Non-tuberculous mycobacteria pulmonary disease: A review of trends, risk factors, diagnosis and management

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Non-tuberculous mycobacteria (NTM) reports have been on the rise globally, with increasing incidence and prevalence accompanied by poor outcomes. The rise has been attributed to an ageing population with increasing comorbid illnesses, and improved laboratory techniques in diagnosing the disease. However, despite the increase, some parts of the world still lack data, especially sub-Saharan African countries. The lack of data in our setting is difficult to explain, as we have a significant burden of NTM risk factors (i.e. HIV, tuberculosis and bronchiectasis). This review therefore serves as a reminder and a challenge to start searching, and reporting on our experiences. The review will highlight the rising incidence, important risk factors, diagnosis and management of NTM pulmonary disease.

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Non-tuberculous mycobacteria (NTM) are mycobacteria other than tuberculous (MOTT), with more than 200 species identified to date.[1] The organisms are found in the environment, particularly in the soil, water and dust, with an ability to form biofilms.[2] Contrary to historical belief, there is evidence of human-to-human transmission, first reported in the cystic fibrosis (CF) cohort, and subsequently outside the CF context.[3,4] For the disease to occur, a pathogenic species and an ideal host with risk factors are prerequisites. Risk factors include immunosuppression, such as HIV infection and drugs (corticosteroids and anti-tumour necrosis factor alpha agents), structural lung diseases (chronic obstructive pulmonary disease (COPD)), non-cystic fibrosis bronchiectasis (NCFBr), and post-transplant patients.[5-7] Other risk factors include rheumatoid arthritis (RA), gastro-oesophageal reflux disease (GORD), Lady Windermere syndrome and environmental soil exposure.[8-11] The clinical presentation varies, depending on the system involved, the extent of the disease (local v. disseminated disease) and the NTM species isolated. NTM commonly affect the lungs, but other organs that can be involved include the lymph nodes, gastrointestinal tract, skin, soft tissue, bones and bone marrow. Disseminated disease, in multiple organ systems, also occurs. The diagnosis and management of NTM infections is often based on the guidelines of the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA), British Thoracic Society (BTS) and the recent 2020 clinical practice of NTM pulmonary treatment guideline. [12-14] To determine the incidence of NTM worldwide remains a challenge. Some of the reasons for this include the fact that infections are not reported as a public health matter, that not every positive specimen translates into disease (i.e. positive specimens may be due to colonisation) and that not all cases fit the requirements for diagnosis based on the ATS/IDSA criteria.

Methods

We searched the PubMed and Google Scholar databases. The terms used were 'non-tuberculous mycobacteria', 'radiology in non-tuberculous mycobacteria' and 'macrolide resistance in NTM'. The articles used were based on systematic reviews (level 1), meta-analysis (level 2), non-randomised controlled cohort studies (level 3) and guidelines (level 4). The articles used were not limited on basis of year of publication, type or language used.

Incidence of NTM

Reports from a national survey in the USA over a 2-year period, 1981 - 1983, estimated a prevalence of 4 201 cases of NTM infection at a rate of 1.78 cases per 100 000 population.[15] A decade later, reports from the USA indicated that there had been an annual increase of cases from 20 to 47 per 100 000 persons, translating into an increase of 8.2% per year.[16] Studies from Northern Australia during the period 1989 - 1997 reported 58 cases, with an average yearly incidence of 3.9 cases per 100 000 persons.[17] Similar reports from Ontario, Canada, showed an isolation prevalence of 9.1 per 100 000 population in 1997, 14.1 per 100 000 population in 2003 and 19 per 100 000 population in 2007, representing an increase of 8.4% per year.[18]

