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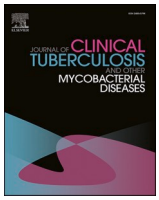

Case Report

Epidemiology of nontuberculous mycobacteria in the Finger Lakes region of New York

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ABSTRACT

Clinical-epidemiologic data for all nontuberculous mycobacteria isolated in the 9 County Finger Lakes region of NY from 226 patients between 04/01/2018–03/31/2020 were retrospectively analyzed. Only 51% of patients meeting diagnostic criteria were treated, while 25% not meeting diagnostic criteria were also treated, indicating important knowledge gaps and research opportunities.

1. Background

Nontuberculous Mycobacteria (NTM) are a diverse group of approximately 200 species within the Mycobacterium genus. They are increasingly recognized for their ability to cause a wide array of human disease. [1] NTM are ubiquitous in the environment and frequently isolated from soil and several water sources. [2] Pulmonary NTM (PNTM) disease is the most common clinical presentation, frequently in patients with underlying bronchiectasis, cystic fibrosis, and structural lung disease. [3] Extrapulmonary NTM (ENTM) infection is less common, often affecting immunocompromised hosts or individuals undergoing cosmetic or medical procedures. [4,5].

Recent studies indicate a rise in the incidence and prevalence of PNTM disease around the world. [6–11] Similar trends in the prevalence of PNTM are reported in the United States. [12–15] While fewer studies address ENTM disease, there is evidence of some regional variability in the prevalence of disease and geographic diversity in NTM species. [16,17].

Many of the preceding epidemiologic studies relied on health claims or microbiologic data alone without details of the clinical presentation. In addition, the diagnosis and management of NTM remains a challenge despite the availability of specific microbiologic, radiographic, and clinical criteria by the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) [18,19].

We performed active laboratory surveillance for NTM within the New York Finger Lakes region to assess the epidemiology of pulmonary and extrapulmonary disease and to explore characteristics involved in the decision-making process for the treatment of NTM disease.

2. Methods

2.1. Data collection

We retrospectively identified all positive NTM isolates collected between April 1st 2018 and March 31st 2020 at URMC and RRH laboratories as part of The Centers for Disease Control and Prevention's (CDC's) Emerging Infections Program (EIP) and expanded the surveillance to 9 counties in Western New York [20].

These labs receive samples for 9 counties that comprise the Finger Lakes region (Genesee, Livingston, Monroe, Ontario, Orleans, Seneca, Wayne, Wyoming, and Yates) with an estimated population of 1,222,868 based on 2020 U.S. Census Bureau data.

A case report form was completed using electronic medical records (EMR). Demographic, comorbidities, clinical, microbiologic, and radiologic data were collected and managed using the Research Electronic Data Capture (REDCap) system. Additional information on treatment and referral patterns were also obtained.

This study was approved by both URMC and RRH health systems Institutional Review Board.

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2.2. Study population and definitions

All patients with at least one culture growing NTM were included in this study. Patients were separated into PNTM and ENTM based on the source of their index cultures. The first positive culture obtained during the surveillance period was designated the index culture.

Patients with positive NTM specimens during the 6 months prior to the index culture, or with clinical documentation of preceding NTM, were considered prevalent. All other patients were considered incident. Pulmonary patients were evaluated to determine if they met ATS/IDSA clinical, microbiologic, and radiographic criteria for PNTM disease. Clinical criteria were based on symptoms present within 30 days of the date of index specimen collection. Radiographic criteria were determined based on imaging findings present within 90 days of index specimen collection. Patients were separately evaluated to determine if clinicians diagnosed PNTM disease irrespective of diagnostic criteria.

EMR were reviewed for specialist referral within 30 days of identification of NTM from the index culture. Patients who were already being managed by a specialist prior to identification on the index culture were counted as being referred to that specialty.

