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Major Article

Evaluating differences in tuberculosis and nontuberculous mycobacterial lung disease in Florida

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Background: Currently, very little data exists that compare the features of pulmonary nontuberculous mycobacteria (NTM) and *Mycobacterium tuberculosis* (TB). Both have similar symptomology and analogous preliminary laboratory results, as both present with positive acid-fast bacilli stains. The objective of this study was to provide data that would help guide clinicians in their decision making regarding isolation precautions for patients, with a preliminary positive result for mycobacteria, prior to species identification.

Methods: We conducted queries for patients who had positive respiratory cultures for mycobacteria via our electronic medical record system, between January 1, 2011, and December 31, 2017. Additionally, we collected demographic and medical history, clinical presentation, and radiographic findings. The 2-sample unpaired Student t test, the X^2 test, and logistic regression were used to compare each group.

Results: Through logistic regression, 8 variables were significantly associated with patients who grew either TB or NTM. History of incarceration, born outside of the United States, cavitation, and lymphadenopathy were associated with TB; tobacco smoke exposure, pre-existing lung disease, immunosuppression, and bronchiectasis were associated with NTM. Incidence of HIV and hemoptysis was not significantly different between the 2 groups.

Conclusions: Through the use of our study findings, improper use of airborne isolation precautions may be reduced or avoided.

REVIEW OF PUBLISHED LITERATURE

When a patient presents with acid-fast bacilli (AFB) in a respiratory specimen, infection preventionists and public health professionals are often faced with a challenging decision.[1]

Nontuberculous mycobacteria (NTM) and *Mycobacterium tuberculosis* (TB) produce similar symptoms, with the shared feature of a positive AFB stain, making these 2 organisms difficult to discern prior to species identification. However, the implications for infection control for these 2 organisms are very different. Unlike pulmonary TB, in which transmission occurs person-to-person via inhalation of airborne organisms, NTM are acquired through environmental reservoirs via the inhalation of aerosolized contaminated water.[2]

The significant differences in transmission and communicability between patients with TB and patients with NTM presents an issue when considering appropriate isolation precautions within the hospital. Although TB requires the immediate implementation of airborne precautions, NTM do not require isolation of any kind.[3,4]

Additionally, clinical manifestations of NTM are variable and nonspecific, with chronic pulmonary disease being the most common presentation. Symptoms may be influenced and exacerbated by various comorbidities such as chronic obstructive pulmonary disease (COPD), cystic fibrosis (CF), and bronchiectasis.

Historically, respiratory infections owing to mycobacteria were caused almost entirely by TB.[5] However, over the last decade other species of mycobacteria have become increasingly prevalent as the causative agents of pulmonary infections in the United States.[6,7] There are currently >150 known species of NTM, most of which are ubiquitous and naturally occurring in soil and water.[1] Water sources known to harbor these organisms include plumbing systems within both residential and organizational settings, reservoirs for drinking

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and drainage water, and brackish marshes or swamplands. Therefore, areas that are humid and border the ocean or other large bodies of water have higher incidence rates of NTM. In 2010, there were 11,580 documented cases of NTM in Florida, with a corresponding annual cost of $98,527,193.[8] It should be noted that these numbers are considered an underestimate, owing to the fact that NTM are not a reportable organism/disease and, therefore, may frequently go undocumented or unreported.[9]

Currently, there is limited knowledge regarding the epidemiology of NTM disease, especially in populations comprised of hospitalized patients.[10] Very little data exists that compare the clinical features, demographic information, and other relevant characteristics of pulmonary disease, owing to NTM and TB, respectively. Additionally, to our knowledge, no studies have been conducted within institutions located in the southeastern United States.

