Nontuberculous Mycobacteria among Patients with Cystic Fibrosis in the United States

Screening Practices and Environmental Risk

Jennifer Adjemian^{1,2}, Kenneth N. Olivier³, and D. Rebecca Prevots¹

¹Epidemiology Unit and ³Laboratory of Clinical Infectious Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland; and ²United States Public Health Service, Rockville, Maryland

Abstract

Rationale: Persons with cystic fibrosis (CF) are at greater risk of nontuberculous mycobacterial (NTM) infections than the general population. However, among patients with CF, geographic variation in prevalence is poorly understood.

Objectives: To describe the prevalence and screening practices of NTM among U.S. patients with CF.

Methods: CF Patient Registry data from 2010–2011 were obtained to estimate the prevalence of NTM among patients with CF 12 years of age or older by state. Climatic data were also obtained and predictors of NTM infection analyzed using regression analysis. Geographic clustering and mycobacterial culture rates by state were also assessed.

Measurements and Main Results: Among patients with CF 12 years of age or older, 58% had mycobacterial cultures; 14% were positive for NTM. Most states ($n = 31$) had a prevalence of 10–20%; seven states predominantly in the West and Southeast had a prevalence of 20% or greater, including Alaska, which cultured patients more frequently than any other state. Nearly 60% of positive cultures were for *Mycobacterium avium* complex, although this ranged by state, from 29% in Louisiana to 100% for Nebraska/Delaware. Significant ($P < 0.002$) spatial clustering of NTM was detected, centering in Wisconsin, Arizona, Florida, and Maryland. Higher saturated vapor pressure increased risk for NTM (odds ratio = 1.06; 95% confidence interval = 1.02–1.10). The proportion of patients

cultured for mycobacteria varied greatly by state of residence (median = 46%; range = 9–73%).

Conclusions: NTM prevalence varies significantly among patients with CF by geographic area, and is largely influenced by environmental factors. However, NTM culture practices vary greatly, with some high-prevalence states screening less than 25% annually. Routine screening for all patients with CF is needed for timely detection.

Keywords: nontuberculous mycobacteria; pulmonary; epidemiology; cystic fibrosis; spatial

At a Glance Commentary

Scientific Knowledge on the Subject: Individuals with cystic fibrosis (CF) are at significantly greater risk of acquiring nontuberculous mycobacterial (NTM) infections than the general population. However, among patients with CF, geographic variation in prevalence across the United States is poorly understood.

What This Study Adds to the Field: NTM prevalence varies significantly among patients with CF by geographic area, and appears to be largely influenced by environmental factors. However, NTM screening practices also vary greatly by state, with some high-prevalence states only routinely culturing less than one-quarter of their patients with CF for mycobacteria.

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Correspondence and requests for reprints should be addressed to Jennifer Adjemian, Ph.D., Quarters 15 B-1, 8 West Drive, MSC 2665, Bethesda, MD 20892-2665. E-mail: jennifer.adjemian@nih.gov

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The prevalence of nontuberculous mycobacterial (NTM) disease varies widely by geographic area across the United States (1). Infection with NTM is typically thought to result from environmental exposures, including soil and water sources (2). Although individual host susceptibility is important to disease risk (1, 3, 4), geographic variation in prevalence is largely a function of environmental and climatic factors (1, 5).

Persons with cystic fibrosis (CF) are at significantly greater risk of acquiring NTM infections than the general population, with an estimated prevalence of 13–23% (6). In the United States, NTM disease among patients with CF is predominantly due to infections with *Mycobacterium avium* complex (MAC) or *M. abscessus* (6, 7). However, even among patients with CF, geographic variation in prevalence across the United States has been noted (6). With NTM disease now widely recognized as a significant cause of clinical decline and morbidity in patients with CF (8–10), improved understanding of the epidemiology of NTM in this patient population is important for better managing patient care and treatment.

Starting in 2010, the CF Foundation (CFF) began tracking detailed data on mycobacterial cultures obtained from U.S. patients with CF in the CF Patient Registry (CFPR), further emphasizing the importance of routinely screening for NTM in this population (11). These data facilitate a more in-depth investigation into not only nationwide geographic variations in NTM prevalence among patients with CF, but also differences that may exist in national mycobacterial culture practices. Therefore, using these data from the CFPR, we sought to evaluate geographic risks and NTM clustering at the state level among U.S. patients with CF, as well as any variations that exist among state-level NTM screening rates.

Methods

CFPR data from 2010–2011 were obtained from the CFF and used to estimate the prevalence of MAC and *M. abscessus* among patients with CF by state. For this study, NTM cases were defined as patients who were 12 years of age or older with positive MAC or *M. abscessus* mycobacterial cultures among all those who

received a mycobacterial culture from 2010 to 2011; for patients cultured both years, we also evaluated trends in those with positive cultures in both 2010 and 2011. Noncases were defined as patients with all negative mycobacterial cultures when tested for mycobacteria from 2010 to 2011.

