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REVIEW

Non-tuberculous mycobacterial pulmonary infections

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Abstract Non-tuberculous mycobacterial (NTM) infections are increasingly rapidly worldwide. The reason for this phenomenon is unclear, but may include the ageing population, the increasing use of immunosuppressive drugs, the increasing prevalence of diseases that confer susceptibility to NTM, such as COPD and bronchiectasis, and growing testing for NTM. Awareness of the NTM related diseases is rising but is still suboptimal. Guidelines from the American Thoracic Society and Infectious Diseases Society of America have provided a framework for evaluating disease and evaluating care. Compliance with these guidelines is, however, very poor globally.

NTM infections are amongst the most challenging cases that respiratory and infectious diseases physicians face. The challenges include intrinsic antibiotic resistance, complex drug regimens, poor tolerability and significant side effects associated with therapy and poor response rates. The decision to initiate treatment is therefore often difficult and requires careful evaluation of benefits and risks. Optimal management of NTM infections requires multidisciplinary care with close collaboration between physicians, microbiologists, physiotherapist/allied health professionals, primary care physicians and the patient.

There remains a need for greater research into the epidemiology, clinical evaluation and treatment of NTM pulmonary disease. Randomised clinical trials are now being conducted which may provide useful data on the effectiveness of some new and existing therapies.

In this review, we discuss the growing importance of NTM pulmonary disease and the opportunities for progress in clinical research for these conditions.

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Introduction

Nontuberculous mycobacterial pulmonary disease (NTM-PD), also referred to variously as NTM-pulmonary disease or NTM-lung disease is caused by infection with a range of pathogenic species of NTM.[1–3] These diseases are relatively rare but place a major burden on patients and their physicians because they are complex to manage, requiring prolonged antibiotic regimens with a great deal of complexity in the microbiology, radiology, drug treatments, drug–drug interactions and other aspects of treatment.[1,2] With these factors combined, NTM patients are among the most complex and challenging cases that pulmonologists face in clinical practice. NTM are also responsible for non-pulmonary disease and disseminated disease. These forms of the disease will not be discussed here.

The incidence and prevalence of these infections is rising alongside increases in the prevalence of predisposing diseases like chronic obstructive pulmonary disease (COPD) and bronchiectasis, and the increasing life expectancy of patients with cystic fibrosis.[4–9] All pulmonary physicians need to know to suspect NTM pulmonary disease, how to recognise and diagnose it and to understand the priniciples of treatment.

In this concise review, we discuss the clinical aspects of NTM pulmonary disease with a focus on diagnosis and therapy.

Epidemiology

More than a hundred NTM species have been described and the number is growing (www.bacterio.cict.fr/m/mycobacterium.html). Fortunately most of them have no clinical significance and relatively few are responsible for lung disease. NTM are ubiquitous in the environment and are readily identified in community and household water sources amongst other habitats.[1] As a result, humans are constantly being exposed to NTM, but NTM-PD remains uncommon because only a small proportion of individuals appear to be susceptible.[10–13] It is remarkable that in the past decade, data have been published from Europe, North America, Australia and Asia all reporting a consistent increase in the incidence and prevalence of NTM-PD.[14–20] The extent to which this increase is real, or reflects increased testing and reporting is unclear. Unlike TB, NTM infection is not a reportable disease in the majority of countries which limits the quality and reliability of data collection.

Regional differences in the prevalence of NTM disease have been demonstrated around the world including 9.8 per 100,000 from Canada in 2010,[14] 8.6 per 100,000 from Oregon, USA[15] or less than 1 in 100,000 from Brazil.[16] NTM isolation appears to be highly prevalent in Asia by contrast with one study suggesting a national prevalence in Japan of between 33 and 65 per 100,000, predominantly due to *Mycobacterium avium* complex (MAC).[17] Although estimates closer to those reported in Canada and US were found in a study from Taiwan.[18]

In Europe, a recent study from the UK identified a rising incidence of NTM isolation driven almost exclusively by an increase in MAC disease with incidence rising from 5.6 per 100,000 to 7.6 per 100,000 over the period 2007–2012.[21] Ringshausen et al. reported a prevalence of 2.3 per 100,000 for NTM pulmonary disease in 2009 in Germany rising to 3.3 per 100,000 in 2014.[22]

Thus internationally the rates of NTM disease are therefore relatively similar, allowing for differences in the methods of reporting, the definition of cases and the different methods employed in the studies.

A large observational study in Europe identified important genographic variation in the species isolated from patietns with MAC being most frequent in Northern Europe (accounting for 44% of all NTM isolates vs 31% in Southern Europe) and a predominance of *Mycobacterium xenopi* in Southern Europe (accounting for 21% of NTM isolates in Southern Europe vs 6% in Nothern Europe).[23]

Thus NTM-PD remains a rare disease, but one of increasing importance. It is a problem worldwide and although the distribution of different species varies according to geographical location, MAC is the predominant species in nearly all studies.[14–23]

Clinical characteristics

NTM-PD is typically chronic, slowly progressive and difficult to diagnose. It can present at any age, but is most common in patients older than 50.[24–27] NTM-PD is strongly associated with conditions that compromise pulmonary or systemic immunity such as bronchiectasis, COPD, cystic fibrosis or other chronic respiratory disorders and systemic immunodeficiency.[28–34] The disease is often subclassified into nodular-bronchiectatic and fibrocavitary ''phenotypes''. Although there is a high degree of overlap between these subtypes, they are clinically useful.[24–27] In Europe and the USA the nodular-bronchiectatic phenotype patients are typically elderly causasian females while fibrocavitary disease is strongly associated with co-morbid COPD and is therefore more common in men.[27]

A distinct ''morphotype'' of individuals with nodular-bronchiectatic NTM-PD has been reported in the United States consisting of post-menopausal females with tall stature, low body mass index, scoliosis, pectus excavatum, mitral valve prolapse and middle lobe and lingula bronchiectasis. Post menopausal females often with middle and lingula nodular bronchiectactic NTM disease are referred to as ''Lady Windermere syndrome''.[35,36] A MAC-associated hypersensitivity pneumonitis-like illness has also been reported to occur following exposure to aerosolized MAC mainly in indoor hot tubs and is referred to as hot tub lung.[7]

The symptoms of NTM-PD are non-specific. Diagnosis is often delayed because symptoms may appear to be part of the underlying disorder, or may be misdiagnosed. Patients most frequently have cough, sputum productions, breathlessness, profound fatigue, weight loss and fever.

Diagnosis

As previously noted, NTM are present in the environment and particularly in environmental water sources. They may therefore contaminate sputum specimens or be transiently present in the airways without causing disease leading to