The main objective of this study was to evaluate the differences in clinical presentation and comorbidities between TB- and NTM-positive patients at University of Florida Health Shands Hospital in Gainesville, Florida. The goal was to generate data that will be generalizable for hospitals within the southeastern United States and ultimately assist public health officials and other clinicians with decisions for patients who are positive for acid-fast bacilli (AFB) and not yet been identified on a species level (NTM vs TB). Through the use of our study findings, improper use of airborne isolation precautions may be reduced or avoided. This would also translate to more appropriate use of health care resources (including airborne isolation personal protective equipment) as well as the prevention of unnecessary stress for patients and staff, and increased patient safety.

METHODS

This study was conducted at a 1,100-bed academic medical center in north-central Florida. The study was approved by the University of Florida Institutional Review Board (# IRB201800128).

Data collection

Study data were collected and managed using electronic data capture tools (REDCap; Vanderbilt University, Nashville, TN) hosted at the University of Florida.[11] The institution's electronic medical record system, Epic, was queried for all patients who had a positive respiratory culture for mycobacteria, between January 1, 2011, and December 31, 2017. Only the first occurrence of Mycobacteria in the sputum was used. Patients who presented with a coinfection of 2 or more species were categorized based on the first species identified. Patients ages ≤10 years were excluded from this study as the literature suggests that the lungs, specifically the alveoli, are underdeveloped throughout the first several years of life.[12] This difference in the stage of development or morphology may introduce bias to some of the collected variables of interest. In addition to this, individuals ages ≤10 years inevitably have less cumulative environmental exposure and were less likely to have radiographic procedures, owing to the risks related to radiation exposure.

Table 1 shows several demographic and medical history variables that were collected. Tobacco smoke exposure was included either through past or current use and/or second-hand exposure. Incarceration included employment or volunteer work at a prison. Homelessness or exposure to homeless shelters included both residents and those exposed through volunteer work. Immunosuppressive therapy included the use of any of the following: systemic corticosteroids, inhaled corticosteroids, disease-modifying anti-rheumatic drugs, tissue necrosis factor-α inhibitors, antineoplastic/chemotherapy agents, and calcineurin inhibitors. Additional variables included heart or lung transplant, lung cancer, bacterial pulmonary coinfections (at the same time the Mycobacterial culture was collected), and any other pre-existing lung condition, including interstitial lung disease, idiopathic pulmonary fibrosis, hypersensitivity pneumonitis, sarcoidosis, pneumoconiosis, and α-1 antitrypsin deficiency. Clinical presentation included a variable for "incidental finding," which indicated whether this diagnosis was an incidental discovery after admission for a nonpulmonary complaint. Radiographic variables were found using results from either an x-ray or a computed tomography scan, with the computed tomography scan being the preferred source of information (Table 2). The species of mycobacteria and year of collection were also documented. The patient's preferred language was used as a proxy for immigration status, in conjunction with birth place data found during chart review, to populate the variable "foreign born." A study conducted in 2013 using the American Community Survey, a survey facilitated by the U.S. Census Bureau that reaches approximately 3.5 million households, found that 97.4% of individuals who spoke a language other than English as their main or preferred language were born outside of the United States.[13]

Table 1
Comparison of demographic information and comorbidities in patients culture-positive for NTM versus TB

