Species-Specific Risk Factors, Treatment Decisions, and Clinical Outcomes for Laboratory Isolates of Less Common Nontuberculous Mycobacteria in Washington State

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Abstract

Rationale: Nontuberculous mycobacteria (NTM) are a diverse group of environmental organisms that infrequently cause human disease. Understanding of the epidemiologic and clinical characteristics associated with NTM disease is needed to refine diagnostic and treatment strategies, particularly among the less commonly isolated species.

Objectives: To improve knowledge of geographic variance of NTM species, to correlate detailed clinical information with isolation of specific NTM, and to examine the decision to treat and outcomes for specific NTM.

Methods: Mycobacterial cultures submitted to the University of Washington mycobacterial laboratory from 1998 to 2011 were examined. We report isolation frequency and demographic information from all samples with clinical variables. We also examined treatment decisions and outcomes in a subset of patients with *Mycobacterium abscessus* complex, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium gordonae*, *Mycobacterium kansasii*, *Mycobacterium lentiflavum*, *Mycobacterium porcinum*, and *Mycobacterium xenopi*.

Results: Cultures of NTM were available from 3,470 patients, 937 of whom had clinical data available. When we compared patients born within or outside Washington State, we found that the mycobacterial species frequency varied. Among 168 patients with one of the studied environmental mycobacteria, 72% had major comorbid conditions. Bronchiectasis was common among patients with pulmonary isolation of any NTM, including those with nonpathogenic *M. gordonae*. Although mortality was high (37%), few deaths were directly attributable to mycobacterial infection. Among 56 patients who met American Thoracic Society criteria for NTM lung disease, 22 were treated, and 19 of those had *M. abscessus* complex and *M. kansasii*. The treatment regimens used tended to follow published guidelines.

Conclusions: Isolation of NTM varied by geographic region of origin and location within Washington State. Several clinical risk factors were specific to individual species. Comorbid conditions were common in patients with and without mycobacterial disease. Among patients with one of the studied organisms, there was a high mortality rate more frequently related to comorbid conditions than to mycobacterial disease.

Keywords: atypical mycobacteria; *Mycobacterium* pathogenicity; *Mycobacterium* epidemiology; *Mycobacterium xenopi*; *Mycobacterium chelonae*

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The nontuberculous mycobacteria (NTM) are a diverse group of over 150 species (1) that are ubiquitous in soil and water reservoirs (2–4). NTM disease is increasing (5)

and is an important cause of morbidity and financial burden (3, 6). Advances in isolation and identification techniques have expanded awareness of the heterogeneity of

NTM, but they have also increased uncertainty in clinical decision making when NTM are identified in clinical specimens. The American Thoracic Society

(ATS) provides diagnostic and treatment criteria (3), but few data exist regarding the application of these guidelines and associated outcomes (7). Moreover, previous large studies of environmental mycobacteria often lack detailed clinical data to incorporate epidemiologic findings into this discussion (8–10). Region-specific and species-specific data that integrate microbiologic and clinical information may enhance the utility of the ATS guidelines.

In this article, we describe the epidemiology of NTM isolated in a Washington State reference laboratory between 1998 and 2011 using modern diagnostic methods and correlate these observations with clinical data to examine factors associated with colonization and disease caused by the less common NTM. Additionally, we examine features that influence treatment decisions and clinical outcomes.

Methods

Study Design

We examined all cultures of NTM submitted to the Clinical Microbiology Laboratory at Harborview Medical Center, Seattle, Washington, from 1998 to 2011. This national reference laboratory receives samples from the University of Washington healthcare system and referral laboratories primarily within Washington State. We performed a retrospective data review of those patients who had been seen within the University of Washington healthcare system who had a non-*Mycobacterium avium* complex (non-MAC), non-*Mycobacterium gordonae* NTM that had appeared in 10 or more patients. Detailed records from referral institutions were not available. The institutional review board at the University of Washington approved this study.

Microbiologic Sample Processing, Culture, and Identification

Sample processing and mycobacterial cultures were performed using standard techniques (11, 12). Mycobacterial species were identified from culture by biochemical or molecular methods, including amplification of IS6110 for *Mycobacterium tuberculosis* (Mtb); amplification of 16S ribosomal RNA (rRNA) for MAC; and probe hybridization for Mtb, MAC, *M. gordonae*, and *Mycobacterium kansasii*. For specimens not identified by the above

techniques, the *rpoB* gene was amplified and sequenced, followed by 16S rRNA and *hsp65* if additional differentiation was required. The 16S rRNA gene and *rpoB* are single-round amplifications. The *hsp65* target includes nested amplifications for Mtb complex and MAC-specific primers and fluorescence resonance energy transfer probes. *Mycobacterium abscessus* complex includes *M. abscessus* ssp. *abscessus*, *M. abscessus* ssp. *massiliense*, and *M. abscessus* ssp. *bolletii* (formerly *M. massiliense* and *M. bolletii*). Discrimination among these subspecies by polymerase chain reaction was not adopted by the laboratory until 2012. Body site was categorized as pulmonary (including sputum, endobronchial aspirate, or lung tissue); skin and soft tissue; disseminated (including blood or bone marrow); lymph node; sterile sites (including cerebrospinal fluid, pleural

fluid and tissue, visceral tissues, and bone); and other, which included stool, urine, and sites that were not specified.

