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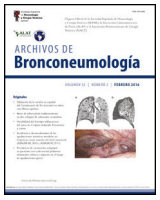

Editorial

Non-Tuberculous Mycobacterial Pulmonary Disease—Where are we Now?

Non-tuberculous mycobacteria (NTM) comprise all mycobacteria other than those that cause tuberculosis or leprosy. While several NTM species may cause significant disease, those comprising the *Mycobacterium avium* complex (MAC) and the subspecies of *Mycobacterium abscessus* (MAB) are among the most common encountered clinically. The lungs are the commonest site of NTM infection. There remains a poor evidence base in NTM pulmonary disease (NTM-PD) with knowledge gaps in relation to epidemiology, infection control, pathogenesis heterogeneity and optimal treatment regimens. Interest is however increasing among academics, clinicians and industry alike, with an increase in publications and clinical trial development. In this editorial, we consider some of the latest data pertaining to the epidemiology, diagnosis and management of NTM-PD.

The number of NTM infection cases continues to rise globally. In a systematic review and meta-analysis of 47 studies from over 18 countries encompassing 285,681 positive NTM isolates, 81% of the studies identified increasing trends, with a +4.0% annual rate of change for NTM infection and disease per 100,000 persons/year.[1] Increasing prevalence and incidence have been reported in studies from Africa, Asia, Europe, North America, South America and Oceania, with variation depending on the NTM species and MAC being the most common species in most regions.[2] It should however be noted that NTM infections are not notifiable in most countries and the annual prevalence of NTM-PD may be stable in some areas.[3]

While several studies have investigated putative transmission of MAB clones between cohorts with cystic fibrosis (CF), less has been published on the potential transmission of other NTM species between individuals with CF, non-CF bronchiectasis or other chronic respiratory disease. Through whole genome sequencing of longitudinal sputum MAC isolates collected from a cohort in a tertiary NTM treatment centre in London, van Tonder et al. demonstrated the presence of putative transmission clusters for *M. avium* subsp. *avium*, *M. avium* subsp. *hominissuis*, *Mycobacterium intracellulare* and *Mycobacterium chimaera*.[4] Epidemiological links however were not identified for most individuals within the clusters and the absence of environmental sampling meant that transmission dynamics could not be fully elucidated. In another study investigating the potential transmission of MAC in a CF centre in Vermont, Gross et al. found that there was no significant genetic similarity between environmental and respiratory MAC isolates; but there was some similarity between respiratory *M. chimaera* isolates and those found in a hospital water biofilm sample.[5] This reinforces the notion that healthcare settings may possibly provide a reservoir for environmental acquisition of NTM; but direct human-to-human transmission has not been unequivocally proven.

Diagnosing NTM-PD is contingent upon microbiological, radiological and clinical criteria being satisfied. Danho et al. found that time-to-positivity (TTP) in Mycobacterium Growth Indicator Tube automated broth culture may predict culture conversion. A TTP of >7 days at baseline and >15 days at 3 months was predictive of culture conversion at 6 months in a cohort treated for MAC-PD.[6] Culture-based techniques for mycobacteria can be slow in providing final results, causing delays in clinical decision-making. To address this, Ellis et al. developed molecular assays to quantify the burden of six NTM species. They demonstrated that a custom qPCR assay for *M. abscessus* in particular had a high sensitivity and specificity when applied to NTM DNA extracted from longitudinally acquired sputum samples from individuals with NTM-PD; and that there was a significant decrease in mycobacterial burden associated with the use of NTM-PD treatment.[7] Such molecular tests may hold potential utility in monitoring response to treatment in future.