	NTM (N = 564) n (%)	TB (N = 43) n (%)	*P* value[†]
Demographics and social history			
Foreign born[*]	13 (2.3)	21 (48.8)	<.001
Smoke exposure[*]	353 (62.6)	19 (44.2)	.017
Homelessness[*]	18 (3.2)	5 (11.6)	.005
Alcohol abuse[*]	56 (9.9)	9 (20.9)	.025
IV drug use[*]	39 (6.9)	4 (9.3)	.556
Incarceration[*]	43 (7.6)	10 (23.3)	.001
Sex			.010
Man	266 (47.2)	29 (67.4)	—
Woman	298 (52.8)	14 (32.6)	—
Race			–[‡]
White	475 (84.2)	14 (32.6)	—
Black	52 (9.2)	12 (27.9)	—
Asian	9 (1.6)	6 (14)	—
Native American	3 (0.5)	0 (0)	—
Multiracial	2 (0.4)	0 (0)	—
Other	23 (4.1)	11 (25.6)	—
Ethnicity			<.001
Non-Hispanic	544 (96.5)	34 (79.1)	—
Hispanic	20 (3.6)	9 (20.9)	—
Age, y (mean)	57.3	44.6	<.001
Comorbidities			
GERD	286 (50.7)	6 (14)	<.001
Renal disease	114 (20.2)	3 (7.0)	.034
Diabetes	152 (27.0)	9 (20.9)	.389
HIV	30 (5.3)	2 (4.7)	.850
Immunosuppression	188 (33.3)	5 (11.6)	.003
Bacterial coinfection	158 (28.0)	1 (2.3)	<.001
Transplant or cancer (heart/lung)	99 (17.6)	2 (4.7)	.029
CF	94 (16.7)	0 (0)	.004
Asthma	86 (15.3)	4 (9.3)	.290
COPD	370 (65.6)	6 (14.0)	<.001
Other pre-existing lung condition	201 (35.6)	4 (9.3)	<.001

CF, cystic fibrosis; *COPD*, chronic obstructive pulmonary disease; *GERD*, gastro-esophageal reflux disease; *NTM*, nontuberculous mycobacteria; *TB, Mycobacterium tuberculosis; IV*, intravenous.
[*]All dichotomous variables use "YES" as the reference group.
[†]The x^2 test was used for categorical variables, and the Student t test was used for continuous variables.
[‡]No *P* value was calculated for race as there were too few individuals in the TB group to conduct a multi-level variable analysis.

Statistical analyses

The 2-sample unpaired Student t test was used to analyze the difference in means between groups in regard to age, the only continuous variable of interest. The unpaired Student t test is appropriate as the populations are unrelated and the size of the population is large

Table 2
Comparison of clinical presentation and radiographic findings in patients culture-positive for NTM versus TB

(Reference = YES)	NTM (N = 564) n (%)	TB (N = 43) n (%)	*P* value*
Clinical presentation			
Fever	124 (22.0)	25 (58.1)	<.001
Dyspnea	368 (65.3)	27 (62.8)	.745
Cough	489 (86.7)	34 (79.1)	.162
Hemoptysis	94 (16.7)	12 (27.9)	.061
Night sweats	66 (11.7)	12 (27.9)	.002
Weight loss	109 (19.3)	24 (55.8)	<.001
Symptoms > 2 weeks	464 (82.3)	28 (65.1)	.006
Incidental finding	23 (4.1)	6 (14.0)	.003
(Reference = YES)	NTM (N = 551)† n (%)	TB (N = 43) n (%)	*P* value*
Radiographic findings			
Cavitation/cavitary lesion	112 (20.3)	18 (41.9)	.001
Pleural effusion	101 (18.3)	16 (37.2)	.003
Lobe involvement			
Upper	351 (63.7)	34 (79.1)	.042
Middle	240 (43.6)	13 (30.2)	.089
Lower	331 (60.1)	26 (60.5)	.960
Infiltrates	55 (10.0)	5 (11.6)	.730
Bronchiectasis	301 (54.2)	4 (9.3)	<.001
Nodules	317 (57.5)	28 (65.1)	.332
Miliary pattern	1 (0.2)	8 (18.6)	<.001
Lymphadenopathy	37 (6.7)	13 (30.2)	<.001

NTM, nontuberculous mycobacteria; *TB, Mycobacterium tuberculosis.*
*The x^2 test was used for categorical variables.
†Radiographic information was missing for 13 patients.

