Nine hundred thirty seven subjects were identified. A subset of patients (n=371) receiving care at one of the major medical centers (Oregon Health and Science University (OHSU), Kaiser, Legacy, Providence, or the Veteran's Affairs Hospital) in the Portland metropolitan area or at Salem Hospital was identified. This sample was chosen because of the ability of the study team to access medical records in these locations. Medical record review was done on this subset and further information on comorbidities, symptoms, radiography, and treatment of NTM pulmonary disease was obtained. Based on this record review, subjects were classified as meeting or not meeting ATS/IDSA disease criteria. Comorbidities indentified included underlying pulmonary disease, immunosuppressive disease (including taking immunosuppressive medications), rheumatologic disease, cancer, and diabetes. They were identified based on review of problem lists and provider notes. Smoking status was identified as never or ever smokers.

Selection Criteria

The criteria for the original study included isolation of NTM in a respiratory specimen as indicated by report of the microbiology laboratories. Criteria for this subsequent analysis included: inclusion in original study (i.e. isolation of NTM in respiratory specimens during 2005-2006), inclusion in subset in which medical

record review was performed, and age 18 years or greater. Of the 371 subjects, there were 367 subjects who met the inclusion criteria.

Measurement of Covariates

The covariates of interest, other than date and cause of death, were recorded during the original study during 2009/2010 (Table 1). Theses covariates captured information at the time of isolation (2005-2006), i.e. analysis of the covariates provides a description of factors that would be present at isolation of NTM and thus can allow for analysis of factors present at the time of isolation that could be associated with future outcomes.

Table 1: List of variables for analysis

Measure	Source	Analysis Coding
Dead (outcome)	Vital records	0=alive 1=dead
ATS/IDSA disease criteria (primary exposure)	Medical records	0=no 1=yes
Age at isolation of NTM	Medical records	Age in years (continuous)
Sex	Medical records	0=female 1=male
Bronchiectasis	Medical records	0=no 1=yes
COPD/emphysema	Medical records	0=no 1=yes
Cystic fibrosis	Medical records	0=no 1=yes
Lung cancer	Medical records	0=no 1=yes
Previous TB	Medical records	0=no 1=yes
Interstitial lung disease (ILD)	Medical records	0=no 1=yes
History of prior NTM (before 2005)	Medical records	0=no 1=yes
Cancer (except lung cancer)	Medical records	0=no 1=yes
Immunodeficiency	Medical records	0=no 1=yes
Autoimmune disease	Medical records	0=no 1=yes
Tobacco smoking	Medical records	0=no 1=yes
Immunosuppressive medication	Medical records	0=no 1=yes
NTM species	Medical records	0= *M gordonae* 1=MAC 2= rapid growers (*M abscessus, M fortuitum*) 3=other species or not speciated
NTM therapy started prior to 2007	Medical records	0=no 1=yes 2=unknown

Cavity on chest imaging	Medical records	0=no 1=yes
Cause of death, primary	Vital records	Alphanumeric ICD-10 code
Cause of death, contributing	Vital records	Alphanumeric ICD-10 code
Date of death	Vital records	Date

Primary outcome

Death. Death was examined through December 31, 2012. The Link Plus program (available from the CDC) was used to perform probabilistic matching (31). The NTM database from the prior study was matched to the vital records registry to identify cohort members who died after isolation of NTM in a respiratory specimen. Matching was performed using first, middle, and last name as well as birth year. Manual checks were performed for matches that didn't meet all listed criteria and age, zip code, and commonality of name were taken into account. Additional cohort members who died were identified via a Lexus Nexus Search. The cohort was divided into two groups, those who died before December 31, 2012 and remaining cohort members. Primary and contributing causes of death as indicated in the vital records registries were recorded for each deceased cohort member. Cause of death was coded with ICD-10 codes.

Primary exposure

ATS/IDSA disease criteria. Subjects were identified during the prior study as either meeting or not meeting ATS disease criteria based on medical record review. This was coded as a dichotomous variable (yes or no) using the criteria previously described (12).

Covariates

NTM species. The original dataset was examined and NTM species was coded as a categorical variable: MAC, *M gordonae*, rapid growers, or other NTM species. Rapid growers included *M abscessus* and *M fortuitum.* Other NTM species included isolates that were not speciated as well as NTM species that did not fit into other categories.

Sex. Sex was coded as a dichotomous variable, male or female.

Age at isolation of NTM. Age was included as a continuous variable and was classified according to age when NTM was isolated (age at first NTM isolation during 2005-2006).

Underlying lung disease. The original database was examined and coded as dichotomous variables the presence of COPD/emphysema, cystic fibrosis, prior tuberculosis, lung cancer, prior isolation of NTM, and ILD. Prior isolation of NTM and interstitial lung disease were not collected as primary data in the original study. A text field allowed for prior researchers to enter other diseases that would be of interest. This field was examined and dichotomous variables were created to indicate if subject had ILD or prior isolation of NTM.

Immunocompromised. The original database was examined and a dichotomous variable indicating whether the subject was taking a medication that could compromise the immune system (prednisone, azathioprine, methotrexate, tumor necrosis factor (TNF)-alpha antagonist, rituximab, chemotherapy, and other immunosuppressive medications listed in text field). The distribution of other immunosuppressed states such as recipient of organ transplant, HIV/AIDS, and other immune disorders in the cohort were combined into a dichotomous variable.

Autoimmune disease. The original database was examined and the presence of autoimmune disease, rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus was coded as a dichotomous variable.

Smoking status. This was included as a dichotomous variable (any history of smoking or never smoker).

Radiographic findings. Bronchiectasis and cavitary lung disease were included as dichotomous variables. A new dichotomous variable for bronchiectasis was created and included bronchiectasis listed in medical record or found on chest imaging (chest x-ray or computerized tomography (CT) scan). A new dichotomous variable for cavitary lung disease was created and included evidence of a cavity on chest x-ray or CT scan.

NTM therapy. NTM therapy was included as a categorical variable: started therapy, did not start therapy, or unknown if started therapy prior to 2007.