For each patient receiving a mycobacterial culture, in addition to demographic and clinical data available through the CFPR, climatic data at the residential zip code-level were obtained from Weather Source (Amesbury, MA) using Ultra Weather data, which were computed by overlaying multiple past weather sources (including weather station, satellite, radar, and weather balloon data). Data obtained included the mean, minimum, and maximum monthly and annual precipitation, temperature, wind speed, dew point, vapor pressure, saturated vapor pressure, relative humidity, and specific humidity levels from the years 2000–2010. Predictors of testing positive for NTM were analyzed using multivariate logistic regression. The final model was selected using backward stepwise selection procedures; variables known to affect NTM risk (age and prior chronic macrolide use status) were retained to control for any confounding effects.

Geographic clustering among MAC and *M. abscessus* cases, both combined and separately by species, was assessed using SaTScan v7.0 software (Kulldorff M. and Information Management Services, Inc., Boston, MA). For each CF patient with a mycobacterial culture in 2010 and/or 2011, their NTM case status and the latitude and longitude coordinates for the zip code centroid were uploaded into SaTScan. The distribution of NTM cases and non-cases was then assessed using models that assumed a binomial distribution to detect areas in the United States with significantly ($P \leq 0.05$) greater-than-expected numbers of patients with CF who were also NTM cases relative to those patients with CF who were noncases. Specifically, a spatial scan test was conducted to calculate the likelihood of being a case both within and outside of a defined circular window within the grid covered by the U.S. study population, with the null hypothesis stating that both areas were of equal risk. Through 999 iterations, this window scanned the total geographic area, varying the diameter from zero (a single geocoordinate point)

to a maximum radius of 300 km. Significant clusters identified represented “high-risk areas” for being an NTM case. Maps of all high-risk areas identified were generated using ArcMap 10.2 (Environmental Systems Research Institute, Inc., Redlands, CA).

CF mycobacterial culture practices were also assessed by calculating the mycobacterial culture rate among patients with CF aged 12 years and older, to look at variations in NTM screening rates by state. Correlations among state-level NTM screening rates and NTM prevalence were also assessed.

Results

Of 18,003 patients with CF aged 12 years and older present in the CFPR in 2010 or 2011, 58% ($n = 10,527$) were cultured for mycobacteria (mean age = 27 yr; range = 12–82 yr), and 14% ($n = 1,384$) had one or more positive culture for MAC and/or *M. abscessus* (mean age = 27 yr; range: 12–79 yr), whereas 7% ($n = 407$) of those screened in both 2010 and 2011 ($n = 5,534$) were positive both years. The proportion of patients cultured for mycobacteria varied greatly by state of residence (median = 60%), ranging from 10% in Rhode Island to over 80% for Alaska, Colorado, Nevada, Tennessee, Texas, and Hawaii, although the majority of states ($n = 39$) cultured over 50% (Figure 1).

The median state-level prevalence of NTM among cultured patients with CF was 12%, although this ranged from no positives in Rhode Island (out of only nine cultured) and in the District of Columbia to 28% for Alaska. Although 50% of patients in Hawaii with cultures were positive, this reflects a very small sample size ($n = 2$), and is therefore a less reliable estimate (Figures 1 and 2). A total of 11 states, predominantly in the Northeast and Midwest, had a prevalence of 5–10%; 31 states had a prevalence of 10–20%; and seven states, almost all in the West and Southeast, reported a prevalence of 20% or more, including Alaska, which cultured patients more frequently than any other state. State-level prevalence was significantly, but weakly, correlated to the percentage of patients cultured by state ($R = 0.3$; $P = 0.02$). Approximately 60% of all positive cultures were for MAC (state-level median = 61%), although this

Figure 1. Proportion of cystic fibrosis patients aged 12 years or older who were cultured for nontuberculous mycobacteria (NTM) and, of those, the percentage that were culture positive, by state, from 2010 to 2011. *Fewer than 10 patients with CF were cultured for mycobacteria.

distribution also ranged by state, from 29% in Louisiana, where the majority of isolates were *M. abscessus*, to 100% for Nebraska and Delaware (Figure 3).