Treatment regimens for NTM-PD are complex due to the use of multiple drugs, medication interactions, side effects and *in vitro* drug susceptibility testing results for NTM isolates not necessarily correlating with *in vivo* effectiveness. The use of amikacin liposome inhalation suspension (ALIS) has been extensively investigated in treatment-refractory MAC pulmonary disease (MAC-PD). In the CONVERT study, Griffith et al. demonstrated that adding ALIS to guideline-based therapy (GBT) for refractory MAC-PD resulted in improved rates of culture conversion at six months.[8] Winthrop et al. subsequently showed that culture conversion continued beyond six months when using ALIS with GBT and that the most frequent adverse effects associated with treatment were respiratory in nature.[9] Additionally, culture conversion is sustained when using ALIS with GBT for 12 months following initial conversion.[10] More recently, Siegel et al. have investigated the utility of adding ALIS to multidrug regimens used in MAB pulmonary disease (MAB-PD). In a MAB-PD cohort in which all pretreatment isolates were susceptible to amikacin but most were macrolide-resistant, 6/33 individuals developed amikacin resistance following the addition of ALIS, potentially due to insufficient companion drugs.[11] Among the 15 participants for whom longitudinal culture data demonstrated culture conversion, 10 individuals had sustained culture conversion at 12 months.[11] In view of the generally poor clinical outcomes associated with MAB-PD, these findings are noteworthy and suggest that larger scale prospective trials are warranted.

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Various novel treatments have been under evaluation for the treatment of NTM-PD. Omadacycline, an aminomethylcycline, has shown potential efficacy when used in multidrug treatment regimens for MAB. In a retrospective analysis of 117 patients treated with omadacycline for MAB infections, Mingora et al. found that 44/95 (46%) of the cohort with MAB-PD had at least one negative culture at the end of the period of microbiological assessment; 17/95 (18%) met the definition for culture conversion.[12] Furthermore, among those with refractory MAB-PD, 7/31 (23%) culture converted at the end of the assessment period.[12] Notable side effects that limited the duration of treatment included the development of haematological abnormalities (anaemia, thrombocytopaenia, leukopaenia, eosinophilia) or liver function test derangement (transaminitis, hyperbilirubinaemia), although none of these were deemed to be life-threatening.[12] Additionally, the potential utility of clofazimine in treating MAC-PD is increasingly recognised. Zweijpfenning et al. recently demonstrated that using clofazimine in place of rifampicin alongside ethambutol and a macrolide in MAC-PD resulted in similar degrees of sputum culture conversion.[13]

Furthermore, inhaled granulocyte–macrophage colony stimulating factor has been evaluated in 24 individuals with refractory MAC-PD and 8 individuals with MAB-PD. Thomson et al. found that inhaled molgramostim in addition to GBT was associated culture conversion in 7/24 (29.2%) MAC-PD cases and 1/8 (12.5%) MAB-PD cases with no significant safety signal.[14] Inhaled nitric oxide (iNO) therapy may also show some promise. In a study of adults with NTM-PD, 4/10 (40%) of participants had negative mycobacterial sputum cultures after addition of iNO treatment; of these, three participants reverted to culture positivity three months following iNO cessation.[15] Another emerging therapeutic option for NTM-PD is the use of bacteriophage therapy. In a study of 20 individuals with treatment-refractory pulmonary, extrapulmonary or disseminated mycobacterial infections who were treated with phages on compassionate grounds, at least half of the cohort subsequently had positive clinical outcomes and no adverse reactions were reported.[16] Other agents under investigation in phase 1–3 trials include epetraborole and SPR720 (a novel bacterial DNA gyrase inhibitor).[17]

There remain a number of unanswered questions with respect to the long-term clinical trajectories of individuals who have been treated for NTM-PD. Factors predisposing individuals to relapse or reinfection require further exploration. This should be with a view to identifying clinical biomarkers that can be used clinically to identify those at greatest risk of future NTM infection recurrence. Furthermore, the association between NTM and other infections should be evaluated. There is known to be a link between NTM and concomitant or sequential fungal pulmonary infection, but the mechanisms underlying this association and the appropriate strategies for monitoring and treatment are still to be determined.[18] The value of multidisciplinary clinical management, particularly in relation to airway clearance, pulmonary rehabilitation and nutritional support, must also be remembered.[19] Additionally, long-term morbidity associated with treated NTM-PD, such as the lasting impact on lung function, psychological outcomes and quality of life, merit study. The creation of validated patient-reported outcome measures is vital if this is to be achieved.

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