Clinical Data

Demographic and clinical information, including age, sex, ethnicity, birthplace by continent if outside Washington State, bronchiectasis, and HIV serostatus was obtained from the subset of patients who were evaluated within the University of Washington health system. The geographic origin of sample isolates included in this study was determined by the location of the submitting laboratory or clinical entity and divided *a priori* into six regions within the state by geographic or municipal boundaries. These regions included Seattle; the Olympic Peninsula; north of Seattle; south of Seattle (divided by city limits); east of Seattle (the region bordered

Figure 1. Distribution of patients with microbiologic and clinical data. A sample was classified as positive by polymerase chain reaction (PCR) only and not included in further analysis if the identification was made directly from the sample with *Mycobacterium*-directed sequence primers. MAC = *Mycobacterium avium* complex; NTM = nontuberculous mycobacteria.

on the west by Lake Washington and on the east by the Cascade Mountains); and east of the Cascades, a mountain range that divides the State of Washington into two zones. Eastern Washington receives less than one-third of the rainfall and has greater seasonal temperature variation than the more temperate western Washington. For species observed in more than 10 patients, not including MAC, a detailed abstraction of clinical documentation was performed by a single investigator using a standardized data extraction method.

Risk Factors

Risk factors included history of Mtb disease; tobacco use (active if within the previous year); excessive alcohol consumption (by self or clinician identification); history of intravenous drug use, homelessness, or incarceration; or current use of immunosuppressive medication. Comorbid conditions included HIV, solid organ or stem cell transplant, diabetes, chronic lung disease (chronic obstructive pulmonary disease [COPD], cystic fibrosis [CF], pulmonary fibrosis, and others), and malignancy (considered inactive if in remission or not receiving therapy for >1 yr). Imaging results were included if a chest radiograph or computed tomographic scan was obtained at the time of diagnosis or within 6 months if clinically relevant.

Outcomes

Outcomes included decision to treat with antimicrobials, treatment regimen, vital status, and whether a patient met ATS criteria for NTM lung disease. These criteria were defined as (1) pulmonary symptoms or consistent radiographic changes (bronchiectasis and/or nodules by chest radiograph or computed tomographic scan) and (2) a positive culture result from more than two expectorated sputum samples or at least one bronchoscopic sample or lung biopsy (3). The presence of an alternative diagnosis was evaluated as either definite or possible. Treatment regimen included all antimicrobials used over the course of therapy. Death was considered potentially related to the NTM if it was documented as a possible contributing factor or if a patient was being treated for mycobacterial disease at the time of death.

Figure 2. (A) Map of Washington State divided into six regions by geography and municipal boundaries, including the Olympic Peninsula, Seattle, north of Seattle, south of Seattle, east of Seattle, and east of the Cascades. The border between Seattle and north of Seattle is the King County–Snohomish County border (and the Seattle city limits). The border between Seattle and the region south of Seattle is the southern city limits. The region east of Seattle is bordered on the west by Lake Washington and on the east by the Cascade Mountain Range (and the eastern border of King County). (B) Relative proportions of the most commonly isolated nontuberculous mycobacteria (NTM) submitted to the University of Washington mycobacterial reference laboratory by location of submission, including *Mycobacterium avium* complex (MAC). (C) Relative proportions of the most commonly isolated non-MAC NTM. Those submitted from out of state are not shown. Isolates identified only as *Mycobacterium fortuitum* complex are not included, because these may represent *M. fortuitum*, *Mycobacterium chelonae*, *Mycobacterium porcinum*, or others.

Table 1. Demographics and sample sites of patients with less common nontuberculous mycobacteria species

	<i>Mycobacterium abscessus</i> complex*	<i>Mycobacterium chelonae</i>	<i>Mycobacterium fortuitum</i> †	<i>Mycobacterium gordonae</i>	<i>Mycobacterium kansasii</i>	<i>Mycobacterium lentiflavum</i>	<i>Mycobacterium porcinum</i>	<i>Mycobacterium xenopi</i>
n‡	47	25	17	121	27	31	11	10
Median age, yr	43	56	58	58	59	51	62	54
Male sex, %	51.1	56.0	94.1	53.7	70.4	58.1	36.4	90.0
Race, %								
White	83.0	80.0	52.9	57.9	63.0	48.4	72.7	60.0
Black	2.1	12.0	11.8	15.7	7.4	25.8	9.1	30.0
Asian	14.9	8.0	23.5	22.3	22.2	25.8	18.2	10.0
Site of isolation, %								
Pulmonary	89.4	44.0	88.2	97.5	96.3	100	90.9	80.0
Skin and soft tissue	6.4	52.0	5.9	1.7	0	0	0	20.0
Disseminated	4.3	0	0	0	0	0	9.1	0
Sterile site	0	0	6	0	0	0	0	0
Other	0	4.0	0	0.8	3.7	0	0	0
Birthplace§, %								
Washington State	36.2	28.0	17.6	22.5	37.0	16.1	18.2	30.0
North America	44.7	52.0	47.0	38.3	37.0	41.9	36.4	60.0
South America	0	0	0	0.8	0	0	9.1	0
Africa	2.1	8.0	11.8	10.8	0	22.6	9.1	0
Asia	14.9	8.0	23.5	21.7	22.2	19.4	18.2	10.0
Europe	2.1	4.0	0	5.8	3.7	0	9.1	0
Middle East	0	0	0	0.8	0	0	0	0

Demographic characteristics shown are of patients with clinical data available who had non-*Mycobacterium avium* complex nontuberculous mycobacteria isolated by culture.