Despite this increasing trend globally, there are few studies that have been published in South Africa (SA) documenting the occurrence of NTM. In a gold-mining workforce, Corbett *et al.*[19] prospectively studied NTM isolates from the sputum of miners in the Free State Province and found that of 118 isolates, 32 (27%) cases met the ATS/IDSA definition for pulmonary NTM disease. Of these, 23 were due to *M. kansasii*, 7 due to *M. scrofulaceum* and there was 1 each of *M. avium* and *M. abscessus*. Similarly, an observational study by van Halsema *et al.* [20] describing clinical relevance of NTM in a gold-mining workforce found 228 (98%) out of 232 infected individuals to be male, with a median age of 44 years. *Mycobacterium avium* complex (MAC; 38 individuals), *M. gordonae* (60) and *M. kansassi* (50) were the common NTM species isolated. The MAC individuals tended to be more symptomatic, with higher documented HIV rates in those who were tested (57/74; 77%).[20] In KwaZulu-Natal Province, Sookan and

Coovadia,[21] using a commercial DNA strip assay, documented that among 200 specimens with suspected NTM isolates, 133 (65%) were confirmed to be NTM positive with the molecular test, with MAC species being the most common isolate, accounting for 76 (57.2%) cases. A systematic review and meta-analysis of NTM pulmonary samples in the sub-Saharan region from only 37 articles that met inclusion criteria found a prevalence of 7.5%, in keeping with findings of van Halsema *et al.*,[20] with males and a younger age group more affected, with a median age of 39 years. In addition, MAC (28%) was the most common isolated species in 19 of 37 studies, and there was a higher rate of HIV co-infection (40.5%) and previous history of pulmonary tuberculosis (32.4%) in the majority of the patients.[22]

Risk factors for NTM infection

Despite an increase in the NTM trends, a positive isolate does not always equate to clinically significant disease. There are, however, a number of factors that increase the risk of patients developing the disease. In a study by Sonnenberg *et al.*,[23] previous tuberculosis, silicosis and duration of underground work were found to be independent risk factors for NTM disease in SA miners. In patients with no underlying lung diseases, risk factors for the disease include GORD, drugs such as corticosteroids and transplant patients. NTM disease in HIV-seropositive patients commonly presents as disseminated disease, occurring at advanced stages of immunosuppression. These infections are common in patients with CD4 cell counts in the range of <100 cells/μL, with MAC being the most frequent isolate. [24,25] A SA study by Pettipher *et al.*[26] documented a 10%-point prevalence of disseminated MAC in SA black patients with CD4 cell counts <100 cells/μL. A US study by Lapinel *et al.*[27] demonstrated NTM prevalence of 49% in HIV-positive patients who presented with pneumonia. Of note, there were no differences in the CD4 counts of the NTM and non-NTM groups. However, in contrast to the Lapinel *et al.* study, McCarthy *et al.*[28] found that none of their patients who were on antiretrovirals had NTM. However, in a SA gold mine, HIV-associated *M. kansasii* disease was uncommon, and most likely to occur at earlier stages of HIV infection, with unusually high CD4 cell counts of 480 cells/mm^3.[29] Despite the contrasting results in the CD4 counts, HIV infection is a well-recognised risk factor for NTM disease, with reports documenting CD4 counts as low as <50 cells/mm^3.[30] In HIV-seronegative patients, structural lung diseases are a common risk factor for NTM infections. In NCFBr patients, a recent meta-analysis of eight separate studies by Chu *et al.*[31] found that among 1 492 patients, the overall prevalence was 9.3%. A recent South Korean study of NTM prevalence in NCFBr patients reported a prevalence of 12.8 per 100 000 in 2012, increasing to 25.2 per 100 000. This demonstrates an increasing prevalence of NTM. Among the NCFBr patients, there were factors that further increased the likelihood of NTM infections, and these included female gender, older age, lower body mass index (BMI) (mean <23 kg/m^2) and childhood infections.[32-35]

COPD is the most common structural lung disease associated with NTM infection. In a study from Taiwan, 47 of 251 COPD patients had >1 NTM isolate, with MAC being the most common species among multiple isolates (36.2%) and single isolate (28.6%) groups.[36] The presence of multiple NTM isolates in patients with COPD has been shown to worsen exacerbations and to be associated with a decline in forced expiratory volume in 1 second compared with patients with single or no NTM isolates.