Statistical Analysis

Statistical analyses were performed with the software packages Stata 12 (StataCorp, College Station, TX) and SAS 9.3 (SAS Institute Inc., Cary, NC).

Specific Aim 1: Categorize each member of the 2005-2006 cohort as currently alive or deceased and document date of death.

Cohort members were categorized as alive or dead using the method described earlier. In brief, the Link Plus program (31) was used to perform probabilistic

matching. Each cohort member was categorized as dead or alive. They were followed through December 31, 2012. All cohort members who were still alive after this date were categorized as alive for study purposes. Crude mortality rates were calculated for each year, 2005-2012. Age-adjusted mortality rates for each year were calculated using direct standardization and the 2000 US Standard (32).

Specific Aim 2: Describe cause of death in 2005-2006 cohort.

Primary and contributing causes of death as indicated in the vital records registries were recorded for each deceased cohort member. Descriptive statistics were used to examine the most common primary and contributing causes of death with frequencies and proportions reported.

Specific Aim 3: Use descriptive statistics to describe the age, NTM species isolated, comorbidities, gender, smoking status, radiographic findings, and ATS/IDSA disease status of each group and perform univariate analysis to analyze relationship between death and each covariate.

Summary statistics. Summary statistics were performed for each covariate stratified by outcome (dead vs. alive). The distributions of the continuous covariates were evaluated for normality and appropriate transformations made. Means and standard deviations were reported for continuous variables while frequencies and proportions were reported for categorical variables.

Simple statistics. Simple statistics were performed to examine the relationship between the primary exposure and each of the covariates. Chi-square tests, Fisher's exact tests, and t-tests were used where appropriate. Tests were considered statistically significant at a two-sided p-value of less than 0.05.

Univariate analysis. Using simple logistic regression the relationship between each of the covariates and the outcome (death) was analyzed. All covariates with a p-value less than 0.25 were included in the variable selection procedure.

Specific Aim 3: Evaluate the association between ATS/IDSA disease criteria and death and identify factors that may modify this association.

Multiple logistic regression. Multiple logistic regression was used to fit the model. All variables with p-values <0.25 in the univariate analysis were included in the next steps for model selection. Given the prespecified significance of NTM species, ATS/IDSA disease criteria (primary exposure), NTM therapy, and sex these variables were included in the model selection procedure despite not having a p-value less than 0.25. Immunosuppressive disorders and autoimmune disease were not included as it was thought that use of immunosuppressive medications was a better indicator of a suppressed immune system at the time of NTM isolation. The covariate cancer (other than lung cancer) was not included as it was not part of the *a priori* list of potential confounders. Prior TB was not included because of the low number of observations. ILD and prior isolation of NTM were not included because these covariates were not specifically abstracted from the charts in the prior study

therefore a number of diagnoses might have been missed leading to misclassification.

Forward and backwards stepwise selection procedures using a significance level of 0.25 to stay in the model and 0.2 for addition to the model were performed. Because ATS/IDSA disease criteria was the primary exposure of interest it was forced into the model. Lowess curves were used to examine the linear relationship of continuous covariates.

Covariates not selected for inclusion were added back to the model individually and the likelihood ratio test was used to determine whether they improved the fit of the model ($p<0.05$). Interaction terms were examined with the likelihood ratio test used to determine if they improved the fit of the model ($p<0.05$). Model diagnostics including residual analysis were performed to assess the validity of the assumption of logistic regression. Hosmer-lemeshow goodness of fit test was used to examine the fit of the final model.

Sensitivity analysis. Sensitivity analysis was performed to assess the reliability of the logistic regression model in finding an association between the primary exposure and death. A time to event (survival) analysis was performed to determine if a similar model would be obtained as the model via logistic regression. A variable indicating if event of interest occurred was generated (censor: =1 if dead, =0 if

alive). A variable (time) was generated using date of death (or date of study end) - date of culture isolation.

For categorical predictors the Kaplan-Meier survival curves and log-tank tests of equality across strata were examined. For continuous covariates a univariate Cox proportional hazard regression was performed. All covariates with a p-value less than 0.25 were included in the initial model. The primary exposure, ATS/IDSA disease criteria was also included despite having a p-value greater than 0.25. The covariates in the initial model were examined and those with a p-value less than 0.05 (except for the primary exposure) were removed from model. The covariates were than added back to the model individually and the likelihood ratio test was used to examine whether the fit of the model was improved by the addition of the removed covariates ($p<0.05$). Interaction terms were examined in a similar manner with the likelihood ratio test ($p<0.05$). The proportionality assumption was evaluated by including time dependent covariates in the model. The Schoenfeld and scaled Schoenfeld residuals were also used to test proportionality. The goodness of fit of the final model was examined using Cox-Snell residuals.

Human Subjects Protection

This study utilized a data set from a prior study that was performed under the supervision of the Oregon Health Authority (OHA). This prior study was considered a public health surveillance project and thus did not undergo institutional review

board (IRB) approval. The original data set was stored on a computer at the OHA behind a firewall and password protected.

The OHA IRB has approved this current study. The death match was performed at the OHA. Once the death match had been performed, subjects' names and other identifying information were removed from the analysis files. The original database is accessible only by study staff and maintained in a password-protected database behind the OHA firewall.

Results

Specific Aim 1: Categorize each member of the 2005-2006 cohort as currently alive or deceased and document date of death.

One hundred sixty-five members of the cohort were classified as having died prior to January 1, 2013. The crude mortality rate for the study period (January 1, 2005-December 31, 2012) was 449.6/1000. For each study year, crude mortality rates and age-adjusted mortality rates were calculated (Table 2). The age-adjusted mortality rates were highest in the first 3 years, which indicates that the risk of death is highest in the time immediately after isolation of NTM and this risk is attenuated over time.

Table 2: Crude and age-adjusted mortality rates per year

Year	Crude rate/1000	Age-adjusted rate/1000
2005	73.6	5.3
2006	105.9	3.6
2007	78.9	2.6
2008	53.6	1.6
2009	71.7	1.9
2010	85.4	2.2
2011	44.4	1.2
2012	60.5	1.7

Specific Aim 2: Describe cause of death in 2005-2006 cohort using information from vital records registry.

