

information could be even more successful and is of particular importance in mild OSA.

The use of machine learning and predictive analytics across various platforms is vital for implementation efforts aimed at bringing billions of dollars of research findings to the bedside (14). Our eagerness to implement these modern tools needs to be balanced with a careful understanding of the setting and real-world circumstances of the implementation efforts. Hornero and colleagues have taken an important step toward automated detection of OSA in children (13). The real-world implementation of the clinical prediction pathway incorporating the machine learning technique proposed by Hornero and colleagues awaits further testing (13). ■

**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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## Moving Nontuberculous Mycobacteria Infections into the 21st Century

During the last many years, pulmonary physicians have become increasingly familiar with, and often vexed by, patients with infections caused by nontuberculous mycobacteria (NTM). These NTM infections now outnumber cases of tuberculosis (TB)

in the United States (1), but research about these infections has lagged far behind that of TB. The list of important unanswered questions about NTM infections is long (2): Why are some bacteria pathogenic and others not? Are there particular environmental factors or exposures that predispose to NTM infections? What is the best way to diagnose a clinically important infection? What is the natural history of NTM infection? How should patients with

Originally Published in Press as DOI: 10.1164/rccm.201708-1630ED on August 25, 2017

NTM infection or colonization be assessed and monitored for progression? Which patients require antibiotic treatment? What is the proper antibiotic treatment? Are there host factors that predispose toward infection with NTM?

For many years, it had been felt that *Mycobacterium avium* complex (MAC) pulmonary infection closely mimicked tuberculosis and occurred mainly in men with underlying pulmonary disease (3, 4). A more nuanced understanding was provided by Prince and colleagues in a series of patients, mostly women, without underlying disease and largely without cavitory lesions (5). In 1992, Reich and Johnson described six elderly women with positive sputum cultures for MAC who had noncavitory parenchymal infiltrates, mostly in the lingula and middle lobe (6). They ascribed this syndrome to voluntary suppression of cough, resulting in retained secretions and focal bronchiectasis that created a favorable environment for growth of MAC. They termed this syndrome of MAC infection in previously well women without cavitory lesions Lady Windermere syndrome, after the title character in Oscar Wilde's 1892 play, *Lady Windermere's Fan*. The physiologic mechanism they proposed seems somewhat far-fetched: they posited that there was voluntary suppression of cough, citing the aphorism (previously unknown to me) that "ladies don't spit" (6). The literary reference is misleading as well. In Wilde's play, Lady Windermere is a young woman on the eve of her 21st birthday (7). Her fan, a gift from her husband, is both a symbol of Victorian modesty and a plot device that leads to the play's main dramatic twist. No one in the play, it appears, has a significant pulmonary problem.

It seems long past time to retire the inaccurate eponym of Lady Windermere syndrome (8). However, despite the misleading literary reference and unlikely medical reasoning, Reich and Johnson nonetheless described a group of patients now very familiar to pulmonologists. More detailed descriptions were provided by Kim and colleagues a decade ago (9). There seems to be a distinct group of taller women, often with skeletal abnormalities such as scoliosis or pectus deformities, with nodular infiltrates and bronchiectasis rather than cavitory lesions, with no obvious evidence of immunodeficiency, and often with cystic fibrosis transmembrane conductance regulator mutations, although without cystic fibrosis, who have sputum cultures positive for *Mycobacterium avium* complex organisms. In this issue of the *Journal*, Chen and colleagues (pp. 1599–1604) seek to understand whether in fact there are host genetic factors in such patients that create vulnerability to MAC infection (10).

In a cohort drawn from familial and sporadic cases of pulmonary NTM infection, whole-exome sequencing and linkage analysis were performed in hopes of identifying genes that might be associated with the clinical syndrome. Investigators were able to map a region on the long arm of chromosome 6 that had a significant linkage association with familial NTM infection, and further work refined the strongest association to the TTK protein kinase gene (*TTK*) on chromosome 6q14.1. Several other genes (*MAP2K4*, *RCOR3*, *KRT83*, *IFNL1*, and *SLC29A1*) also were associated with NTM infection, although not quite as strongly as *TTK*.

Although there was clear genetic linkage between *TTK* and NTM infections in the cohort studied, the biological and mechanistic linkage is less clear. With a not particularly rare allelic frequency of 0.05, the contribution of the gene to overall genetic susceptibility may be small (11), but understanding its functional

significance may provide important insight into disease pathogenesis, and possibly into the development of so-called host-directed therapies for patients with NTM infections. *TTK* encodes a protein kinase that is a component of the nuclear spindle assembly checkpoint, which is a surveillance mechanism that ensures the fidelity of chromosome segregation during cell division and replication (12). This protein has been a target of great interest in oncology research, as small molecule inhibitors of TTK kinase activity lead to cancer cell death by apoptosis (13). TTK kinase inhibitors are in early stages of clinical testing for a variety of tumors. The genes *MAP2K4* and *IFNRI*, rare variants of which were also linked to NTM infection, if somewhat less strongly than *TTK*, have been linked to susceptibility to other infectious diseases, mostly viral infections, through modulation of T-cell function (14). A great deal of work lies ahead to elucidate the possible role of *TTK* and of the other genes identified in this article in susceptibility to infection with NTM.

It is important to note that the patients included in this report may not be representative of all patients with NTM infections. In the absence of mandatory reporting for NTM, data about the typical patient with NTM are difficult to come by, but several clinical syndromes have been described (15). Nodular bronchiectatic forms of pulmonary NTM infection, usually caused by MAC, are well-recognized, but cavitory disease is also well-known in MAC infection, and overall, the female:male distribution may not be as markedly skewed as is the general impression. A study by Henkle and colleagues in Oregon developed population-based estimates of the epidemiology of NTM infections in that state and found that the median age of patients was 69 years, but there was only a modest sex predominance, with 56% females (1). Among patients younger than 60 years, 54% were males. Radiographic and clinical features of patients could not be determined.

Chen and colleagues have provided elegant evidence of genetic influences on susceptibility to infection with NTM, and their study adds significantly to our understanding of host factors linked to these infections (10). Physicians and patients alike are in the frustrating situation of having many more questions than answers about NTM infections. Studies such as this one, reporting on genetic associations for NTM infections, represent an important step forward in elucidating fundamentally important disease mechanisms. ■

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**Author disclosures** are available with the text of this article at [www.atsjournals.org](http://www.atsjournals.org).

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