3. Results

Between April 1st 2018 and March 31st 2020, 670 samples grew NTM from 226 unique patients. Of these 226 patients, 196 had PNTM and 30 had ENTM isolates. The prevalence of positive cultures per year for PNTM was 8.0/100,000 population and 1.2/100,000 population for ENTM across all 9 counties of the Finger Lakes Region. The incidence rate per year was 6.8/100,000 population for PNTM and 1.1/100,000 population for ENTM. We found a prevalence rate of 5.6/100,000 population per year for PNTM when accounting only for patients meeting microbiologic criteria. Patients with PNTM were older than patients with ENTM (median age 69 vs 54) and more likely to be female (58% vs 37%,). The majority of patients with both PNTM and ENTM were White. Underlying lung disease was the most common comorbid condition in patients with PNTM (32% had COPD and 31% had bronchiectasis). Gastroesophageal reflux disease was the second most common comorbid condition (32%). Patients with ENTM were more likely to have an underlying immunodeficiency (13% vs 4%), either HIV with a CD4 count of less than 200 or a hematologic malignancy (Table 1).

Among the 196 PNTM patients, 9 grew more than one NTM species. None of the 30 ENTM patients grew multiple NTM species. *Mycobacterium avium* complex (MAC) was the most common NTM isolated from both pulmonary and extrapulmonary sources (Table 2). *Mycobacterium gordonae* was the next most commonly isolated NTM in pulmonary isolates followed by *Mycobacterium xenopi* and *Mycobacterium abscessus*. For extrapulmonary NTM, rapidly growing mycobacteria made up a larger proportion of isolates (40 %) with *M. chelonae* being the most commonly isolated organism after MAC.

All patients with ENTM and most patients with PNTM (91 %) experienced at least one symptom associated with NTM disease. Patients were more likely to experience symptoms related to the site of infection than systemic symptoms. Most patients experienced more than one symptom within two weeks prior to initial sample collection (Table 1).

Patients with PNTM isolates were assessed for meeting microbiologic, radiologic, and clinical criteria to indicate presence of disease. Only 42 % of 196 patients fulfilled all three criteria (Table 1). Among the 82 patients meeting all diagnostic criteria, only 51 % were treated. Three patients did not fulfill any criteria, 18 % met one, and 39 % met two. Clinicians considered 54 % of the 196 patients with PNTM isolates to have NTM disease. In comparison, patients with ENTM isolates were more often diagnosed to have true NTM infection (77 %) compared to patients with PNTM and were also more likely to be treated.

A total of 213 patients were referred to specialists within 30 days of initial specimen collection. Patients with PNTM isolates were most often referred to a pulmonologist (83 %) with fewer referred to infectious diseases or surgeons (Table 1). One patient was referred to the county health department. Patients with ENTM were more likely to be referred to infectious diseases and surgery.

The acquisition of susceptibilities for PNTM and ENTM along with treatment based on available susceptibilities is shown in Table 2. Susceptibilities were obtained more frequently in patients with ENTM; however, proportion who were treated with available susceptibilities was similar between PNTM and ENTM patients (74 % and 71 %, respectively).

Table 1
Clinical characteristics and management patterns of patients with NTM.

	PNTM[a] N = 196 (%)	ENTM[b] N = 30 (%)
Age (median)	69	54
Gender		
Female	114 (58)	11 (37)
Male	82 (42)	19 (63)
Race		
Black	10 (5)	5 (17)
White	175 (89)	23 (77)
Other	4 (2)	0 (0)
Unknown	7 (4)	2 (7)
Ethnicity		
Hispanic	3 (2)	0 (0)
Not Hispanic	174 (89)	30 (100)
Unknown	19 (10)	3 (10)
Comorbidities		
Underlying lung disease	128 (65)	3 (10)
Cystic Fibrosis	13 (7)	
COPD	63 (32)	
Bronchiectasis	60 (31)	
Emphysema	38 (19)	
Heart Disease	32 (16)	3 (10)
GERD	63 (32)	0 (0)
Diabetes	33 (17)	8 (27)
Chronic kidney disease	12 (6)	2 (7)
Neurologic Disease	17 (9)	2 (7)
Any immunodeficiency	7 (4)	7 (23)
HIV CD4 < 200	5 (3)	4 (13)
Solid organ transplant	1 (1)	0 (0)
Hematologic transplant	1 (1)	3 (10)
Malignancy	41 (21)	7 (23)
Solid organ Malignancy	34 (17)	3 (10)
Hematologic Malignancy	10 (5)	4 (13)
Any tobacco use	108 (55)	18 (60)
Symptoms		
Asymptomatic	24 (12 %)	0 (0 %)
One symptom	47 (24 %)	7 (23 %)
Two or more	125 (64 %)	23 (77 %)
Fever	26 (13 %)	8 (27 %)
Night sweats	11 (6 %)	2 (7 %)
Weight loss	25 (13 %)	3 (10 %)
Fatigue	40 (20 %)	4 (13 %)
Dyspnea	93 (47 %)	NA
Cough	143 (73 %)	NA
Hemoptysis	27 (14 %)	NA
Pain at site	NA	18 (60 %)
Redness, swelling	NA	18 (60 %)
Drainage, pus	NA	12 (40 %)
Specialist referral		
Pulmonology	162 (83 %)	1 (3 %)
Infectious Diseases	66 (34 %)	27 (90 %)
Surgery	15 (8 %)	10 (30 %)
Other	1 (1 %)	1 (3 %)
None	12 (6 %)	1 (3 %)
Diagnostic criteria met		
None	3 (2)	NA
One	35 (18)	NA
Two	76 (39)	NA
Three	82 (42)	NA