The most common primary causes of death in this cohort were pulmonary diseases (Table 3). COPD/emphysema was the most common (15.8%), followed by lung cancer (11.9%) and bronchiectasis (4.4%). Pulmonary mycobacterial disease was the primary cause of death in 4 subjects (2.4%).

Table 3: Primary causes of death

Cause of Death	N (%)
COPD/emphysema	26 (15.8)
Lung Cancer	19 (11.5)
Bronchiectasis	7 (4.2)
Non-Hodgkin's lymphoma	5 (3.0)
Coronary artery disease	5 (3.0)
Pulmonary mycobacterial infection	4 (2.4)
Related to underlying infection	4 (2.4)
Breast cancer	4 (2.4)
Pneumonia, unspecified	4 (2.4)
Interstitial pulmonary disease	4 (2.4)
Other disorders of lung	4 (2.4)

The most common contributing causes of death (Table 4) included tobacco use (40.0%) and pneumonia (14.0%). Pulmonary mycobacterial disease was cited as contributing cause of death for 4 subjects while mycobacterial disease (not identified as pulmonary) was cited as a contributing cause of death in 3 subjects.

Table 4: Contributing causes of death

Cause of death	N (%)
Related to tobacco use	66 (40.0)
Pneumonia, unspecified	23 (14.0)
COPD, unspecified	20 (12.1)
Congestive heart failure	15 (9.1)
Respiratory failure, unspecified	14 (8.5)
Hypertension	14 (8.5)
Atherosclerotic heart disease	12 (7.3)
Unspecified diabetes mellitus without complications	8 (4.8)
Septicemia, unspecified	6 (3.6)
Osteoporosis, unspecified	4 (2.4)
Pulmonary mycobacterial infection	4 (2.4)

The age-adjusted mortality rates for subjects who carried a diagnosis of COPD/emphysema (most common primary cause of death) were examined and compared to those without COPD/emphysema (Table 5). For those without COPD/emphysema, the mortality rate fell as time after isolation increased but for those with COPD/emphysema the rates remained stable at around 4/1000 deaths. For those with COPD/emphysema the risk doesn't appear to be attenuated with increased time after isolation of NTM.

Table 5: Annualized age-adjusted mortality rates for subjects with diagnosis of COPD/emphysema (n=105) and without COPD/emphysema (n=262)

	Age-adjusted mortality rate/1000	
	COPD	**Without COPD**
First 3 years after isolation (2005-2007)	4.56	3.26
Second 3 years after isolation (2008-2010)	4.19	1.09

Specific Aim 3: Use descriptive statistics to describe the age, NTM species isolated, comorbidities, sex, smoking status, and ATS disease status of each group and perform univariate analysis to analyze relationship between death and each covariate.

The cohort included 367 adults who isolated NTM in respiratory specimens during the years 2005-2006 (Table 6). The average age was 64.8 years with more females than males (52.9% vs. 47.1%). Ninety-nine (27.0%) cohort members had bronchiectasis and 105 (28.6%) had COPD/emphysema. One hundred sixty two (44.1%) were current or former smokers and 69 (18.8%) had taken an immunosuppressive medication during the time of NTM isolation. Half of the cohort met ATS/IDSA disease criteria. MAC was the predominant organism (76%) followed by *M gordonae* (9.5%) and rapid growers (4.9%). Thirty-five (9.5%) cohort members isolated another NTM species or didn't have the NTM isolate speciated. Given the large number of subjects missing information on race this covariate was not considered in the analysis.

Table 6: Characteristics of adults who isolated NTM in respiratory specimens during 2005-2006 (n=367)

	Mean (SD) or N (%)
Age	64.79 (15.38) yrs
Dead	165 (45.0)
Sex	
Female	194 (52.9)
Male	173 (47.1)
Bronchiectasis	99 (27.0)
COPD/emphysema	105 (28.6)
Cystic Fibrosis	4 (1.1)
Lung cancer	27 (7.4)
Prior TB	14 (3.8)
ILD	12 (3.3)
Prior isolation of NTM	16 (4.4)
NTM therapy started	
No	182 (49.5)
Yes	73 (19.9)
Unknown	112 (30.5)
Tobacco smoking	162 (44.1)
Autoimmune disease	20 (5.4)
Immunosuppressive medications	69 (18.8)
Immuosuppressive disorder	20 (5.5)
Cancer (not lung cancer)	30 (8.2)
ATS/IDSA disease criteria	180 (49.1)
NTM species	
MAC	279 (76.0)
Rapid growers	18 (4.9)
M gordonae	35 (9.5)
Other species	35(9.5)
Cavity	63 (17.1)

Frequencies were examined in the dead and alive groups (Table 7). The average age was lower in those who were still alive at the end of the study period (60.1 vs. 70.6 years). The percentage of males in the dead group was higher than in the alive group (49.7 vs. 45.1%). Bronchiectasis was more frequently found in those who were still alive (29.7 vs. 23.6%) while cavitary lung disease was present in about

17% in both the alive and dead group. Comorbidities (including COPD/emphysema and lung cancer) were more common in those who died. Use of immunosuppressive medications was more common in those who died (24.9 vs. 13.9%). More people who were living at the end of the follow-up period were known to have started NTM therapy (22.8 vs. 16.4%). Approximately half of each group met ATS/IDSA disease criteria. The distribution of NTM species was approximately the same in each group with MAC the predominant organism.