**Mycobacterium abscessus* complex includes *M. abscessus* ssp. *abscessus*, *M. abscessus* ssp. *massiliense*, and *M. abscessus* ssp. *bolletii* (the latter two formerly known as *M. massiliense* and *M. bolletii*, respectively) because discrimination among these subspecies by polymerase chain reaction was not adopted by the laboratory until 2012.

†*Mycobacterium fortuitum* does not include organisms identified as *M. fortuitum* complex.

‡Number of patients with data available.

§One patient with *Mycobacterium gordonae* did not have birthplace data available.

||Not including patients from Washington State.

Data Analysis

Statistical analyses were performed using Stata version 14.0 software (StataCorp, College Station, TX) to compare risk factors and outcomes between patients with pulmonary NTM meeting ATS criteria and a reference group of individuals from whom *M. gordonae* was isolated. *M. gordonae* was selected to represent a group of patients who might have NTM isolated but not have invasive disease, because this is generally accepted to be a nonpathogenic organism. Categorical differences were evaluated with the chi-square test, and differences in means were evaluated using Student's *t* test. *P* < 0.05 was considered statistically significant.

Results

Identification and Microbiology

Among 100,563 specimens submitted for mycobacterial analysis from 1998 to 2011, 4,724 samples from 3,470 patients had a positive culture or polymerase chain reaction–based identification of NTM. Seventy-four of these samples were from

outside Washington State and were excluded (Figure 1).

Identification and nomenclature of NTM evolved over the course of the study period (see Table E1 in the online supplement). NTM were isolated 2.4 times more often than Mtb. Of NTM with more than 10 isolates, *Mycobacterium szulgai* (64%), *M. abscessus* complex (55%), and *Mycobacterium xenopi* (50%) were most likely to have a positive smear, similar to Mtb (49%). In contrast, only 31% of MAC isolates had a positive smear (Table E2). The most commonly isolated species was MAC, including *Mycobacterium avium* and *Mycobacterium intracellulare* complexes (52.1%), followed by *M. gordonae* (16.5%), *M. abscessus* complex (4.4%), *Mycobacterium chelonae* (4.3%), *Mycobacterium fortuitum* (3.7%), *M. kansasii* (2.2%), *Mycobacterium lentiflavum* (1.8%), and *M. xenopi* (0.9%) (Table E3).

Site of Isolation

For certain organisms, including *Mycobacterium marinum* or *Mycobacterium ulcerans*, and to a lesser extent *M. chelonae*, skin and soft tissue

sources were more common than other sites (85.7% for *M. marinum* or *M. ulcerans*; 36.4% for *M. chelonae*). Few organisms were identified as causing disseminated disease, primarily MAC, and more rarely *M. abscessus* complex, *Mycobacterium heckshornense*, and *Mycobacterium porcinum*. Organisms causing invasive disease in a sterile site included MAC and *M. abscessus* complex, *M. chelonae*, *M. fortuitum*, and *Mycobacterium mucogenicum/phocaicum*. Lymphadenitis was an uncommon finding (1.7% of all NTM isolates, of which 77% were MAC) (Table E3).

Geography

A total of 4,650 of the NTM isolates were derived from patients within Washington State. More than 75% of these were from the Seattle area. The most frequently identified organisms (after MAC) differed slightly by region of sample derivation. *M. kansasii* was not found north of Seattle, whereas *Mycobacterium simiae* was found only in Seattle and farther north. East of the Cascade Mountains, the most common organisms isolated were *M. fortuitum*

followed by *M. kansasii* and *M. gordonae* (Figure 2).

To determine whether location of patient origin contributed to the relative frequency of organisms isolated, we reviewed demographic records for the 937 patients with clinical information available; these samples were all obtained in Seattle. Although an individual's specific geographic exposures or duration of time spent in Washington State were rarely available, location of birth was uniformly collected at patient registration. Of the patients, 28.9% were native to Washington State, and 23.7% were born outside the United States (Table 1). The most commonly isolated NTM species from patients of all regions were MAC followed by *M. gordonae* and *M. abscessus* complex (Figure 3).