In solid organ transplant recipients, NTM infections are more commonly seen in lung and heart transplant patients than kidney and liver transplant patients, who have very low infection rates. Reported incidences of NTM infections with lung, heart, kidney and liver transplants are 4.4%, 2.4%, 0.8% and 0.04%, respectively. [37-39]

Diagnosis of NTM infection

The presentation and diagnosis of NTM infection depends on the organ involved, which may include the lungs, lymph nodes, skin, soft tissue, bursae, tendon sheaths, joints, bones and disseminated disease. [12] Pulmonary involvement is by far the most common presentation of NTM disease. Both the ATS/IDSA, BTS and ATS/ERS/IDSA/ESCIM guidelines state that for a diagnosis of NTM lung disease, certain clinical features (cough, fever and constitutional symptoms), and microbiological criteria (two positive early morning sputum samples on different days, or one specimen obtained from a broncho-alveolar lavage) need to be fulfilled. [12-14] These symptoms should be accompanied by specific chest radiographical changes, including the presence of cavities, or the presence on high-resolution computed tomography scan evidence of multifocal bronchiectasis or nodules. The clinical criteria of symptoms (cough, dyspnoea, haemoptysis, constitutional symptoms) are unfortunately not specific to NTM pulmonary disease, as these may be explained by the underlying respiratory disease and active *Mycobacterium tuberculous* (MTB) infection. There are two distinct radiological patterns that are used to classify the disease: fibro-cavitary and nodular bronchiectasis. The differentiation between these two patterns has major clinical implications, as the fibro-cavitary pattern is associated with poorer outcomes and high mortality.[40] To include other radiological findings that fall outside these radiological patterns, Cowman *et al.*[41] used latent class analysis and came up with three radiological subgroups (class 1 - cavitary, class 2 - nodular and class 3 - bronchiectasis), and similarly to other reports, the cavitary group was associated with markers of disease severity (high C-reactive protein and low BMI) and high mortality. In a 20-year review of radiological findings in NTM by dos Anjos *et al.*,[42] cavitation (88.9%) was the most common finding, followed by bronchiectasis (77.8%) and pulmonary nodules (55.6%) as the least common. The fibro-cavitary changes are typically described in elderly male smokers with COPD,[43] while nodular bronchiectasis is predominant in elderly post-menopausal females, typically lean, with skeletal deformities (scoliosis and pectus excavatum) without an underlying lung disease, also known as Lady Windermere syndrome.[44] When comparing radiological cavities in the MTB and NTM patients, there were varying differences in their phenotypes. Among the NTM patients, the cavities tend to be thin walled (6.9 (standard deviation (SD) 3.7) mm v. 10.9 (5.6) mm, $p<0.001$) with adjacent pleural thickening (62.5% NTM v. 25% MTB group).[45] Some of the ancillary findings in the NTM group in this study were pleural effusions, ill-defined satellite tree-in-bud nodules and fewer non-cavitary nodules >10 mm. There seem to be further differences in the radiological pattern depending on the immune status of the patients. Lee *et al.*[46] reviewed CT scan findings of both groups, the non-AIDS immune-compromised and immune-competent, and cavitation was found to be a predominant feature in the non-AIDS immune-compromised group, while ill-defined nodules were common in the

immune-competent. Disseminated disease in HIV-seropositive and HIV-seronegative patients requires culture isolation of NTM organisms in the blood or other closed sites, such as bone marrow. Typical clinical presentation of NTM infections in HIV-seropositive patients includes unexplained fevers, weight loss, anaemia and diarrhoea, in the presence of low CD4 count <50 cells/μL.

Diagnosis of involvement at other sites, including lymph nodes, soft tissue and bones, requires a positive NTM culture of tissue involved. Lymphadenitis tends to be unilateral and nontender, and commonly affects submandibular, axillary and cervical nodes and the lymph nodes.[12] The diagnosis requires specific isolation of the pathogen from lymph node cultures. Culture from drainage material for skin and soft-tissue infections and synovial biopsy for bone involvement is warranted for the diagnosis.