Table 7: Covariates stratified by outcome (alive (n=202) vs. dead (n=165))

	Alive (n=202)	Dead (n=165)
	Mean (SD) or N (%)	
Age (years)	60.08 (15.85)	70.56 (12.61)
Sex		
Female	111 (54.9)	83 (50.3)
Male	91 (45.1.)	82 (49.7)
Bronchiectasis	60 (29.7)	39 (23.6)
COPD/emphysema	36 (17.8)	69 (41.8)
Cystic Fibrosis	4 (1.2)	0 (0)
Lung cancer	7 (3.5)	20 (12.1)
Prior TB	5 (2.5)	9 (5.5)
ILD	3 (1.5)	9 (5.5)
Prior isolation of NTM	6 (3.0)	10 (6.1)
NTM therapy started		
No	99 (49.0)	83 (50.3)
Yes	46 (22.8)	27 (16.4)
Unknown	57 (28.2)	55 (33.3)
Tobacco smoking	79 (39.1)	83 (50.3)
Autoimmune disease	6 (3.0)	14 (8.5)
Immunosuppressive medications	28 (13.9)	41 (24.9)
Immuosuppressive disorder	14 (6.9)	6 (3.6)
Cancer (not lung cancer)	9 (4.5)	21 (12.7)
ATS/IDSA disease criteria	98 (48.5)	82 (49.7)
NTM species		
MAC	154 (76.2)	125 (75.7)
Rapid growers	10 (4.9)	8 (4.9)
M gordonae	20 (9.9)	15 (9.1)
Other species	18 (8.9)	17 (10.3)
Cavity	34 (16.8)	29 (17.6)

The cohort was divided equally among those who did and didn't meet ATS/IDSA disease criteria. As expected, given that chest imaging findings were one of the criteria for ATS/IDSA disease classification, bronchiectasis and cavities on imaging were more common in those who met ATS/IDSA disease criteria, 34.4 vs. 19.8% and 25.0 vs. 9.6% respectively. COPD/emphysema and lung cancer were distributed

equally between the groups. More females met ATS/IDSA disease criteria (58.9 vs. 47.1%). MAC was more common among those who met disease criteria (87.8 vs. 64.7%). Approximately 33% of those who met disease criteria started NTM therapy vs. only 7.5% of those who didn't meet case criteria. (Table 8)

Table 8: Covariates stratified by primary exposure (ATS/IDSA disease criteria) with associated statistical tests

	Doesn't meet ATS/IDSA disease criteria (n=187)	Meets ATS/IDSA disease criteria (n=180)	p-value
	Mean (SD) or N (%)		
Age (years)	63.80 (16.59)	65.82 (13.98)	0.210
Sex			
Female	88 (47.1)	106 (58.9)	0.023
Male	99 (52.9)	74 (41.1)	
Bronchiectasis	37 (19.8)	62 (34.4)	0.002
COPD/emphysema	53 (28.3)	52 (28.9)	0.908
Cystic Fibrosis	3 (1.6)	1 (0.6)	0.623
Lung cancer	14 (7.5)	13 (7.2)	0.923
Prior TB	9 (4.8)	5 (2.8)	0.416
ILD	5 (2.7)	7 (3.9)	0.568
Prior isolation of NTM	6 (3.2)	10 (5.6)	0.271
NTM therapy started			
No	116 (62.0)	66 (36.7)	<0.0001
Yes	14 (7.5)	59 (32.8)	
Unknown	57 (30.5)	55 (30.6)	
Tobacco smoking	84 (44.9)	78 (43.3)	0.760
Autoimmune disease	9 (4.8)	11 (6.1)	0.584
Immunosuppressive medications	33 (17.7)	36 (20.0)	0.564
Immunosuppressive disorder	10 (5.4)	10 (5.6)	0.930
Cancer (not lung cancer)	11 (5.9)	19 (10.6)	0.102
NTM species			
MAC	121 (64.7)	158 (87.8)	<0.0001
Rapid growers	9 (4.8)	9 (5.0)	
M gordonae	33 (17.7)	2 (1.1)	
Other species	24 (12.8)	11 (6.1)	
Cavity	18 (9.6)	45 (25.0)	<0.0001

The characteristics of the subgroup (n=11) with a mycobacterial cause of death was examined and compared to the dead (from any cause) cohort members (Table 9). In general the groups were similar but the mycobacterial group had higher frequencies of rapid growers, COPD/emphysema, bronchiectasis, and tobacco smoking. There were more males in the group with a mycobacterial cause of death (54.6 vs. 49.7%).

Table 9: Characteristics of group with mycobacterial cause of death (n=11) and all causes of death (n=165)

	Dead cohort (n=165)	**Mycobacterial dead (n=11)**
	Mean (SD) or N (%)	
Age	70.56 (12.61)	73.81 (8.89)
Sex		
Female	83 (50.3)	5 (45.4)
Male	82 (49.7)	6 (54.6)
Bronchiectasis	39 (23.6)	4 (36.4)
COPD/emphysema	69 (41.8)	5 (45.5)
Cystic Fibrosis	0 (0)	0
Lung cancer	20 (12.1)	1 (9.1)
Prior TB	9 (5.5)	0
ILD	9 (5.5)	0
Prior isolation of NTM	10 (6.1)	0
NTM therapy started		
No	83 (50.3)	1 (9.1)
Yes	27 (16.4)	6 (54.5)
Unknown	55 (33.3)	4 (36.4)
Tobacco smoking	83 (50.3)	8 (72.7)
Autoimmune disease	14 (8.5)	2 (18.2)
Immunosuppressive medications	41 (24.9)	2 (18.2)
Immuosuppressive disorder	6 (3.6)	0
Cancer (not lung cancer)	21 (12.7)	2 (18.2)
ATS/IDSA disease criteria	82 (49.7)	9 (81.8)
NTM species		
MAC	125 (75.7)	9 (81.8)
Rapid growers	8 (4.9)	2 (18.2)
M gordonae	15 (9.1)	0
Other species	17 (10.3)	0
Cavity	29 (17.6)	2 (18.2)

Univariate analysis was performed to examine the association between covariates of interest and outcome (death) (Table 10). Age was significantly associated with death (OR 1.05 (95 % CI: 1.04, 1.07). Imaging findings (bronchiectasis and cavitary lung disease) were not significantly associated with death. NTM associated factors including ATS/IDSA disease criteria, NTM species, and NTM therapy were not significantly associated with death. COPD/emphysema, lung cancer, and immunosuppressive medications were significantly associated with death.