Significant ($P < 0.002$) spatial clustering of NTM cases among patients

with CF was detected in four geographic locations. These clusters centered in Wisconsin (relative risk [RR]=4.2; latitude = 43.325, longitude = -89.561, radius = 147 km), Arizona (RR = 4.0; latitude = 35.280, longitude = -111.723,

radius = 250 km), South Florida (RR = 1.8; latitude = 27.194, longitude = -80.846, radius = 291 km), and Maryland (RR = 1.5; latitude = 38.575, longitude = -75.781, radius = 283 km) (Figure 2). When evaluated by species, four significant

Figure 2. State-level prevalence and significant ($P < 0.05$) clusters of nontuberculous mycobacteria (NTM) among patients with cultured cystic fibrosis, 2010–2011.

Figure 3. Percentage of nontuberculous mycobacteria isolates identified as *Mycobacterium abscessus* among patients with cultured cystic fibrosis by state, 2010–2011.

($P < 0.0001$) clusters of *M. abscessus* cases were identified, which centered in South Florida (RR = 3.0; latitude = 26.609, longitude = -80.129 , radius = 258 km), Wisconsin (RR = 8.4; latitude = 42.989, longitude = -89.555 , radius = 126 km), Louisiana (RR = 5.2; latitude = 30.538, longitude = -91.048 , radius = 101 km), and North Carolina (RR = 2.8; latitude = 35.470, longitude = -76.779 , radius = 242 km). For MAC cases, only one significant ($P < 0.0001$) cluster was detected, centering in Arizona (RR = 6.1; latitude = 27.194, longitude = -80.846 , radius = 291 km).

In multivariate models evaluating climatic factors, each one-unit increase in the mean annual saturated vapor pressure, which ranged by zip code from 7.9 to 64.9 millibars, was associated with a 6% increase in risk for being an NTM case (odds ratio [OR] = 1.06; 95% confidence interval

[CI] = 1.02–1.10; $P < 0.0001$). Other variables included in the model and that were controlled for due to their known effects on NTM risk in patients with CF (11) were patient age (OR = 1.02; 95% CI = 1.02–1.03) and prior chronic macrolide use (OR = 0.52; 95% CI = 0.43–0.64); although not statistically significant, region of residence was also included as a confounder, due to its effect on variable estimates ($>10\%$ change between model coefficients).

Discussion

NTM prevalence varies significantly among patients with CF by geographic area, and appears to be largely influenced by environmental factors, with a fourfold-increased risk of infection of any NTM

species in the highest-risk areas identified here relative to the national average.

However, NTM culture practices vary greatly, with some high-prevalence states only routinely screening less than a quarter of their patients with CF. Routine screening for NTM among patients with CF, especially in high-prevalence areas, is important for timely detection and appropriate treatment practices.

The environmental factor most predictive of NTM in a patient with CF was the saturated vapor pressure associated with his or her residential zip code. Vapor pressure is a measure of the amount of water, or moisture, in the air, and saturated vapor pressure reflects the maximum amount of water that the air can hold at a given temperature. One of the main ways water vapor increases in the air is through evaporation. Similarly, in

a previous study, higher potential evapotranspiration levels—which represent the amount of evaporation that would occur if sufficient water sources were available in the environment—were linked to increased prevalence levels of NTM disease in older adults in the United States (5). Thus, it appears that environments that foster greater levels of moisture in the atmosphere increase the risk for NTM exposure and subsequent pulmonary disease. Higher vapor pressure and temperature levels, which are highly correlated with each other, have also been linked to other bacterial respiratory diseases, including infection with *Legionella* from the environment (12), and with *Pseudomonas aeruginosa* infection among patients with CF (13).

The increased risk of NTM infection in high-moisture environments may be due to greater numbers of aerosolized mycobacteria circulating in the air, as well as on surfaces with which people come into contact throughout their day. In studies evaluating bioaerosols of the troposphere, which is the atmosphere nearest to the surface, live bacterial organisms have been shown to be abundant, with thousands to millions of cells per cubic meter of air (14, 15). One recent study found that 70% of all bioaerosols sampled represented bacteria, and 22% were from the phylum *Actinobacteria* (15), which, although broad, does include mycobacteria. Although natural host defense mechanisms of the upper airway manage to eliminate most aerosolized particles (16), patients with CF have impaired airway clearance, making them more vulnerable to aerosolized pathogens (6, 7). Furthermore, among all people, infectious agents that are less than 5 μm in size can reach the small airways and alveoli (16). Unfortunately, the spatial variability in airborne microbial diversity has received little attention, limiting our understanding of how climatic and environmental variations might affect potential exposure levels and health outcomes for people.