Among the less common NTM, frequency of isolation differed slightly in those native to Washington State in comparison to those born elsewhere (Table 1 and Figure 3). For example, although patients native to Washington State contributed a smaller proportion (28.7%) of NTM samples than patients from the rest of the United States (47.2%), the percentage of *M. kansasii* isolates obtained from patients native to Washington State was equivalent to that obtained from patients from the rest of the United States (37.0%). *M. xenopi* was detected primarily in patients from North America, including three patients native to Washington State. Of those with *M. fortuitum*, a relatively high proportion were from Asia (23.5%), and of those with *M. lentiflavum*, a relatively high proportion were from Africa (22.6%) (Table 1). Together, these data suggest that NTM have specific geographic associations, including distinct patterns within Washington State, and that both place of residence and place of origin may contribute.

Risk Factors by Organism

We reviewed the charts of patients with the most common non-MAC NTM species to identify risk factors associated with isolation of specific NTM (Table 2), chosen by those with more than 25 positive samples associated with clinical data. Patients with *M. simiae* were reviewed, but this group comprised only six patients.

Overall, this was a highly medically complex population, including those with

Figure 3. Commonly isolated nontuberculous mycobacteria (NTM) in patients native to Washington State in comparison to nonnative Washington State residents by continent of origin. The 10 most common non-*Mycobacterium avium* complex NTM species are shown with the patient's birthplace by continent in comparison to Washington State. North America includes Canada and Mexico but excludes Washington State. Asia includes the Pacific Islands (n = 4). Patients from Oceania (n = 1), South America (n = 7), and the Middle East (n = 4) are not shown. The number of subjects is otherwise as listed in Table 1.

M. gordonae. Among 217 patients, 83% had one or more comorbid conditions, including HIV, diabetes, lung disease, malignancy, or immunosuppression (including all but one of the patients with *M. gordonae*). Although HIV was relatively uncommon, the majority of CD4 counts at diagnosis of the NTM were less than 100 (median, 95; range, 2–722; n = 26). For patients with HIV infection, the median number of CD4 cells per milliliter for four patients with HIV and *M. kansasii* was 60 (range, 12–110); for three patients with *M. lentiflavum*, it was 25 (range, 14–347); and for three patients with *M. xenopi*, it was 128 (range, 9–221). In contrast, the median among those with *M. gordonae* (n = 8) was 168 (range, 3–722).

Chronic lung disease and bronchiectasis were very common, particularly among patients with *M. abscessus* complex, though they were absent among patients with *M. xenopi*. COPD was not more likely among those with *M. kansasii* (25.9%) than among those with any organism (25.3%). Chest imaging was

infrequently normal (20%). Diffuse infiltrates were most common, followed by masses or nodules. Malignancy was most common among *M. gordonae* and *M. xenopi*, and active immunosuppression was most common among patients with *M. chelonae* or *M. xenopi* (though least common among those with *M. kansasii*). Homelessness and intravenous drug use were most common among patients with *M. fortuitum*. Finally, a history of Mtb was most common among patients with *M. lentiflavum*. Together, these data point out associations between specific NTM and certain clinical risk factors.

Risk Factors by Site of Isolation

Among 214 patients with one of the studied mycobacterial species, 191 were isolated from pulmonary sources, 18 from skin or soft tissue, and 5 from disseminated or sterile site infections (Table 3). The two sterile site infections were both vertebral osteomyelitis, one with *M. fortuitum* and the other with *M. xenopi*. One of these patients had a history of injection drug use,

Table 2. Clinical risk factors of individuals with less common nontuberculous mycobacteria species