Table 10: Univariate Logistic Regression

Covariate	Coefficient	Standard error	OR (95% CI)	p-value
Age (years)	0.052	0.008	1.05 (1.04, 1.07)	<0.001
Sex				
Female	Referent	Referent	Referent	0.375
Male	0.187	0.210	1.21 (0.80, 1.82)	
Bronchiectasis	-0.311	0.239	0.73 (0.46, 1.17)	0.191
COPD/emphysema	1.198	0.242	3.31 (2.06, 5.33)	<0.001
Lung cancer	1.346	0.453	3.84 (1.58, 9.33)	0.001
Prior TB	0.821	0.568	2.27 (0.75, 6.92)	0.138
ILD	1.342	0.675	3.83 (1.02, 14.37)	0.032
Prior isolation of NTM	0.746	0.527	2.11 (0.75, 5.93)	0.150
NTM therapy started				
No	Referent	Referent	Referent	
Yes	-0.357	0.284	0.70 (0.40, 1.22)	0.258
Unknown	0.141	0.241	1.15 (0.71, 1.84)	
Tobacco smoking	0.455	0.212	1.57 (1.04, 2.39)	0.032
Autoimmune disease	1.108	0.500	3.03 (1.14, 8.07)	0.020
Immunosuppressive medications	0.720	0.272	2.05 (1.21, 3.50)	0.008
Immunosuppressive disorder	-0.679	0.500	0.51 (0.19, 1.35)	0.159
Cancer (not lung cancer)	1.140	0.413	3.13 (1.39, 7.03)	0.004
Case criteria				
No	Referent	Referent	Referent	0.827
Yes	0.047	0.210	1.05 (0.69, 1.58)	
NTM species				
M gordonae	Referent	Referent	Referent	
MAC	0.079	0.362	1.08 (0.53, 2.20)	0.969
Rapid growers	0.065	0.585	1.07 (0.34, 3.35)	
Other species	0.231	0.481	1.26 (0.49, 3.23)	
Cavity	0.052	0.278	1.05 (0.61, 1.82)	0.851

Specific Aim 4: Evaluate the association between ATS/IDSA disease criteria and death and identify factors that may modify this association.

Variables for consideration included age, sex, bronchiectasis, COPD/emphysema, lung cancer, NTM therapy, tobacco smoking, immunosuppressive medications, NTM species, and ATS/IDSA disease criteria. Both forwards and backwards selection resulted in a model that included ATS/IDSA disease criteria, lung cancer, COPD/emphysema, immunosuppressive medications, age at isolation, and sex. None of the covariates excluded during the model selection procedures were found to significantly improve the fit of the model. Given that most interaction terms were not thought to add any clinical significance, only interaction terms for the primary exposure (ATS/IDSA disease criteria) with gender, COPD, immunosuppressive medications, and lung cancer were investigated. None of the interaction terms were found to significantly improve the fit of the model.

The final model (Table 11) included ATS/IDSA disease criteria, age at isolation, sex, COPD/emphysema, lung cancer, and immunosuppressive medications. In the final model, ATS/IDSA disease criteria were not significantly associated with increased odds of death (odds ratio (OR) 1.04, 95% CI: 0.66, 1.66). Male sex, COPD/emphysema, lung cancer, and immunosuppressive medications were associated with increased odds of death after isolation of NTM.

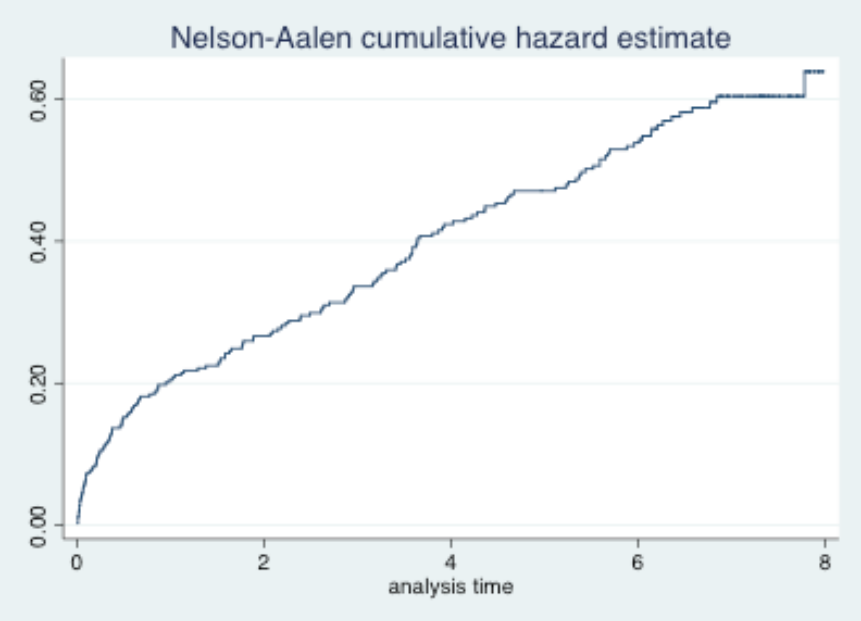
Table 11: Final multivariate analysis

	OR (95% CI)
ATS/IDSA disease criteria	1.04 (0.66, 1.66)
Age at isolation	1.06 (1.04, 1.08)
Male	2.02 (1.22, 3.36)
COPD/emphysema	2.36 (1.41, 3.95)
Lung cancer	3.81 (1.48, 9.82)
Immunosuppressive medications	1.84 (1.01, 3.35)

Sensitivity analysis

A survival analysis was performed to evaluate factors associated with death in those who isolate NTM in respiratory specimens. New variables were generated to indicate if the event of interest (death) occurred and time to event or end of study (years). The cumulative hazard curve was generated (Figure 1). Examination of the curve shows that risk of death appears highest immediately after isolation, which is consistent with age-adjusted mortality rates by year.