(n = 607). To determine whether there is a significant difference in proportions between NTM and TB with regard to various categorical variables, the X^2 test for independence was used. The *P* values for all variables were 2-tailed. Logistic regression was performed to identify significant risk factors associated with the outcome of TB compared with NTM. This was performed using the stepwise method. Common pulmonary comorbidities (CF, COPD, asthma, and "other pre-existing lung conditions," excluding lung cancer and lung transplant) were combined into 1 variable to simplify the regression equation. Only patients with available radiographic information (n = 594) were included in the logistic regression analysis. The data analysis for this study was performed using SAS software (version 9.3; SAS Institute, Inc, Cary, NC).

RESULTS

Through the query described earlier, a total of 607 unique patients with mycobacterial cultures (564 NTM and 43 TB) were identified. Approximately 98% of the patients had radiographic data available (n = 594). Of the 564 NTM infections, 32 species were identified, with the majority consisting of *M avium* complex (54.5%), *M abscessus* (15.7%), *M gordonae* (7.3%), and *M fortuitum* (5.3%).

Demographics and comorbidities

Patients with TB were more likely to be male, non-white, Hispanic, foreign-born, have a history of homelessness, alcohol abuse,

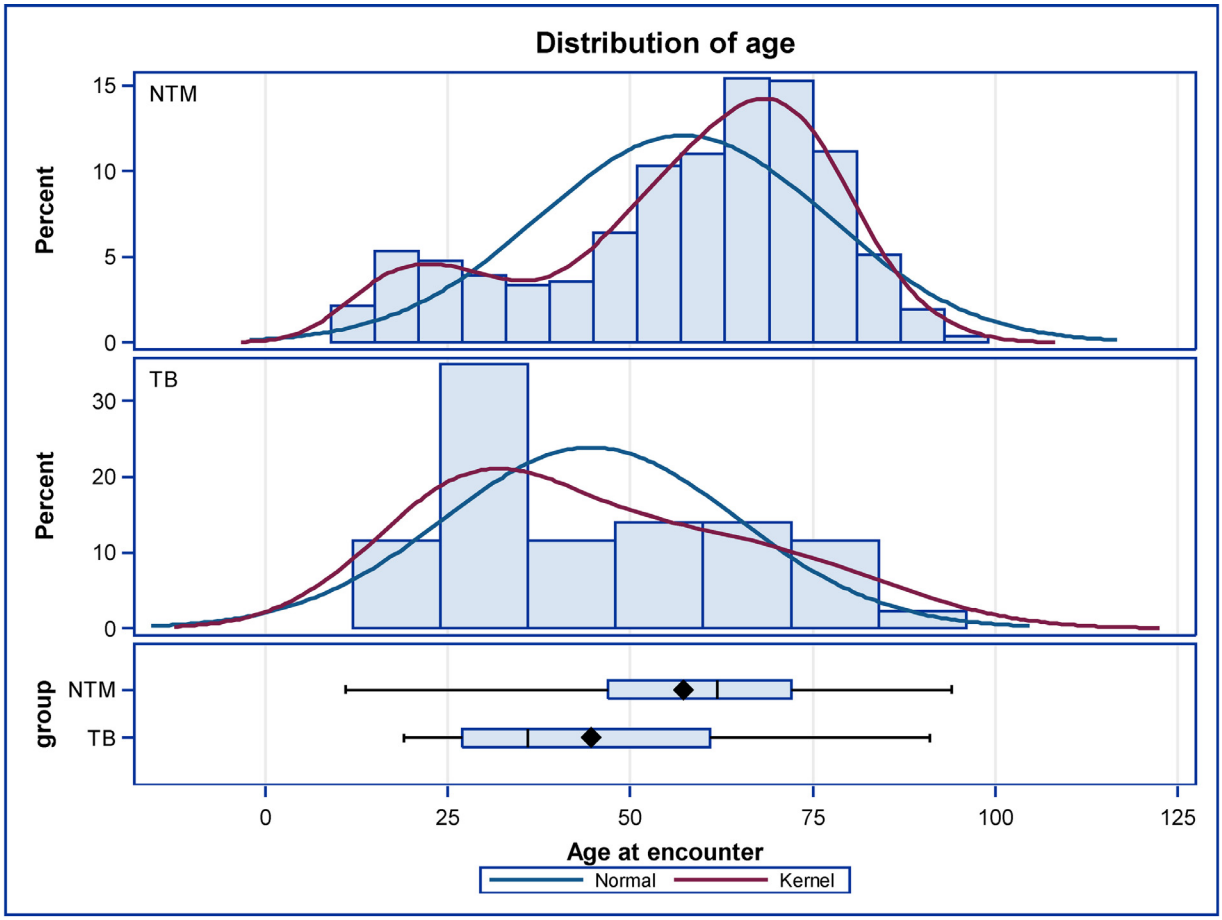

Fig 1. Age distribution of patients with NTM (top) versus TB (bottom). *NTM*, nontuberculous mycobacteria; *TB, Mycobacterium tuberculosis.*

intravenous drug use, incarceration, and less likely to have smoke exposure than those with NTM (Table 1).

Patients with TB were less likely than those with NTM to have any of the following comorbidities, including: GERD, renal disease, diabetes, immunosuppression, bacterial coinfection, heart/lung transplant or lung cancer, CF, asthma, COPD, and any other pre-existing condition (Table 1). The prevalence of HIV was similar in both groups, with 4.7% and 5.3% for TB and NTM, respectively (*P* value =.85).