	<i>Mycobacterium abscessus</i> complex	<i>Mycobacterium chelonae</i>	<i>Mycobacterium fortuitum</i>	<i>Mycobacterium gordonae</i>	<i>Mycobacterium kansasii</i>	<i>Mycobacterium lentiflavum</i>	<i>Mycobacterium porcinum</i>	<i>Mycobacterium xenopi</i>
Risk factors, n*	47	25	17	49 [†]	27	31	11	10
History of <i>Mycobacterium tuberculosis</i> , %	6.5	12.0	17.7	15.9	11.1	29.1	27.3	0
Lung disease, %	47	25	17	46	27	31	11	10
None	27.7	68.0	52.9	50.0	59.3	64.5	81.8	100
COPD	25.5	24.0	35.3	29.6	25.9	22.6	18.2	0
Cystic fibrosis	36.2	4.0	0	2.3	3.7	3.2	0	0
Pulmonary fibrosis	6.4	0	11.8	4.6	11.1	3.2	0	0
Other	4.2	4.0	0	13.0	0	6.5	0	0
Bronchiectasis, %	83.0	32.0	35.3	27.1	40.7	38.7	45.5	0
CXR findings, %								
Normal	14.7	40.0	28.6	25.0	8.7	24.1	27.3	11.1
Infiltrate	26.5	30.0	28.6	50.0	52.2	31.0	18.2	22.2
Cavitary lesion	2.9	0	7.1	0	8.7	3.5	0	22.2
Mass or nodule	5.9	5.0	7.1	12.5	8.7	13.8	9.1	33.3
Other	8.8	10.0	21.4	12.5	13.0	17.2	5.5	11.1
Reason for culture, %								
None or routine	21.7	0	5.9	14.6	3.7	0	0	0
Cough or hemoptysis	52.2	36.0	58.8	65.9	59.3	66.7	80.0	30.0
Imaging findings	13.1	4.0	11.8	7.3	11.1	13.3	10.0	50.0
Other	13.1	60.0	23.6	12.2	25.9	20.0	10.0	20.0
Active tobacco use, %	10.9	12.0	41.2	37.0	29.6	25.8	18.2	60.0
Immunosuppression, %	30.4	44.0	18.8	28.9	7.7	16.7	18.2	60.0
History of malignancy, %	2.8	28.0	11.8	39.6	18.5	9.7	9.1	50.0
History of transplant, %	17.0	20.0	11.8	13.6	3.7	6.5	0	30.0
HIV [‡] , %	0	0	9.1	17.9	21.0	17.6	12.5	33.3
Median CD4 cells/ml	—	—	343	169	60	24	64	128
Diabetes, %	38.3	28.0	23.5	13.6	18.5	12.9	0	10.0
Major comorbid disease, %	80.9	76.0	64.7	97.9	70.4	58.1	54.6	100
EtOH abuse, %	11.1	1.0	23.5	23.9	23.9	12.9	18.2	30.0
History of homelessness, %	2.2	0	29.4	14.0	14.8	19.4	18.2	20.0
History of IVDU, %	0	8.0	26.7	13.0	18.5	10.0	9.1	20.0
History of jail/prison, %	3.2	0	20.0	7.1	15.8	21.7	18.2	14.3
Outcomes								
Multiple organisms, %	36.2	12.0	11.8	0	37.0	25.8	36.4	10.0
Multiple positive cultures, %	55.3	44.0	29.4	14.6	33.3	9.7	45.5	40.0
Met ATS criteria [§] , %	59.5	27.3	33.3	20.8	30.8	9.7	50.0	75.0
Alternative diagnosis, %	23.3	40.9	46.2	93.8	37.5	69.6	40.0	20.0
Treatment, %	47.8	50.0	23.5	0	22.2	0	9.1	30.0
Deceased , %	42.9	48.0	41.2		36.0	31.0	22.2	50.0
Possibly related	21.4	0	0		4.0	0.0	0	20.0
Other known cause	11.9	16.0	17.6		8.0	13.8	11.1	20.0
Cause unknown	9.5	28.0	23.5		24.0	17.3	11.1	10.0
Follow-up								
Median follow-up, yr	2	2	2	3	3	2	<1	3

Definition of abbreviations: ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; CXR = chest radiograph; IVDU = intravenous drug use.

*The maximum number of patients with data available.

[†]Fifty of 121 *Mycobacterium gordonae* patients were selected for detailed review. One was excluded after identification because of concomitant isolation of *Mycobacterium hassiacum*.

[‡]HIV status is listed if there was documentation of testing in the clinical record, either by patient report or by test result.

[§]Includes only patients with pulmonary samples.

^{||}Two patients of the 121 total with *M. gordonae* received therapy, one with positive culture of a lung biopsy specimen and the second by bronchoalveolar lavage. The latter initially had some improvement with therapy; however, neither had long-term improvement in their symptoms. These two patients were not included among those selected for detailed review.

[¶]Deaths of *M. gordonae* patients are not listed, because these were extracted after the close of the study period.

and the other had post-transplant immunosuppression.

Of the three with bacteremia, one had *M. porcinum* associated with a central venous catheter, and the other two had *M. abscessus* complex that was not line associated. Among 13 patients with skin or soft tissue infections with *M. chelonae*, 4 were associated with a medically implanted foreign object and 1 with a surgical wound. Patients with soft tissue infections caused by NTM were more likely to be immunosuppressed

(66.7% vs. 23.3%; $P < 0.0001$) and less likely to have pulmonary disease, though 10% still had bronchiectasis.

Clinical Characteristics Associated with Meeting ATS Criteria

To examine the distinguishing features of patients meeting ATS criteria with these less commonly isolated organisms, we analyzed a control group of patients with isolation of *M. gordonae*, which is generally

considered to be nonpathogenic. In our sample of 121 patients with isolation of *M. gordonae*, only 2 were treated for invasive disease.

We selected 50 patients with pulmonary isolation of *M. gordonae* in the absence of other organisms and compared them with the group of patients with pulmonary isolation of non-MAC, non-*M. gordonae* NTM meeting ATS criteria (Table 4). The *M. gordonae* group had a median age of 57.5 years and was more

Table 3. Clinical risk factors and outcomes of patients with isolation of non-*Mycobacterium avium* complex, non-*Mycobacterium gordonae* nontuberculous mycobacteria by site of isolation