In addition, bacterial exposure may be increased in areas with higher saturated vapor pressure due to greater associated indoor moisture levels that may foster bacterial growth (12, 17). Specifically, when saturated air at a given temperature comes into contact with a cooler surface, as might be the case inside homes and buildings, the air then cools to the

temperature of that surface, reducing the maximum vapor pressure and resulting in the excess water from the air being deposited onto surfaces in the form of condensation. Excessive residential moisture has been linked in numerous studies to significantly increased risks for bacterial respiratory infections, with estimated attributable risks ranging from 8 to 20% (17). In addition, pathogenic NTM have been isolated from water sources and aerosolized water droplets generated in people's homes (18, 19). Thus, it is quite probable that mycobacteria more readily thrive in higher moisture-level environments, placing people residing in these areas—especially those with CF—at even greater risk for NTM disease.

Although the risk of NTM infection is greatest in patients with CF residing in warmer, moister climates, patients with CF throughout the United States are vulnerable to NTM lung disease. The CFF recommends that the sputum of all patients with CF be screened at least annually for NTM (20), and has been collecting detailed mycobacterial data on all patients with CF through the CFPR since 2010.

However, we found tremendous variations in mycobacterial culture practices by state, with some of the higher prevalence states culturing the smallest percentages of patients. For instance, Wisconsin had an 18% prevalence of NTM and also represented the state within which the highest-risk spatial cluster was identified; there, resident patients with CF were over four times more likely than the national average to be positive for NTM during 2010 through 2011. However, only 18% of patients with CF in Wisconsin were cultured for mycobacteria over that 2-year period, making it very likely that at least some patients with CF residing there have an undiagnosed, or at least unreported, NTM infection. Both Indiana and Montana similarly had higher prevalence levels, but lower screening rates. Meanwhile, in Rhode Island, no NTM-positive cultures were detected, although again, fewer than 10% of patients were even screened. On the other hand, in Alaska, over 73% of all patients were cultured for mycobacteria, and of those, 28% were positive, making it the state with both the highest percentage of patients screened and the highest percentage of positive patients outside of Hawaii, although the numbers in Hawaii were too limited to allow for any valid

inferences to be made in this study, despite its recognized higher prevalence of NTM disease (1, 5). Clinicians may be currently targeting only those patients whom they deem to be at higher risk for NTM disease, and thus the prevalence rate reported in some states may be more a result of selective screening practices than reflective of a true increased disease burden. Nonetheless, given that the prevalence observed here is similar to what has been previously reported (6), selective screening practices were most likely not a large source of bias in our estimates. However, this observation can only be validated by routinely screening all patients with CF as advised by the CFF.

Similar to the non-CF population, a higher prevalence of NTM and geographic clustering was observed in certain states, including Florida and Wisconsin, and particularly in the southeastern region (1, 5, 6, 21). In addition, we found that a greater percentage of positive cultures detected in most of the southern, southeastern, and several northeastern states were due to infection from *M. abscessus* compared with most western and mid-western states, where MAC was responsible for most infections observed. In some respects, the distribution of *M. abscessus* among NTM-positive patients with CF more similarly follows the overall prevalence trends noted among patients without CF in the United States; that is, states recognized as having a higher prevalence for NTM among all individuals also seem to be more likely to have a greater proportion of patients with CF with NTM due to *M. abscessus* infection. Infections from *M. abscessus* can be more severe and more difficult to treat than those caused by MAC in patients without CF (22, 23), so it is possible that infections may be more frequently recognized and reported, which may influence NTM prevalence maps that are not stratified by species.

The state-level prevalence estimates reported here are limited by the fact that all patients with CF were not routinely screened for mycobacteria, which is, in turn, affected by the proportion of patients who were able to produce a sputum sample for analysis. Because the CFF began collecting detailed mycobacterial data starting only in 2010, many CF centers were just starting to look more closely at NTM at that time, and estimates obtained from more recent years may

more accurately reflect the NTM prevalence rates. In addition, practices vary greatly, not only among states, but also possibly among CF centers within states. Thus, any rates and trends reported here may have been biased by certain centers within the state that represented outliers. Nonetheless, given the similarities between the high-prevalence areas reported here and those in other studies, the overall trends observed are likely reflective of actual variations observed among patients with CF throughout the nation. For the environmental analysis, this study used data obtained at the zip code of residence level. Although, for some patients, this information may not be

updated in the registry if they move, or may not capture exposures if they spend extensive time elsewhere, for most individuals this is likely reflective of where they spend the majority of their time. Thus, we feel that the climatic variable detected here as being predictive of being an NTM case gives important insight into the epidemiology of NTM exposure and infection in the United States.

Patients with CF are at greater risk for developing NTM infections and related lung disease. Therefore, it is important that patients with CF be routinely screened for NTM, particularly if they live in high-prevalence areas, and that these results be

reported through the CFPR to help inform patient care and disease management practices by CF providers. Further studies are needed to better elucidate the relationship between greater moisture levels in the atmosphere and the increased risk for exposure to NTM, particularly among the CF population. ■

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