Figure 1: Cumulative hazard curve



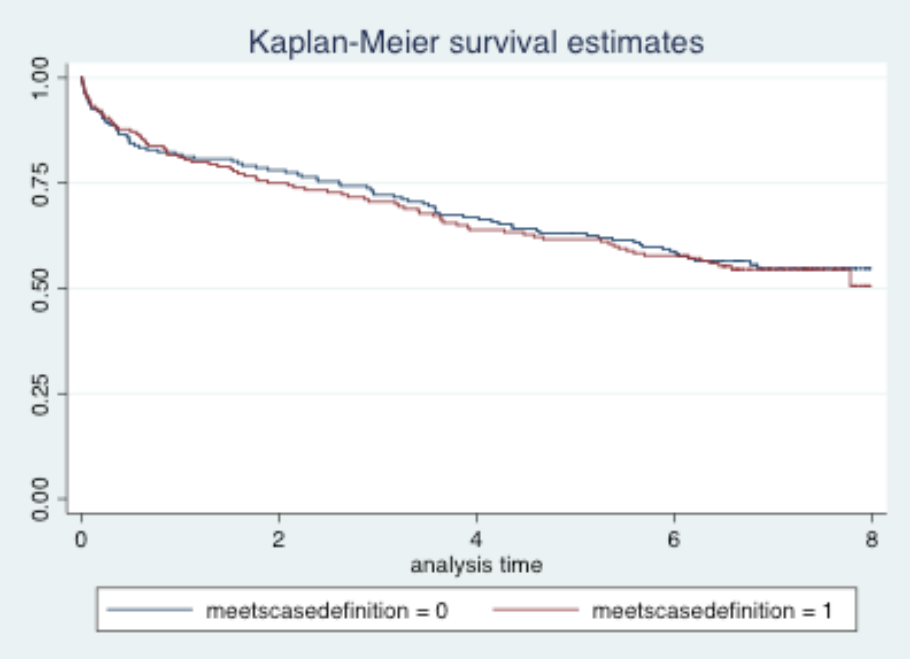
Univariate analysis was performed to examine predictors across strata (Table 12). Comorbidities such as COPD/emphysema, lung cancer, and immunosuppressive disorders varied significantly across strata. Tobacco smoking and age also varied significantly. NTM associated factors: ATS/IDSA disease criteria, NTM species, and NTM therapy did not vary significantly. Kaplan Meier curves were generated for each covariate (Figure 2). Significant overlap is seen on the curves for ATS/IDSA disease criteria and NTM species while the curves for COPD/emphysema are almost parallel indicating differences in survival for those with and without COPD/emphysema but not for those with differing ATS/IDSA disease criteria or isolation of different NTM species.

Table 12: Univariate survival analysis

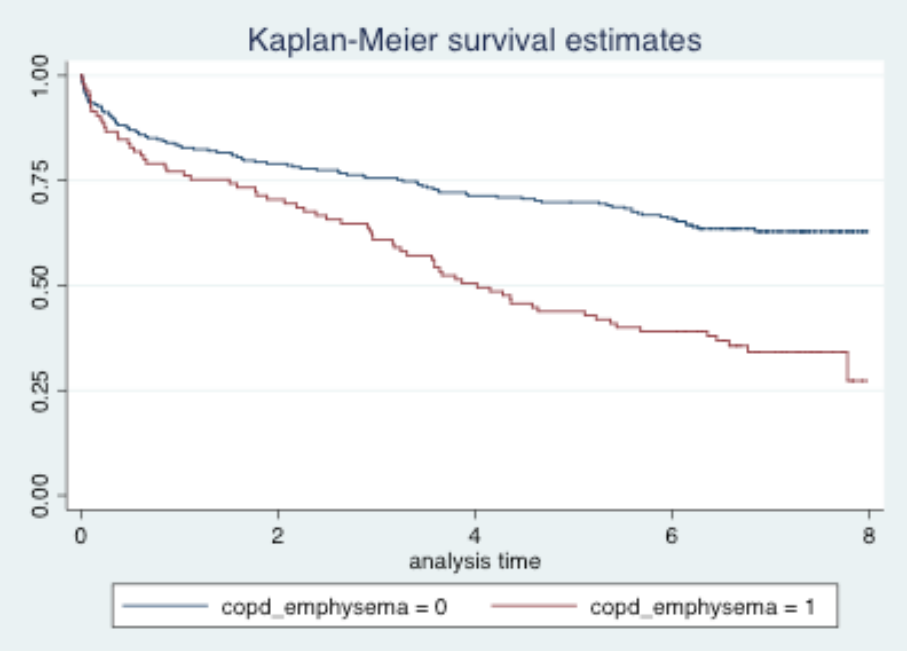
	Test statistic	p-value
Age (years)	41.96	<0.001
Sex	1.33	0.249
Bronchiectasis	3.18	0.075
COPD/emphysema	24.40	<0.001
Lung cancer	27.47	<0.001
Prior TB	3.19	0.074
ILD	4.89	0.027
Cystic fibrosis	2.46	0.117
Prior isolation of NTM	0.72	0.396
NTM therapy started	3.68	0.159
Tobacco smoking	4.63	0.031
Autoimmune disease	4.82	0.028
Immunosuppressive medications	8.13	0.004
Immunosuppressive disorder	1.39	0.238
Cancer (not lung cancer)	13.05	<0.001
ATS/IDSA disease criteria	0.05	0.832
NTM species	0.23	0.972
Cavity	0.00	0.962

