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Pulmonary Disease Due to Nontuberculous Mycobacteria

Current State and New Insights

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Since pulmonary nontuberculous mycobacteria (PNTM) lung disease was last reviewed in *CHEST* in 2008, new information has emerged spanning multiple domains, including epidemiology, transmission and pathogenesis, clinical presentation, diagnosis, and treatment. The overall prevalence of PNTM is increasing, and in the United States, areas of highest prevalence are clustered in distinct geographic locations with common environmental and socioeconomic factors. Although the accepted paradigm for transmission continues to be inhalation from the environment, provocative reports suggest that person-to-person transmission may occur. A panoply of host factors have been investigated in an effort to elucidate why infection from this bacteria develops in ostensibly immunocompetent patients, and there has been clarification that immunocompetent patients exhibit different histopathology from immunocompromised patients with nontuberculous mycobacteria infection. It is now evident that *Mycobacterium abscessus*, an increasingly prevalent cause of PNTM lung disease, can be classified into three separate subspecies with differing genetic susceptibility or resistance to macrolides. Recent publications also raise the possibility of improved control of PNTM through enhanced adherence to current treatment guidelines as well as new approaches to treatment and even prevention. These and other recent developments and insights that may inform our approach to PNTM lung disease are reviewed and discussed. CHEST 2015; 148(6):1517-1527

ABBREVIATIONS: AFB = acid-fast bacilli; AST = antimicrobial susceptibility testing; CF = cystic fibrosis; Cmax = peak serum concentration; DHEA = dehydroepiandrosterone; DNTM = disseminated nontuberculous mycobacteria; *Maa* = *Mycobacterium abscessus* subspecies *abscessus*; MAC = *Mycobacterium avium* complex; *Mam* = *Mycobacterium abscessus* subspecies *massiliense*; MIC = minimum inhibitory concentration; MTBC = mycobacterium TB complex; NB = nodular bronchiectasis; NTM = nontuberculous mycobacteria; PCD = primary ciliary dysfunction; PCR = polymerase chain reaction; PMAC = pulmonary *Mycobacterium avium* complex; PNTM = pulmonary nontuberculous mycobacteria; TNF-α = tumor necrosis factor-α

Nontuberculous mycobacteria (NTM) are species other than the *Mycobacterium tuberculosis* complex (MTBC) and *Mycobacterium leprae*. Molecular biologic techniques have facilitated recognition of > 140 species of mycobacteria, many nonpathogenic for humans. The pulmonary NTM (PNTM) species most commonly implicated in human disease in North America are *Mycobacterium avium* complex (MAC), *Mycobacterium*

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kansasii, and increasingly, *Mycobacterium abscessus*. Since NTM were last reviewed in *CHEST*,[1] our understanding of these organisms has expanded in potentially important ways. This review provides background for several important areas related to PNTM and then focuses on new insights generally published since 2008. We emphasize disease in ostensibly immunocompetent patients and concentrate on the most clinically important species encountered in North America because these insights may also inform our understanding of other species.

Epidemiology

NTM are ubiquitous in the environment and normal inhabitants of natural and drinking water systems, pools and hot tubs (able to survive chlorination), biofilms, and soil. Infection is accepted to occur from the environment; person-to-person spread is believed not to occur. Although exposure and infection (as shown by skin test surveys[2]) is nearly universal in some locales, PNTM occurs in a minority of those infected. Capturing accurate data to estimate PNTM incidence and prevalence is challenging because PNTM is not reportable to public health authorities, and disease diagnosis requires satisfying a constellation of criteria,[3] often necessitating extended patient follow-up.

Recent Insights

Prevalence: The mere presence of NTM in sputum does not equate with disease. This notwithstanding, the annual prevalence of PNTM is increasing as consistently demonstrated by population-based estimates,[4] large inpatient databases,[5] and Medicare records.[6] An analysis of a 5% sample of Medicare Part B beneficiaries calculated a US prevalence (as defined by diagnostic codes on medical claims) of 47 cases per 100,000 population in 2007, with an annual increase of 8.2% per year from 1997 to 2007.[6] Similar experience has been reported in Canada[7] and areas outside North America, although species have differed, with *Mycobacterium xenopi*, *Mycobacterium malmoense*, and *Mycobacterium simiae* being significant species.[8,9] Studies have also variously emphasized the importance of environmental factors, such as climate and soil composition; age; comorbid conditions, particularly cystic fibrosis (CF), COPD, gastroesophageal reflux disease, and rheumatoid arthritis; and immunosuppressive therapies. US prevalence varies by ethnicity, with Asians and Pacific Islanders having the highest prevalence and blacks the lowest. Whites were the only race with women having a higher prevalence than men. Comorbid conditions, especially involving the lungs, were more common among PNTM cases, and individuals with PNTM were 40% more likely to die over the study period than those with PNTM. Adjemian and colleagues[10] also described variability of PNTM by geographic locale, ranging from $>$ 200 per 100,000 in some western states (Hawaii was highest) to $<$ 50 per 100,000 in some Midwestern states. The geographic distribution of PNTM among patients with CF has shown a similar pattern. Factors predicting high-risk PNTM areas are greater population density, higher income, and greater evapotranspiration.[11] Current prevalence studies differ from original reports that the highest NTM prevalence is in the southeastern United States, perhaps reflecting the evolution of PNTM diagnostic criteria, an overall increase in detection due to increased awareness, or improved microbiologic detection techniques.

Transmission and Pathogenesis

The environment has been the historically accepted source of NTM disease transmission. Sequencing of NTM DNA obtained from households of patients with PNTM has shown that in many instances, the NTM from the patient has the exact fingerprint as an isolate obtained from his or her household plumbing.[12]

Host immunity to NTM includes both systemic and local factors and has been reviewed.[13-15] Mycobacteria are inhaled and initially subject to both local clearance factors and systemic innate immune defenses. Mycobacteria are processed by alveolar macrophages, which release cytokines, including IL-12 and tumor necrosis factor-α (TNF-α), augmenting innate immune responses. Macrophages also present mycobacterial antigens on their surface, signaling T lymphocytes to differentiate into T-helper cells producing antigen-specific immunity, including natural killer cells, which further augment host defense. Other important elements involve natural killer cell killing of infected macrophages and IL-8, which supports phagocytosis. Ultimately, mononuclear cells and epithelioid histiocytes surround foci of infected macrophages, resulting in the classic histopathologic granuloma. Given the ubiquitous nature of NTM, infection is common. PNTM, however, is not because NTM generally are not highly virulent, and host defenses typically prevent progression to disease.

Recent Insights

Source of NTM Infection and Disease: Evidence for person-to-person transmission is building, at least in the CF community. Whole-genome sequencing and