The mean age at encounter of those with TB and NTM was 45 and 57 years of age, respectively. The age distribution, which can be visualized in Figure 1, is skewed left for NTM and skewed right for TB. The age distribution for NTM also presents as moderately bimodal in nature, with peaks < 25 and > 50 years (Fig 1).

Clinical presentation

Patients with TB were more likely to have a fever, hemoptysis, night sweats, weight loss, and be discovered incidentally, than those with NTM. Patients with TB were also less likely to have dyspnea, cough, and symptoms for > 2 weeks than those with NTM (Table 2).

Radiographic findings

Patients with TB were more likely to have cavitation, pleural effusion, upper lobe involvement, nodules, a miliary pattern, and lymphadenopathy, and were less likely to have middle lobe involvement, and bronchiectasis than those with NTM (Table 2).

Both TB and NTM patients were similar with regard to lower lobe involvement and presence of infiltrates. These findings also vary by species of NTM as bronchiectasis occurs more frequently in *M abscessus* and *M avium complex* than with all others. Additionally, *M avium complex* and *M gordonae* were more likely to be present in patients who had cavitation than all other species (Fig 2).

Statistical modeling

Although many variables were statistically significant in their prevalence between the 2 groups, when combined into a logistic regression model, only 8 variables were of statistical significance (Table 3). Four of these 8 variables are predictive of TB (foreign born, incarceration, cavitation, and lymphadenopathy) and 4 are predictive of NTM (smoke exposure, any pre-existing lung condition, immunosuppression, and bronchiectasis) (Table 3).

The logistic regression equation is as follows:

$$\begin{aligned}\hat{p} = &-0.87 + 3.2(\text{foreign born}) - 1.58(\text{smoke exposure}) \\ &+ 1.38(\text{incarceration}) - 1.83(\text{any pre-existing condition}) \\ &- 1.78(\text{immunosuppressed}) - 2.38(\text{bronchiectasis}) \\ &+ 1.06(\text{cavitation}) + 1.12(\text{lymphadenopathy})\end{aligned}$$