Figure 2: Selected Kaplan Meier curves

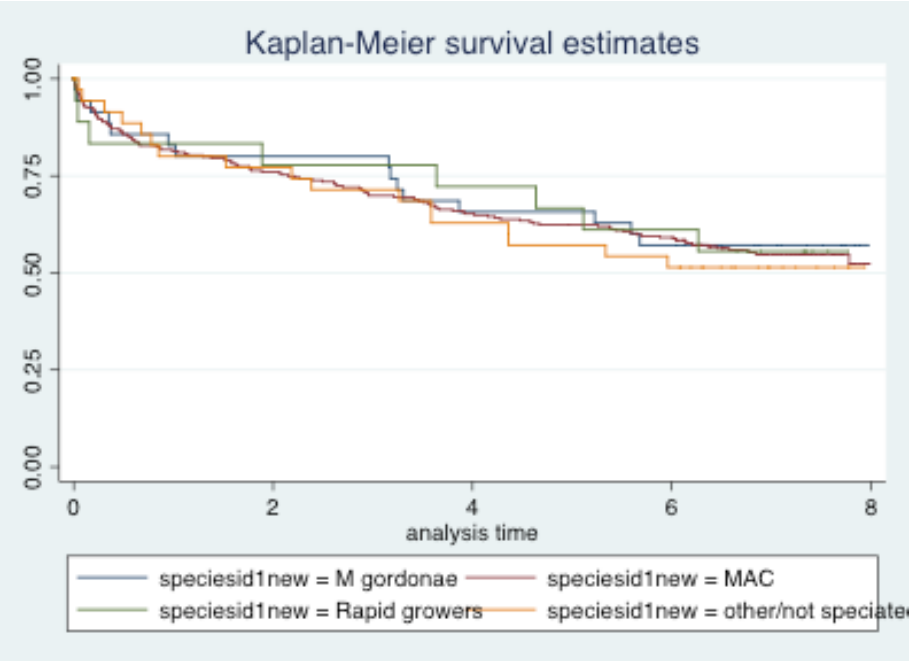
Primary exposure: ATS/IDSA disease criteria



Covariate: COPD/emphysema



Covariate: NTM Species



The preliminary model included the primary exposure, ATS/IDSA disease criteria as well as covariates with a p-value less than 0.25: age, sex, bronchiectasis, COPD/emphysema, lung cancer, NTM therapy, tobacco smoking, and immunosuppressive medications. COPD/emphysema, bronchiectasis, NTM therapy, and tobacco smoking were removed from the model. The covariates that were removed were added back individually to see if the fit of the model improved. COPD/emphysema was added back to the model as it significantly improved the model. Potential interactions were examined. Given that most interaction terms were not thought to add any clinical significance, only interaction terms for the primary exposure (ATS/IDSA disease criteria) with gender, COPD/emphysema, immunosuppressive medications, and lung cancer were investigated. The interaction term with ATS/IDSA disease criteria and lung cancer was found to

significantly improve the model. On further examination, lung cancer appeared to violate the proportionality assumption so the final model was stratified by lung cancer (Table 13). After stratification ATS/IDSA disease criteria remained nonsignificant but the point estimate was increased from 1.04 (95% CI: 0.75, 1.45) in those without lung cancer to 2.33 (95% CI: 0.93, 5.87) in those with lung cancer. In addition, male sex had a hazard ratio of 1.67 (95% CI: 1.18, 2.37) in those without lung cancer but the hazard ratio decreased to 0.81 (95% CI: 0.30, 2.20) in those with lung cancer. The model stratified by COPD/emphysema was also examined (Table 13). In those without COPD/emphysema, male sex had a hazard ratio of 2.06 (95% CI: 1.33, 3.20) while in those with COPD/emphysema the hazard ratio for male sex decreased to 1.23 (95% CI: 0.76, 2.00). The hazard ratio for ATS/IDSA disease criteria did not increase in those with COPD/emphysema as it did for those with lung cancer. Instead it decreased from 1.26 (95% CI: 0.84, 1.88) to 0.95 (95% CI: 0.58, 1.56).

Table 13: Multivariate models stratified by lung cancer and COPD/emphysema

	No lung cancer		Lung cancer	
	Hazard ratio	95% CI	Hazard ratio	95% CI
ATS/IDSA disease criteria	1.04	0.75, 1.45	2.33	0.93, 5.87
Age at isolation	1.04	1.03, 1.06	1.01	0.97, 1.05
Male sex	1.67	1.18, 2.37	0.81	0.30, 2.20
Immunosuppressive medications	1.49	1.01, 2.19	1.38	0.41, 4.67
COPD	1.79	1.27, 2.53	0.67	0.24, 1.86

	No COPD/emphysema		COPD/emphysema	
	Hazard ratio	95% CI	Hazard ratio	95% CI
ATS/IDSA disease criteria	1.26	0.84, 1.88	0.95	0.58, 1.56
Age at isolation	1.05	1.03, 1.07	1.03	1.00, 1.05
Male sex	2.06	1.33, 3.20	1.23	0.76, 2.00
Immunosuppressive medications	1.67	0.98, 2.82	1.43	0.85, 2.38
Lung Cancer	5.61	3.06, 10.31	1.21	0.54, 2.70

Eighty-two subjects met ATS/IDSA disease criteria and died during the study period with an average survival time of 2.28 years (+/- 2.12). Eighty-three did not meet ATS/IDSA disease criteria and died during the study period, with an average survival time of 2.36 years (+/- 2.14). This difference was not statistically significant (p=0.813).

Discussion

In this follow-up of a cohort of Oregonians who isolated NTM in respiratory cultures in 2006-2006, death was common with 45% of the cohort dying during the study period. Pulmonary diseases were the most common causes of death, with

COPD/emphysema and lung cancer number one and two respectively. Age-adjusted mortality was highest in the first three years of the study (2.6-5.3/1000) and higher than in other pulmonary disease states. Age-adjusted mortality for COPD has been shown to be 0.41/1000 and for lung cancer 0.50/1000 (33, 34). NTM disease was documented as the primary or contributing cause of death in a small number (n=11). The higher age-adjusted mortality could be due to the fact that sicker populations have more studies and tests done, hence it is more likely that NTM isolates would be found. It is also possible that NTM isolation itself could be associated with an unknown factor that leads to the higher age-adjusted mortality such as a currently undiscovered genetic predisposition. In addition, it is possible that NTM are a contributing cause of death in a larger number of individuals than is readily measurable by available death certificate information.

NTM related factors including ATS/IDSA disease criteria, NTM species, and NTM therapy were not associated with death in this study. Factors significantly associated with death in the adjusted logistic regression model included diagnosis of COPD/emphysema or lung cancer, male sex, and immunosuppressive medications at time of isolation. In the survival analysis, when stratified by lung cancer, ATS/IDSA disease criteria had an increased association with death but still did not reach statistical significance. Race was not controlled for in this analysis given the large number of subjects for whom race classification was missing. Thus any confounding or effect modification by race was not able to be measured. Cavitary

lung disease was not found to be associated with an increased risk of death as in prior studies (28).

