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Review

Update on pulmonary disease due to non-tuberculous mycobacteria

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SUMMARY

Non-tuberculous mycobacteria (NTM) are emerging worldwide as significant causes of chronic pulmonary infection, posing a number of challenges for both clinicians and researchers. While a number of studies worldwide have described an increasing prevalence of NTM pulmonary disease over time, population-based data are relatively sparse and subject to ascertainment bias. Furthermore, the disease is geographically heterogeneous. While some species are commonly implicated worldwide (*Mycobacterium avium* complex, *Mycobacterium abscessus*), others (e.g., *Mycobacterium malmoense*, *Mycobacterium xenopi*) are regionally important. Thoracic computed tomography, microbiological testing with identification to the species level, and local epidemiology must all be taken into account to accurately diagnose NTM pulmonary disease. A diagnosis of NTM pulmonary disease does not necessarily imply that treatment is required; a patient-centered approach is essential. When treatment is required, multidrug therapy based on appropriate susceptibility testing for the species in question should be used. New diagnostic and therapeutic modalities are needed to optimize the management of these complicated infections.

1. Introduction

Pulmonary disease due to non-tuberculous mycobacteria (NTM) has emerged as an increasingly prevalent clinical entity in the past two to three decades. Advances in imaging and microbiological techniques, particularly molecular techniques, have significantly enhanced our understanding of this disease, but many uncertainties remain, especially in epidemiology and clinical management. The aims of this concise and practical review are threefold: (1) to provide an update regarding the small proportion of the approximately 160 known species of NTM that are commonly associated with lung disease in humans;[1,2] (2) to elucidate the clinical approach to these pulmonary infections; and (3) to focus attention on areas of NTM pulmonary disease in which further research is urgently required.

2. Global epidemiology

Over the past two decades, improving microbiological techniques have enhanced the recovery of NTM from the respiratory tract, and there has been a growing appreciation of their clinical significance. Perhaps driven by these phenomena, but also in addition to them, there seems to have been a genuine increase in the prevalence of pulmonary disease due to these organisms.[3] Interestingly, the increase in proportion of pulmonary disease caused by NTM seems to be associated with a simultaneous decrease in the incidence of tuberculosis.[4] However, obtaining an accurate picture of the epidemiology of NTM disease is compromised by the fact that these infections are not reportable in most of the world. Much of the available epidemiological data on pulmonary NTM therefore come from sentinel surveillance and microbiology laboratory-based studies, with the attendant limitations of those study designs.[5] Furthermore, describing the epidemiology of NTM pulmonary disease is complicated by several challenges: (1) case ascertainment (e.g., patients are variably symptomatic, and the diagnosis often depends on computed

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tomography, which is not universally available and/or used); (2) the presence of the organism in the environment, which clouds the significance of a positive culture in an individual patient; (3) a disease definition based on scant evidence; and (4) reporting of the disease is not required or performed in many jurisdictions, resulting in spotty population-based data. As a result of these challenges, many authors focus on reporting disease prevalence (defined as the proportion of individuals in a given setting/region with disease according to a standardized definition, often but not always based on the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines).[6] Another commonly used measure is isolate incidence (number of individuals with NTM newly isolated from a respiratory source during a time period, without regard to disease status). NTM disease incidence (defined as the number of persons with a new diagnosis of NTM pulmonary disease by a standardized definition) is rarely reported because it is challenging to meaningfully describe given uncertainties in timing of disease onset and variable timing and rate of ascertainment after onset.

In Ontario, Canada, the annual prevalence of NTM isolation from respiratory specimens (without considering whether true disease was present) has recently ranged from 14.1 to 22.2 per 100 000 population.[7,8] In one study, the prevalence of disease was estimated to be 9.8 per 100 000 in 2010.[8] With the exclusion of *Mycobacterium gordonae*, *Mycobacterium avium* complex (MAC) was found to be the most common species both isolated from the respiratory tract and associated with clinical lung infection, followed by *Mycobacterium xenopi* and the rapidly growing mycobacteria (RGM).

