# Editorials

## The Importance of Nontuberculous Mycobacterial Lung Disease

In this issue of the *Journal* (pp. 1066–1074), investigators from the National Institutes of Health (NIH) report a distinctive morphotype among a selected cohort of 63 patients with nontuberculous mycobacterial (NTM) lung disease (1). Consistent with other recently published series, the great majority were middle-aged white females (2, 3). Prominent features included being tall and slender, and having scoliosis, pectus excavatum, and mitral valve prolapse. A higher than anticipated number of these patients had mutations of the CFTR genes. Extensive assessment of cell-mediated immunity did not identify deficits. Previously alluded to as "Lady Windermere's syndrome" by Reich and Johnson (too "fastidious" to cough effectively), this current cohort did not appear unwilling to cough (4).

Case series of NTM lung disease from North America, Europe, and Japan were published sporadically in the latter half of the 20th century. Males with underlying chronic obstructive pulmonary disease or pneumoconiosis constituted the bulk of the patients in these reports (5). However, in 1989, a group from Philadelphia reported 21 cases, 17 females, of *Mycobacterium avium* complex (MAC) lung disease occurring in patients without obvious predispositions (6). Since then, there has been increasing awareness among clinicians of NTM lung infections, with an apparent but unexplained predilection for slender women (7).

Nontuberculous mycobacteria, especially MAC, are found widely distributed in the environment, with recovery of strains consistent with human pathogenic isolates (8, 9). Assuming that exposure to such organisms must be nearly universal, the question of mechanisms of vulnerability is compelling, particularly among women presenting with this infection, most of whom have led medically "blameless" lives. The clear identification of phenotypic features in this NIH study provides several hypothesis-generating leads.

Although broad, systematic data have not been compiled, there is a perception among many clinicians and public health tuberculosis (TB) workers that new cases of NTM lung disease may significantly exceed case rates for TB in their communities or regions. The best data for North America come from Ontario where a single laboratory identifies more than 90% of the NTM isolates in the province. This system has provided an opportunity to study the epidemiology of NTM infection at a truly population-based level. Although adequate clinical information regarding the presence of disease, or advanced infection, is lacking in the Ontario laboratory database, it was observed that nontuberculous mycobacteria were far more frequently isolated from pulmonary specimens than was *M. tuberculosis* (10). Conservatively assuming that 20–40% of pulmonary NTM isolates are associated with disease (11), the incidence of new cases of pulmonary NTM disease in Ontario presumably approximates the incidence of TB.

Rather than comparing "incidence" ratios for NTMs and TB, determining the number of patients who experience clinical illness and undergo therapy in any given timeframe (i.e., prevalence) may be a more accurate way to assess the burdens on the community and the health system. In 2004, there were roughly 14,500 new cases of TB reported in the United States (12). Centers for Disease Control and Prevention data indicated that roughly 82% of patients completed therapy within 12 months, and relapse rates have been consistently less than 5% with modern regimens. By contrast, patients with pulmonary MAC usually suffer through long periods of clinical illness before a diagnosis is made; they are then recommended to take 18 months of three-drug therapy and have a nearly 50% likelihood of recurrence that entails retreatment. While treatment duration ranges from 6 to 9 months for most cases of TB in the United States and Canada, most patients become asymptomatic within weeks of commencing therapy. By contrast, we believe that symptomatic disease duration for pulmonary NTM is likely an order of magnitude greater. In 2003, there were 657 cases of TB reported in the province of Ontario, corresponding to an incidence rate of 5.4 per 100,000. In contrast, we estimate that there were likely 420 new cases of pulmonary NTM disease in Ontario in the same year, corresponding to an incidence rate of 3.5 per 100,000. Preliminary prevalence estimates have been made, assuming that the disease duration for TB is 8 months and for pulmonary NTM is within the range of 4 to 10 years. Using these estimates, the prevalence of TB in Ontario was 3.6 per 100,000 in 2003, whereas the contemporary prevalence of pulmonary NTM disease was in the range of 14 to 35 per 100,000.

Using this model, the burden of TB may be expected to steadily decline in industrialized nations with mature TB programs. Data from the United States, Canada, and several West European nations describe steadily declining numbers of indigenous TB cases, with the preponderance of new cases occurring among foreign-born individuals. By contrast, the prevalence of NTM disease may be expected to steadily increase. The Ontario experience has reflected a slow but steady decrease in cases of TB, an annual decrement of 4%, whereas rates of NTM isolation increases at an annual rate of 8% (12).

This comparison between TB and NTM disease is not intended to be adversarial but to call attention to a burgeoning medical challenge. The medications for NTM infections are expensive, typically difficult to tolerate, and often entail intravenous administration. Many of these patients require physically demanding and time-consuming bronchial hygiene. Limited experience suggests that some of these patients might benefit from resectional lung surgery (13).

These observations make it imperative that more extensive research be done on the epidemiology, sources of infection, risk factors, treatment, and prevention of NTM lung disease. Cases of NTM lung disease are no longer just "curiosities" but may well be the leading edge of a major public health problem. The time for action is now.

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MICHAEL D. ISEMAN, M.D.
*National Jewish Health*
and
*University of Colorado School of Medicine*
*Denver, Colorado*

THEODORE K. MARRAS, M.D.
*University of Toronto*
*Toronto, Canada*

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