In this cohort meeting ATS/IDSA disease criteria was not associated with increased odds of death in the multiple logistic regression model or with an increased hazard ratio in the survival analysis. Although, the findings of this study are consistent with the majority of prior studies, the question remains, does NTM disease increase the risk of death? Perhaps, the measure of NTM disease (ATS/IDSA disease criteria) doesn't accurately characterize those in which NTM would pose an increased risk. This is not unexpected based on prior literature (10, 19, 29) which showed no prognostication value associated with ATS disease criteria in smaller samples of NTM patients or in specific subsets of patients such as those with lung transplants and HIV/AIDS. Adjemian et al. found that "cases" were more likely to die than "noncases" (OR 1.4, 95% CI: 1.3, 1.6) and that odds of death was increased in those with 3 or more comorbidities but those with bronchiectasis were half as likely to die (OR 0.5, 95% CI: 0.4, 0.6) (8). However, they analyzed a Medicare population and used diagnostic codes to define disease rather than ATS/IDSA disease criteria.

MAC was the predominant NTM species in this study, consistent with known higher prevalence of MAC in pulmonary disease. In studies in the United States, MAC has constituted up to 75-80% of pulmonary disease isolates (6, 10). NTM species was not associated with death in either the logistic regression model or the survival analysis. Interestingly, rapid growers were more common in the small subset with a

mycobacterial cause of death; however, the small numbers in this subset make it difficult to know if this is an important finding. Given the small numbers of rapid growers in this cohort (~5%), it would have been difficult to find an association between death and NTM species if it did exist.

There were a large number of subjects for whom receipt of NTM therapy was unknown. It is possible that NTM therapy itself is associated with an increased or decreased risk of death and more accurate information regarding therapy could better elucidate the association between ATS/IDSA disease criteria and death. More accurate classification of NTM therapy may have led to a significant association. In addition, therapy could have been started after the initial chart review was done. Receipt of therapy after the initial chart review could have modified the association between ATS/IDSA disease criteria and death and the effect of this would not have been measured in this current analysis.

An interesting finding is the increased association with death among males. This is in contrast to the recent study of NTM related mortality, which found 1558 (52.1%) deaths in women as opposed to 1432 (47.9%) in men (30). However other studies have found increased risks among males (8). Disease types might have varied between males and females with males suffering from more rapidly progressive disease.

Another finding that was unexpected was the change in the hazard ratio of ATS/IDSA disease criteria when stratified by lung cancer. This study attempted to identify any factors that would modify the relationship between ATS/IDSA disease criteria and death. Although no factors were identified that would lead to a significant association between ATS/IDSA disease criteria and death, lung cancer did change the point estimate and move the lower bounds of the CI closer to one. Lung cancer itself is a condition associated with a high morbidity and mortality. Perhaps in those with lung cancer, the underlying lung parenchyma is more prone to damage from the NTM leading to worse outcomes (including death). However, this trend in the hazard ratio was not seen when the cohort was stratified by COPD/emphysema indicating the relationship between ATS/IDSA disease criteria, death, and underlying lung disease is complex and needs further study.

Overall, the primary exposure of interest (ATS/IDSA disease criteria) was not associated with an increased risk of death in this cohort of Oregonians who isolated NTM in respiratory specimens in 2005-2005. This is an important finding given that literature on this topic is sparse. Based on this study, mortality is higher in those who have isolated NTM in respiratory specimens. NTM might lead to poor outcomes (including death) for a number of reasons. Perhaps NTM contribute to an increased risk of death via an as of yet unmeasured genetic factor or acceleration of damage from other underlying lung diseases.

Strengths and Limitations

This study utilized a cohort from a limited geographic region, those who received care at major medical centers in the Portland metropolitan area as well as Salem Hospital. This sample may not be representative of everyone with NTM pulmonary disease. However, prior studies of NTM disease have found similar distributions of demographic factors and comorbidities so it is likely that results from this study would be generalizable to other populations. This sample was identified in a population-based manner and included subjects treated at several different medical centers thus eliminating the bias of other studies, which were often single center studies.

Record review may have been incomplete so it is possible that all cases of NTM disease were not accurately classified as meeting or not meeting ATS/IDSA disease criteria and thus misclassification is possible. This was likely to have been nondifferential and could have biased towards the null.

The majority of the NTM species in this cohort are MAC. Given the large number of MAC species when compared to other species of NTM a difference in survival between the different NTM species may have been obscured.

The death match was performed using probabilistic methods with manual checks for those who lacked information to complete the match. Misclassification was possible and likely to be nondifferential and could have biased towards the null.

Other variables of interest that may have confounded the impact of ATS/IDSA disease criteria on death were not controlled for in this study and included prior isolation of NTM, other lung diseases, and AFB smear positivity (measure of burden of NTM in respiratory specimens). In addition, some subjects may have started therapy for NTM disease after this record review was done. ATS/IDSA disease status could have changed for subjects during the follow-up period. Interim development of other diseases that could have impacted death was not controlled for in this analysis.

Future Studies and Public Health Implications

Longitudinal studies should be done to better evaluate the effect of NTM therapy and change in ATS/IDSA disease criteria over time on both morbidity and mortality. A study comparing this cohort (or a similar cohort) to a cohort of patients with similar comorbidities but no isolation of NTM could be done to determine if NTM isolation is associated with death. Studies to determine if ATS/IDSA disease criteria is associated with other outcomes including quality of life would be important in further investigating the prognostic value of the ATS/IDSA disease criteria. Finally, studies examining whether other pulmonary diseases or certain symptoms (such as hemoptysis) should be factored into the decision to treat (i.e. Are outcomes improved when patients with certain pulmonary diseases or symptoms are treated for NTM disease?) would help better inform clinicians.

Given that NTM is thought to be environmentally acquired, it is an important public health issue if this disease does indeed lead to increased morbidity and mortality. In addition, those who have isolated NTM may have a higher age-adjusted mortality, and NTM may increase the risk of death in other common pulmonary disease states (such as COPD/emphysema and lung cancer). Future studies that better elucidate the risk associated with isolation of NTM will help define the public health impact of this organism.

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