	Pulmonary	Skin and Soft Tissue	P Value*	Sterile Site	Disseminated
Risk factors, n [†]	191	18		2	3
Median age, yr	57	51	0.53	57	50
Male sex, %	59.2	55.6	0.77	100	66.7
White race, %	63.4	89.9	0.03	100	66.7
History of <i>Mycobacterium tuberculosis</i> , %	15.3	5.6	0.28	0	0
COPD, %	26.4	16.7	0.35	0	0
Cystic fibrosis, %	11.7	0	0.13	0	0
Bronchiectasis, %	49.8	10.5	0.003	0	0
Normal CXR, %	18.6	58.3	0.001	0	0
Active tobacco use, %	27.0	11.8	0.17	0	33.3
Immunosuppression, %	23.3	66.7	<0.0001	50.0	66.7
Active malignancy, %	18.5	16.7	0.78	0	0
History of transplant, %	10.8	33.3	0.006	0	33.3
HIV, %	14.5	0	0.15	0	0
Diabetes, %	19.3	38.9	0.06	0	33.3
Major comorbid disease, %	79.1	72.2	0.50	50.0	66.7
History of EtOH abuse, %	21.3	17.7	0.69	0	0
Homeless, %	12.3	5.9	0.40	0	0
History of IVDU, %	10.3	5.9	0.52	50.0	0
History of jail/prison, %	10.8	0	0.26	0	50.0
Outcomes					
Multiple organisms, %	23.3	0	0.02	0	0
Multiple positive cultures, %	29.8	50.0	0.08	0	100
Alternative diagnosis, %	58.1	5.9	<0.0001	0	0
Treatment, %	14.2	68.4	<0.0001	100	66.7
Deceased, %	42.5	53.3	0.39	100	33.3
Follow-up					
Median follow-up, yr	2	2		4	0

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; CXR = chest radiograph; IVDU = intravenous drug use.

*P value refers to comparison of pulmonary and skin and soft tissue infection groups.

[†]Indicates the maximum number of patients with data available.

Boldface type indicates $P < 0.05$.

likely than the non-*M. gordonae* group to have a major medical condition (97.9% vs. 75.0%; $P = 0.001$). In comparison, the non-*M. gordonae* group was slightly younger (median age, 49.5 yr; $P = 0.04$), more likely to have bronchiectasis (62.5% vs. 27.1%; $P < 0.0001$), and more likely to have abnormal chest imaging (94.6% vs. 71.4%; $P = 0.005$). Only 20% of those with *M. gordonae* met ATS criteria by the same metric; they were much less likely to have multiple positive cultures (82.1% vs. 14.6%; $P < 0.0001$).

Of note, 33.3% of non-*M. gordonae* patients meeting ATS criteria had an alternative diagnosis to account for their presentation, whereas 93.3% of patients with *M. gordonae* did ($P < 0.0001$). Excluding non-*M. gordonae* patients with alternative diagnoses did not

alter the statistical results (data not shown).

Outcomes

Among patients with pulmonary isolates, those with *M. abscessus* complex and *M. kansasii* were most likely to be treated, although those with *M. porcinum* and *M. xenopi* more often met ATS criteria. Of the 56 patients who met ATS criteria for NTM lung disease, 22 were treated (Table 4). Of the 22 treated patients, 19 had *M. abscessus* complex (13) or *M. kansasii* (5). Of those who were not treated, 17 had an alternative diagnosis, including bacterial pneumonia or CF exacerbation (4), MAC (4), *Pneumocystis* (2), malignancy, tuberculosis, *Nocardia*, and sarcoidosis. In the remaining 17, cultures were reviewed and the organism

was not thought to be pathogenic (7), review of the cultures was not documented (3), the patients were lost to follow-up (4), or there was insufficient information (3).

Some patients with pulmonary isolation of NTM were treated without meeting ATS criteria, including five with *M. abscessus* complex, two with *M. simiae*, two with *M. fortuitum*, and one each with *M. kansasii* and *M. chelonae*. Four of five patients with sterile site or disseminated infection were treated with antibiotics; one case of bacteremia was discovered after the patient's death. Finally, of the patients with skin and soft tissue isolation of NTM, 68.4% were treated.

Among patients with pulmonary isolates, the proportion of patients who died within the study period was the same as in those who did or did not receive therapy (33.7% vs. 34.6%; $P = 0.9$). This remained true when we included only those who met ATS criteria (42.9% with therapy vs. 35.3% without; $P = 0.5$) and those without definitive alternative diagnoses (40.9% vs. 37.5%; $P = 0.8$). Among those with skin and soft tissue isolation of NTM, the majority of the patients were deceased at the end of the study period (53.3%), in comparison to only one of three patients with bacteremia (a patient with *M. abscessus* complex).

Treatment Regimens

Table 5 lists the treatment regimens of the patients treated for each organism (including all sites of isolation). In general, these regimens tended to follow ATS recommendations. For example, a macrolide-based regimen for treatment of *M. abscessus* complex was used in 17 of 19 patients, and treatment of *M. kansasii* was composed of rifampin, ethambutol, and isoniazid in 5 of 6 patients, though providers added pyrazinamide in 3 patients. Together, these data suggest that clinicians rely upon published guidelines once a decision to treat has been made. In contrast, the decision to treat is variable, especially for the less well-understood species.