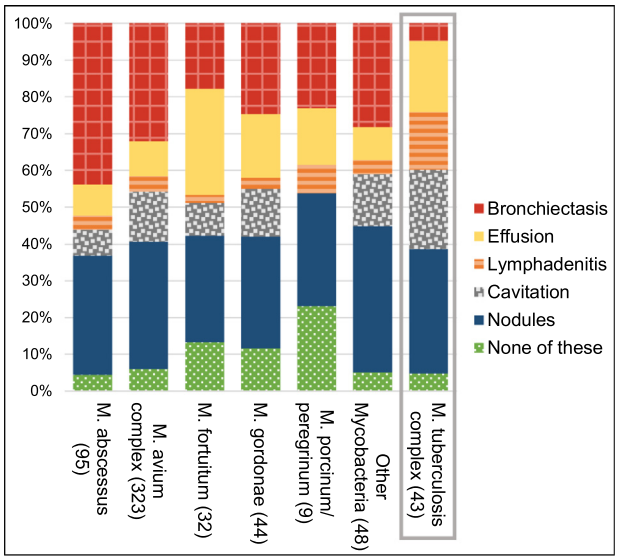

Fig 2. Comparison of radiographic findings between NTM groups and TB. Bronchiectasis occurred more frequently in NTM patients when compared with TB ($P < .05$), and lymphadenopathy/lymphadenitis and cavitation occurred more frequently in TB ($P < .05$). NTM, Nontuberculous mycobacteria; TB, Mycobacterium tuberculosis.

DISCUSSION

This study encompasses 8 years of comprehensive patient data in regard to TB and NTM in a geographic area that is increasingly prevalent for the latter. Additionally, Florida contains a moderate percentage of individuals, approximately 20% in the years 2012-2016, who have emigrated from other countries.[14] This study focuses on describing the epidemiology and speciation of NTM and TB as well as the demographics, symptomology, and radiographic findings in the study population. This information is important as NTM is becoming more prevalent and yet is not a reportable organism. Therefore, NTM is not well documented or regularly followed.

Of the 37 total variables investigated, 28 were found to be significantly different ($P < .05$) between TB and NTM cases (Tables 1-3). NTM patients were more likely to have pre-existing conditions, including exposure to tobacco smoke, and TB patients were more likely to have emigrated from another country. Certain factors such as hemoptysis and being positive for HIV were found to be similar in both TB and NTM patients. This is an important finding because providers often associate TB, rather than NTM, with HIV and hemoptysis, but in fact there was no significant difference. In the context of HIV or hemoptysis, both TB and NTM are significant concerns.

Limitations

Limitations include the reliance of chart review and use of historic data. Some records were incomplete or had gaps in coverage when patients were referred to our facility with incomplete outside records. Additionally, there may have been bias owing to the nature of the data collection process (ie, the reviewers were knowledgeable of the disease prior to searching for the variables of interest). However, a representative sample of records was completed by 2 separate reviewers (EK and ET) and subsequently checked for accuracy and reliability. There is a degree of uncertainty when relying on radiograph interpretations from multiple different radiologists over a

Table 3
Predictors of pulmonary TB versus NTM infection in patients with positive respiratory cultures

Parameter	Estimate	SEM	*P* value*
Intercept	−0.87	0.49	.08
Foreign born	3.24	0.56	<.001
Smoke exposure	−1.58	0.54	.003
Incarceration	1.38	0.61	.023
Pre-existing condition	−1.83	0.45	<.001
Immunosuppression	−1.78	0.67	.008
Bronchiectasis	−2.38	0.71	<.001
Cavitation	1.06	0.50	.034
Lymphadenopathy	1.12	0.55	.041

NTM, nontuberculous mycobacteria; *TB, Mycobacterium tuberculosis.*
*Maximum likelihood estimates from logistic regression analysis.

period of 8 years. However, our large sample size should help minimize error owing to these variations. Other limitations include exclusion of patients <10 years of age.

CONCLUSIONS

Future validation studies of our AFB risk prediction regression model (Table 3) are needed, and we encourage facilities to offer suggestions for modifications based on their own findings.

Further research is also needed into whether our insignificant variables might carry significance in a different patient population or geographic area.

We documented a diverse array of mycobacteria comprising 32 unique species. Further research at other large institutions in the southeast is encouraged so that we may compare our findings with geographically comparable facilities.

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