[a] PNTM – Pulmonary Nontuberculous Mycobacteria.
[b] ENTM – Extrapulmonary Nontuberculous Mycobacteria.

Table 2
Mycobacterium Species, Susceptibilities, and Treatment Patterns[a.]

Organism	PNTM (%)	ENTM (%)	PNTM Susceptibilities (%)	ENTM Susceptibilities (%)	PNTM treated (%)	ENTM treated (%)	PNTM Treated with Susceptibility (%)	ENTM Treated with Susceptibility (%)
Rapid growing mycobacteria	26 (13 %)	12 (40 %)						
Mycobacterium abscessus	13	1	10 (77)	1 (100)	3 (23)	1 (100)	4 (100)	1 (100)
Mycobacterium alvei	1	0						
Mycobacterium chelonae	4	7	1 (25)	6 (86)	–	6 (86)	–	6 (100)
Mycobacterium fortuitum	3	2	1 (33)	2 (100)	1 (33)	2 (100)	1 (100)	2 (100)
Mycobacterium mucogenicum	3	0	–	–	–	–	–	–
Mycobacterium peregrinum	1	0	–	–	–	–	–	–
Mycobacterium septicum	1	0	–	–	–	–	–	–
Mycobacterium smegmatis	0	1	–	1 (100)	–	1 (100)	–	1 (100)
Other RGM	3	2	–	–	–	–	–	–
Mycobacterium wolinskyi	0	1	–	1 (100)	–	1 (100)	–	1 (100)
Slow growing mycobacteria	178 (87 %)	18 (60 %)						
Mycobacterium avium complex	120	9	51 (43)	3 (33)	50 (42)	8 (89)	35 (70)	3 (38)
Mycobacterium celatum	1	0	1 (100)	–	1 (100)	–	1 (100)	—
Mycobacterium gordonae	29	5	1 (3)	–	1 (3)	–	1 (100)	–
Mycobacterium heraklionense	1	0	–	–	–	–	–	–
Mycobacterium kansasii	7	0	5 (83)	–	5 (83)	–	5 (100)	–
Mycobacterium kubicae	1	0	–	–	–	–	–	–
Mycobacterium kumamotonense	1	0	–	–	–	–	–	–
Mycobacterium marinum	0	3	–	2 (67)	–	1 (33)	–	1 (50)
Mycobacterium paragordonae	1	0	–	–	–	–	–	–
Mycobacterium szulgai	3	0	2 (67)	–	3 (100)	–	2 (67)	–
Mycobacterium xenopi	14	1	4 (29)	0 (0)	5 (36)	1 (100)	3 (60)	–
Other	1	0	–	–	–	–	–	–
Total	205	30	76 (37)	16 (53)	69 (34)	21 (70)	51 (74)	15 (71)

[a] This represents the 235 isolates of Non-tuberculous mycobacteria (NTM) obtained from 226 patients. All 9 of the patients with 2 pulmonary NTM were treated for only 1 isolate.