Discussion

In our present study, we examined the clinical and epidemiologic factors

Table 4. Clinical risk factors and outcomes in patients who met American Thoracic Society criteria for nontuberculous mycobacterial lung disease (not including patients with *Mycobacterium avium* complex) in comparison to those with isolation of *Mycobacterium gordonae*

	Met ATS Criteria*	<i>Mycobacterium gordonae</i> Control Subjects†	P Value
Demographics			
n‡	56	49	
Median age, yr	49.5	57.5	0.04
Male sex, %	64.3	52.1	0.21
White race, %	78.6	58.3	0.03
Risk factors			
History of <i>Mycobacterium tuberculosis</i> , %	7.1	16.3	0.15
COPD, %	21.4	29.6	0.35
Cystic fibrosis, %	21.4	2.3	0.005
Bronchiectasis, %	62.5	27.1	<0.0001
Abnormal imaging, %	94.6	71.4	0.005
Active tobacco, %	25.0	34.8	0.28
Immunosuppression, %	29.1	29.6	0.96
Active malignancy, %	19.6	30.2	0.22
History of transplant, %	14.3	14.0	0.96
HIV, %	9.8	17.9	0.33
Diabetes, %	17.9	15.9	0.80
Major comorbid disease, %	75.0	97.9	0.001
History EtOH abuse, %	21.8	23.9	0.80
History of homelessness, %	10.9	13.9	0.67
History of IVDU, %	9.3	13.0	0.55
History of jail/prison, %	13.2	6.7	0.50
History of positive PPD, %	23.5	61.5	0.005
Outcomes			
Multiple positive cultures, %	82.1	14.6	<0.0001
Multiple organisms, %	28.6	0.0	
Met ATS criteria, %	100	20.8	
Alternative diagnosis, %	33.3	93.3	<0.0001
Treatment, %	40.0	0.0	
Median follow-up, yr	2	3	

Definition of abbreviations: ATS = American Thoracic Society; COPD = chronic obstructive pulmonary disease; IVDU = intravenous drug use; PPD = tuberculin purified protein derivative test.

*This group includes patients with any of the reviewed organisms who met ATS criteria, including those with *Mycobacterium abscessus* complex, *Mycobacterium chelonae*, *Mycobacterium fortuitum*, *Mycobacterium kansasii*, *Mycobacterium lentiflavum*, *Mycobacterium porcinum*, *Mycobacterium simiae*, and *Mycobacterium xenopi*.

†Fifty of 121 patients with isolation of *Mycobacterium gordonae* in the absence of other organisms were chosen. One was excluded after identification because of concomitant isolation of *Mycobacterium hassiacum*.

‡Indicates the maximum number of patients with data available.

Boldface type indicates $P < 0.05$.

associated with NTM colonization and disease as well as factors influencing clinical decision making and outcomes in a tertiary hospital system and mycobacterial referral laboratory in Washington State. Our primary findings include geographic observations about NTM in the Pacific Northwest, identification of new clinical risk factors for several species, observations about treatment decisions and outcomes, and significant variability in clinical decision making regarding the less

commonly isolated NTM (6, 9, 14). To our knowledge, this is the largest study with detailed clinical data and the only such study done in Washington State.

Previous studies in the United States suggest that some NTM are geographically restricted. In the United States, *M. kansasii* has appeared to originate primarily in the Midwest, the South, and California (9, 13, 14). Furthermore, *M. kansasii* and *M. lentiflavum* were rarely isolated in a

large series in Oregon, which directly neighbors Washington State (9).

The higher frequency of *M. kansasii* isolated in our series may be due to specific geographic features of Washington State, a changing environment, or increasing globalization and travel. We also observed other geographic differences, including rare isolation of *Mycobacterium scrofulaceum* and absence of *M. malmoense*, which have been reported more frequently elsewhere (15, 16). In contrast to previously published data estimating that *M. xenopi* represents about 12% of isolates from North America (15), we found few patients with *M. xenopi* (0.9% of all isolates), similar to data from Oregon (0.3%) (9).

When we analyzed the location of patient birth and the source of sample collection (Figures 2 and 3), the most commonly isolated NTM species in each category was MAC, followed by *M. gordonae* and *M. abscessus* complex. The exceptions were those who were born in Africa, in whom *M. lentiflavum* was more common than *M. abscessus* complex, and those with isolates obtained east of the Cascade Mountains or north of Seattle, in whom *M. fortuitum* was second and third most common, respectively.

Additional microvariation was observed within Washington State, though the comparison was limited by few patients in certain regions, including that *M. abscessus* complex and *M. lentiflavum* were not isolated from samples from the Olympic Peninsula or east of the Cascade Mountains. Likewise, *M. kansasii* was not isolated from samples from the Olympic Peninsula or north of Seattle. The organisms that were isolated from patients on the peninsula included *M. mucogenicum/phocaicum*, *Mycobacterium paraffinicum*, and *Mycobacterium nebraskense/seolense*, entities that were less common elsewhere. These observations may reflect regional variation in climate or immigration patterns. To our knowledge, this is the first study to demonstrate NTM heterogeneity based on both regional microvariation and the patient's location of origin.