Management of NTM infection

The challenges in managing NTM pulmonary disease range from being able to differentiate colonisation from significant disease, different treatment regimens for specific NTM isolates, to longer treatment durations, which result in drug-drug interactions, drug resistance and adverse events. The ATS/IDSA,[12] BTS[13] and the recent ATS/ERS/ESCMID/IDSA guidelines[14] recommendation for MAC lung disease is a three-drug regimen consisting of rifampicin/rifabutin, a macrolide (azithromycin or clarithromycin) and ethambutol, for a minimum duration of 12 months after culture conversion. Macrolides are the backbone therapy for NTM lung disease, hence macrolide-susceptible MAC lung disease has better outcomes in contrast to macrolide resistance. A retrospective study by Wallace *et al.*[47] evaluating the efficacy of a macrolide (azithromycin or clarithromycin)-containing regimen in MAC pulmonary disease showed overall treatment success in 84% of patients, with no report of macrolide resistance and better tolerance with intermittent doses compared with daily dosing. In a study by Marimoto *et al.*[48] of macrolide-resistant MAC lung disease, the 5-year survival rates were 71%, similar to that of multidrug-resistant tuberculosis at 75%. Similar results were documented in a South Korean study by Moon *et al.*[49] showing poor outcomes in 85% of macrolide-resistant patients and a 5-year mortality rate of 50%. A Griffith *et al.*[50] study of macrolide resistance in MAC lung disease achieved sputum conversion after at least 6 months of injectable aminoglycosides and surgery, which proves the benefit of aggressive therapy and surgical intervention in these patients. The mortality rate at 1 year in patients who failed to achieve sputum conversion was still significant, at 34%. Macrolide resistance has been a major role-player in disease outcomes, and some of the reasons for resistance include macrolide monotherapy, macrolide and fluoroquinolone combination and omission of ethambutol. The recommendation by the guidelines is therefore to test for macrolide resistance prior to treatment initiation, and also to test for resistance to other drugs if there is no sputum conversion. To improve outcomes despite macrolide resistance, the intervention reported both by Marimoto *et al.*[48] and Griffith *et al.*[50] that what was of benefit was the use of injectable aminoglycosides for at least 6 months as well as surgical intervention in eligible patients. In the Marimoto study, in 61% of cases clarithromycin was continued despite the resistance, and it showed no benefit, as was the case with other alternative therapies that were used, including fluoroquinolones and rifabutin, which also did not improve outcomes. However, in an observational cohort study assessing a clofazimine-containing regimen, 41 of 82 patients achieved culture conversion within 12 months of treatment.[51] As a salvage therapy, bedaquiline given for 6 months achieved culture conversion in 50% of patients, with no major adverse events reported.[52] These reports demonstrate some potential activity of these drugs in macrolide-resistant MAC treatment, but larger studies are required to confirm these findings.

Surgical treatment of NTM lung disease

The treatment outcomes of NTM lung disease are poor despite optimal recommended regime therapies, with non-cavitary disease achieving rates of 24%, and 4% in cavitary disease.[53] The indications for surgical intervention were cavitary lesions (65.7%), haemoptysis (14.3%) and poor response to treatment (20%).[54] This led to surgical intervention as a justifiable option in suitable/selected patients. Studies have further proven favourable outcomes with less mortality, in a retrospective study by Fukushima *et al.* [54] comparing outcomes between NTM lung disease patients who were surgically treated v. those non-surgically treated with antimicrobials. In this cohort, long-term negative sputum conversion was 82.2% in the surgical group v. 50% in the non-surgical arm. These results are not significantly different from other reports, with Kang *et al.*[55] and Asakura *et al.*[56] reporting negative sputum culture conversion of 81% and 91%, respectively. The complication rates were similar across studies,[54-56] with 20%, 21% and 22% reported, and these were higher in the post-pneumenectomy patients.

Summary

NTM is a matter of concern considering its rising incidence globally, and the poor outcomes despite antimicrobial therapy. In sub-Saharan African countries, risk factors (HIV, bronchiectasis, tuberculosis) for NTM are at high levels, yet there is still a paucity of data compared with other parts of the world. Whether this is a matter of under-reporting or whether the numbers rather reflect our true disease burden is something that needs further studies to confirm. However, an aggressive approach to NTM is needed in light of poor treatment outcomes, and surgical intervention should always be a consideration in surgically fit patients.

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