In Oregon, USA, the estimated prevalence of pulmonary NTM disease was 8.6 per 100 000.[9] A population-based study in the same state highlighted increasing pulmonary NTM incidence from 4.8 per 100 000 in 2007 to 5.6 per 100 000 in 2012.[10] In other parts of the country, using laboratory surveillance complemented by electronic medical record review within four health systems, the prevalence of pulmonary disease due to NTM was estimated to be 1.4 to 6.6 per 100 000.[11] In 2007, using data from ICD-9 coding (International Classification of Diseases ninth revision), a disease prevalence of approximately 47 per 100 000 was observed among adults aged ≥65 years in the USA, although there was quite marked variance in the regional prevalence of NTM pulmonary disease in different parts of the country.[12]

The available information from Central and South America has been limited, with significant potential for selection bias that calls the generalizability of the data into question.[13] The estimated prevalence of NTM lung disease, as reported, was around 1 per 100 000 or even less. MAC was generally the most common species isolated, followed by *Mycobacterium kansasii* and the RGM.[13,14]

In Europe, due to varying study methodologies and differences in underlying populations studied, the reported prevalence of isolation of NTM from respiratory specimens and the reported prevalence of such disease have been discrepant. For example, in the UK, Greece, and the Netherlands, NTM isolation rates of approximately 2.9 per 100 000, 7.0 per 100 000, and 6.3 per 100 000, respectively, have been found, and the prevalence of NTM pulmonary disease has been estimated to be 1.7 per 100 000, 0.7 per 100 000, and 1.4 per 100 000, respectively.[15–17] For this continent, recent data have also revealed marked geographic variability in the species isolated from patients.[18] MAC was isolated more frequently in Northern Europe (44% among all NTM) than in Southern Europe (31% of all NTM), with *M. avium* being the predominant subspecies. *M. xenopi* was more frequently isolated in Southern Europe (21% of all NTM isolates) than in Northern Europe (6% only).

In Africa, there has been recent enthusiasm to search for NTM in patients with suspected pulmonary tuberculosis.[19,20] While these studies have not categorically classified NTM lung disease, their findings suggest that a proportion of patients with suspected tuberculosis (3.7–15%) might actually have NTM disease instead of tuberculosis. Likewise, other studies have suggested that a significant proportion of patients with suspected multidrug-resistant tuberculosis (18% in each of two studies) might have NTM pulmonary disease instead.[21,22]

In Asia, there has been no population-based study regarding the epidemiology of NTM pulmonary isolates and NTM pulmonary disease to enable in-depth understanding of the size of the problem. The available data come from studies undertaken in some countries and geographical areas of Eastern Asia, notably Japan, South Korea, India, China, Thailand, and Taiwan.[23] A recent study from Japan estimated the national prevalence of NTM lung disease to be 33 to 65 per 100 000 in 2005, with most of the cases due to MAC.[24] The leading role of MAC in the pulmonary isolates of NTM was also observed in most of the other countries in Eastern Asia.[23] The other frequently isolated species included RGM and *M. kansasii*. *Mycobacterium scrofulaceum* and *Mycobacterium szulgai* were also occasionally found in respiratory specimens. A study from Taiwan reported an estimated prevalence of 7.94 per 100 000 inpatients in 2008, with the disease occurring largely in elderly subjects.[25] In some Asian countries where the mainstay of tuberculosis diagnosis is the acid-fast smear, there are concerns that a number of patients diagnosed with tuberculosis, especially putative drug-resistant tuberculosis, might actually have NTM pulmonary disease (30.7% of isolates that tested resistant to isoniazid and rifampicin and 4% of tuberculosis retreatment cases in one study from China, similar to the African data mentioned previously).[26,27] For example, a study from China demonstrated that 3.4% of smear-positive sputum specimens grew NTM, primarily MAC.[28]

In Australia and New Zealand, there have been a few robust population-based studies to address the epidemiology of pulmonary NTM isolation and disease.[29–31] The most recent data have suggested a rising disease incidence/prevalence (it is often challenging to distinguish the two) that reached 3 per 100 000. MAC has consistently been the most commonly isolated pulmonary NTM species associated with pulmonary disease.[29]

Thus the available data, especially those derived from population-based studies undertaken in countries in North America, Europe, and Australia, have suggested a continuing rise in the prevalence of pulmonary NTM isolates and NTM disease in these continents. Studies from some countries and geographical areas in Eastern Asia, such as Japan, South Korea, and Taiwan, have echoed this phenomenon.[5]

The increasing prevalence of pulmonary disease due to NTM is especially notable among the elderly, particularly in the context of aging populations in many countries.[11] The gender predominance is frequently confounded by the differential prevalence of smoking-associated lung damage between men and women.[5]

NTM are ubiquitous organisms found in environmental sources that include drinking and natural water, as well as soil and dust. Human subjects can inhale or ingest NTM in water, aerosols, or dust. NTM are quite resistant to water disinfectants in common use, such as chlorine.[32] This resistance likely contributes to reports describing frequent NTM detection in potable water within Australia and the USA.[32,33] The ability of NTM to persist in urban water supplies may therefore be contributing to the increasing prevalence of pulmonary NTM disease in many countries. The relationships between environmental conditions, exposure, and development of disease are poorly understood and bear further study.

3. Host susceptibility and disease pathogenesis

The early concepts of NTM in the respiratory tract described a dichotomous scenario of colonization versus invasion.[34] In all