We identified several host factors associated with susceptibility to colonization or disease with specific NTM, and for pulmonary isolates, we used *M. gordonae* to place those in context of patients with NTM colonization. Overall,

Table 5. Antimicrobial regimens chosen in patients treated for nontuberculous mycobacterial disease, by drug class

	n*	Number of Drugs (Median)	Aminoglycoside	Carbapenem	Cephalosporin	Ethambutol	Fluoroquinolone	Isoniazid	Linezolid	Macrolide	Pyrazinamide	Rifamycin	Tetracycline†
<i>Mycobacterium abscessus</i> complex	19	3	9	4	10	6	3	0	4	17	0	4	2
<i>Mycobacterium chelonae</i>	10‡	2.5	0	2	0	2	5	0	0	10	0	2	5
<i>Mycobacterium fortuitum</i>	4§	2.5	0	1	0	0	4	0	0	3	0	0	1
<i>Mycobacterium goodii</i>	2	3	0	0	0	2	1	0	0	1	0	2	0
<i>Mycobacterium kansasii</i>	6	3.5	0	0	0	6	0	5	0	1	3	6	0
<i>Mycobacterium porcinum</i>	1	3	0	1	0	0	1	0	0	1	0	0	0
<i>Mycobacterium simiae</i>	3	3	0	1	0	2	2	0	0	3	0	1	0
<i>Mycobacterium xenopi</i>	3	4	0	0	0	3	0	2	0	2	1	3	0

*Indicates the number of patients for whom there is treatment regimen data available. These patients include those with any site of infection, including pulmonary, skin and soft tissue, and disseminated or sterile site disease.

†Tetracycline also includes doxycycline or minocycline.

‡Three additional patients underwent removal of the involved foreign body without use of antimicrobials.

§One patient was also treated with trimethoprim/sulfamethoxazole.

the patients with NTM colonization and disease were medically complex. Of 50 patients with pulmonary isolation of *M. goodii*, 49 had a major comorbid condition and more than 70% of these had abnormal chest imaging, though none of these patients were thought to have mycobacterial disease.

As previously described, *M. abscessus* complex was associated with CF, diabetes, and bronchiectasis (17–19); the high prevalence of CF was not seen in other NTM. Among 10 individuals with *M. xenopi*, 4 of 8 pulmonary cases met ATS criteria, similar to rates seen in European studies (20, 21). In contrast to previous studies, none of the patients with *M. xenopi* had chronic lung disease, though all were relatively immunocompromised via either transplant, malignancy, or HIV (20, 22). Although *M. kansasii* has tended to be associated with COPD (3), the proportion of patients with COPD was similar among those with *M. kansasii* in comparison to other organisms. These data highlight associations of clinical risk factors with specific NTM as well as instances where risk factors or clinical course differ from that described in other regions.

The mortality in this group of patients over the study period was high: 38% of all reviewed patients, 41.5% of those with pulmonary isolates, 41.5% of those with pulmonary isolation meeting ATS criteria, and 53.3% of those with skin and soft tissue infection. We suspect that the higher

mortality seen in the group with soft tissue infection reflects the increased severity of the accompanying comorbidities (66.7% vs. 22.3% on immunosuppressive medication; 38.9% vs. 19.3% with diabetes). Consistent with this observation, both patients with vertebral osteomyelitis died within the study period, whereas only one of three with a bacteremia did.

Very few deaths among patients with pulmonary isolates were thought to be related to mycobacterial infection, and all of those were due to *M. abscessus* complex. Treatment was not associated with a difference in mortality, including among those meeting ATS criteria and those without alternative diagnoses.

Limitations

This study has several limitations, including a retrospective study design and a small sample size for these uncommon organisms. Our population was unique in a few ways. First, males were overrepresented on the whole (62.1%) as well as among subjects with individual mycobacteria, with the exception of *M. porcinum*. This differs from many other large American studies in which researchers have reported a female predominance (5, 6, 23). It is not reflective of a male predominance in our medical record system, however, where the ratio of male to female patients is 0.92.

There was a high prevalence of medical comorbidities, including CF,

which may reflect the University of Washington's position as a tertiary referral center. Interestingly, a substantial number of subjects had a history of tuberculosis (10.2%) or active disease (3.7%). The frequency of cultures positive for *M. tuberculosis* among the submitted samples (2.4% of all acid-fast bacilli cultures in our study) was similar to that of previous studies (1 to 2%) (24–26). We are not aware of reports of the prevalence of tuberculosis in patients with NTM, so it is unclear whether our findings are representative.

Our data suggest that both location of residence and location of birth may contribute to colonization by certain NTM, but we were unable to compile information on duration of residency. We also observed that certain NTM were rarely treated and that treatment did not influence mortality, but we do not have a sufficient number of cases to compare outcomes with regard to therapy by each organism. Finally, although we assessed treatment decisions and mortality, we were unable to evaluate morbidity, which may be an important feature of infection or colonization with NTM.

Conclusions

Our study demonstrates that NTM in Washington State have specific associations with geographic regions, clinical risk factors, and treatment decisions. Among

patients with pulmonary isolates, even patients with colonization were medically complicated. The clinician's decision to pursue therapy was likewise complex, and although treatment was given primarily for patients with *M. abscessus* complex and *M. kansasii*, among those with other organisms, treatment did not significantly alter mortality. Many of these findings differ from those of previously published regional reports and underscore the

heterogeneity associated within this genus of organisms as well as the value in compiling location-based information. ■

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