4. Discussion

The two-year active laboratory surveillance across the Finger Lakes Region of New York identified 226 patients with NTM with a culture positive prevalence rate of 8.0/100,000 population for PNTM and 1.2/100,000 per year for ENTM. When accounting for only those PNTM patients that met microbiologic criteria, the prevalence decreased to 5.6/100,000 population per year. These findings are consistent with a recent CDC EIP pilot study which reported a rate of 4.8/100,000 for PNTM and 1.2/100,000 for ENTM in Monroe County, NY, and an annual prevalence of 7.5/100,000 population across 4 sites. Single center and state-wide studies using microbiologic criteria demonstrated an increase in PNTM, however, variability in regional NTM prevalence indicates the need for more widespread reporting.[21–25].

Although PNTM infection has long been associated with cystic fibrosis [26] there is increasing recognition of its association with non-cystic fibrosis bronchiectasis [10]. One third of our patients meeting criteria for PNTM disease had non-cystic fibrosis bronchiectasis; while a substantial portion had emphysema and/or chronic obstructive pulmonary disease (COPD) without bronchiectasis and met diagnostic criteria. Other studies have reported similar proportions of patients with specific comorbid pulmonary disease, with COPD rates up to 68 % among patients in the Veteran's Health Administration. [13,15,20] Our rates of other comorbid conditions including gastroesophageal reflux disease, diabetes, malignancy, and organ transplant were comparable to prior studies in patients with PNTM. Higher rates of HIV were seen in patients with ENTM consistent with prior literature evaluating extrapulmonary disease from a US healthcare database.[16].

We reported the overall culture positive prevalence rate of 8.0/100,000 population per year for PNTM; however, only 42 % of 196 case met all three diagnostic criteria for disease. This is consistent with the CDC EIP NTM pilot surveillance which reported less than half of cases met diagnostic criteria, often because cases do not meet radiographic criteria. In our study, most patients that did not meet radiographic criteria lacked findings as consistent with the 2020 clinical practice guidelines.[27] However, a subset of the population did not have imaging within 90 days of index specimen collection which is a notable limitation. Only 51 % of PNTM patients that met diagnostic criteria were

treated, while 25 % of patients not meeting diagnostic criteria were treated. Despite established diagnostic criteria for identifying PNTM disease, the decision to treat remains challenging, resulting in wide variability in treatment practices. In a study of patients from a United States bronchiectasis registry, 40 % of patients with *Mycobacterium avium complex* and only 28 % of patients with *Mycobacterium abscessus complex* were treated. In contrast, 82 % of patients with *Mycobacterium avium complex* without HIV were treated in a multicenter retrospective review. [28,29] These findings underscore the need for further research in determining which patients should be monitored and who should receive antibiotics.

Susceptibility testing is recommended prior to initiating treatment for most NTM infections [19]. Surprisingly, 25–30 % of patients with PNTM and ENTM were treated empirically highlighting a critical area for improvement among providers in the region.

Unique to our study was the inclusion of *Mycobacterium gordonae* commonly identified as a colonizer which is not reported in other epidemiologic studies. This may increase the prevalence of NTM in our study. However, we were able to identify one patient who was treated for *M. gordonae* pulmonary disease after specialist referral indicating the need for careful consideration of this organism with low pathogenicity.

Treatment of NTM infections is complicated. Understanding of regional epidemiology and management patterns is fundamental to future changes in practice for improving patient care.

Ethical statement

Our research was reviewed by the Research Subjects Review Board (RSRB) at the University of Rochester Medical Center (URMC) and granted exemption on 7/19/21 for use of secondary research on data or specimens (no consent required). Our study was also granted expedited approval on 3/8/22 by the Rochester Regional Health Institutional Review Board. We further attest that our work is original and sources have been appropriately cited for referenced material. Our work has not previously been published and is not being considered for publication elsewhere. All authors have made significant contributions as stated in the declaration of interest statement. Artificial intelligence was not used in any part of our work.

CRediT authorship contribution statement

Michael Croix: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation. **Ghinwa Dumyati:** Writing – review & editing, Methodology, Formal analysis. **Alexandra Adams:** Writing – review & editing, Methodology, Conceptualization. **Paul Levy:** Writing – review & editing, Methodology, Conceptualization. **Emil Lesho:** Writing – review & editing, Resources. **Dwight Hardy:** Writing – review & editing, Resources. **Sonal Munsiff:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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