Pulmonary non-tuberculous mycobacteria and *Mycobacterium tuberculosis* complex co-infection: A pragmatic approach to its diagnosis and management in South Africa

To the Editor: Non-tuberculous mycobacteria (NTM) are acid-fast bacilli that are Ziehl-Neelsen positive, sharing similarities in constitutional symptoms and radiological presentation with *Mycobacterium tuberculosis* complex (MTBC).[1] NTM and other organisms, such as MTBC, often share similar risk factors, including structural lung disease.[2] Despite clinical and radiological similarities, NTM treatment regimens, therapy duration, clinical monitoring and laboratory testing significantly differ from those of MTBC.[3] NTM is not a diagnosis by exclusion or part of reflex testing. It requires specific line probe assays to be performed by laboratories in South Africa (SA) (Fig. 1). Therefore, tuberculosis healthcare workers must maintain a heightened suspicion for NTM, particularly in symptomatic cases, exhibiting persistent negative results on tuberculosis nucleic acid amplification tests (TB-NAAT) for MTBC (Fig. 1).

There are numerous reports in the literature describing co-infections involving NTM and other organisms, including multiple different NTM species, NTM and aspergillus or other fungi, NTM and MTBC, etc.[7-9] The 2020 diagnostic criteria outlined by the American Thoracic Society/Infectious Diseases Society of America for diagnosing pulmonary NTM disease have remained unchanged since the previous version almost two decades ago (see back of manuscript for guideline criteria).[5,6] Although the current guideline mentions co-infections, the 2007 version had dedicated sections to this concept (see back of manuscript for guideline sections acknowledging co-infections). Both versions incorporate the exclusion of an alternative diagnosis to define NTM pulmonary disease. These diagnostic modalities may involve bacterial or viral respiratory panels, GeneXpert MTB/RIF Ultra (Cepheid, USA), special stains to exclude opportunistic infections such as pneumocystis pneumonia, or rapid point-of-care tests for *Legionella* disease, among others.[10] TB healthcare workers should be aware that a valid alternative diagnosis does not indefinitely exclude the diagnosis of respiratory NTM disease, and could potentially indicate the presence of a co-infection. Therefore, the word 'appropriate' does suggest the need for individual clinical judgment. In addition, not all NTM disease requires immediate treatment: a 'watchful wait' approach can also be considered.

International guidelines suggest prioritising drug susceptibility-based treatment over empirical NTM management.[6] In SA, NTM susceptibility testing is performed centrally at the National TB reference laboratory in Johannesburg. Consequently, it is advisable to engage with TB microbiologists to discuss NTM drug susceptibility testing, with consideration given to individual cases. Expert clinical consultation is important when considering NTM disease with organisms typically indicative of environmental contamination or less frequently encountered, such as *Mycobacterium gordonea*, and those involved in dual infections with other mycobacteria.[5,6]

Providing explicit guidance for a group of organisms, such as NTM, which are widely distributed in the environment and frequently encountered by human hosts, can be extremely challenging. This challenge is exacerbated by the era of culture-independent diagnostics, as well as the advent of modern-day next-generation sequencing and metagenomics technologies.[11] These advancements identify multiple organisms simultaneously. In this context, clinicians must, perhaps more than ever, utilise all available clinical clues and their laboratory resources to make a diagnostic determination, while bearing in mind the underlying concern of potentially overdiagnosing NTM colonisation as active disease in co-infections.

International criteria for diagnosis of NTM pulmonary disease includes the following:

Clinical AND radiological imaging (pulmonary symptoms, nodular or cavitary opacities on chest radiograph, or a high-resolution computed tomography scan that shows multifocal bronchiectasis with multiple small nodules) AND appropriate exclusion of other diagnoses AND confirmatory microbiology (positive same culture results from at least two separate expectorated sputum samples (collected at least one week apart) OR positive culture result from at least one bronchial wash or lavage OR transbronchial or other lung biopsy with mycobacterial histopathological features (granulomatous inflammation or acid-fast bacilli) and positive culture for NTM and one or more sputum or bronchial washings that are culture positive for NTM).

2007: An official American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) statement: diagnosis, treatment and prevention of NTM[5] – 'Lastly, there are clinical problems not directly addressed by these diagnostic guidelines. For instance, the significance of an NTM isolated from a patient during therapy for pulmonary TB is uncertain. The significance of two NTM species isolated simultaneously from a patient is also unknown. The combination of *Mycobacterium avium* complex and *M. abscessus* is especially well recognised. Unfortunately, there is not sufficient information to answer these issues broadly, so that patients in these circumstances must be approached on an individual basis. Both these events are likely to occur with increased frequency because of improved recovery of NTM by mycobacteriology laboratories. Patients who present with these clinical scenarios must be evaluated carefully, on an individual basis, and may require expert consultation.'

2020: Treatment of NTM pulmonary disease: an official ATS/ European Respiratory Society (ERS)/ European Society of Clinical Microbiology and Infectious Diseases (ESCMID)/IDSA clinical practice guideline[6] – 'However, the risk of acquiring resistance to other co-infecting pathogens must be considered when macrolides are used for immunomodulatory purposes in patients whose isolate has documented inducible or mutational macrolide resistance.' 'Although macrolides might still be useful for immunomodulatory effects or antimicrobial effects against other co-infecting organisms, they are not counted as an active drug against *M. abscessus* when inducible or mutational resistance is noted.'

C Opperman
National Health Laboratory Service, Green Point TB Laboratory, Cape Town, South Africa; *SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Cape Town, South Africa; Division of Medical Microbiology, Department of Pathology, University of Cape Town, South Africa*
Christoffel.opperman@nhls.ac.za

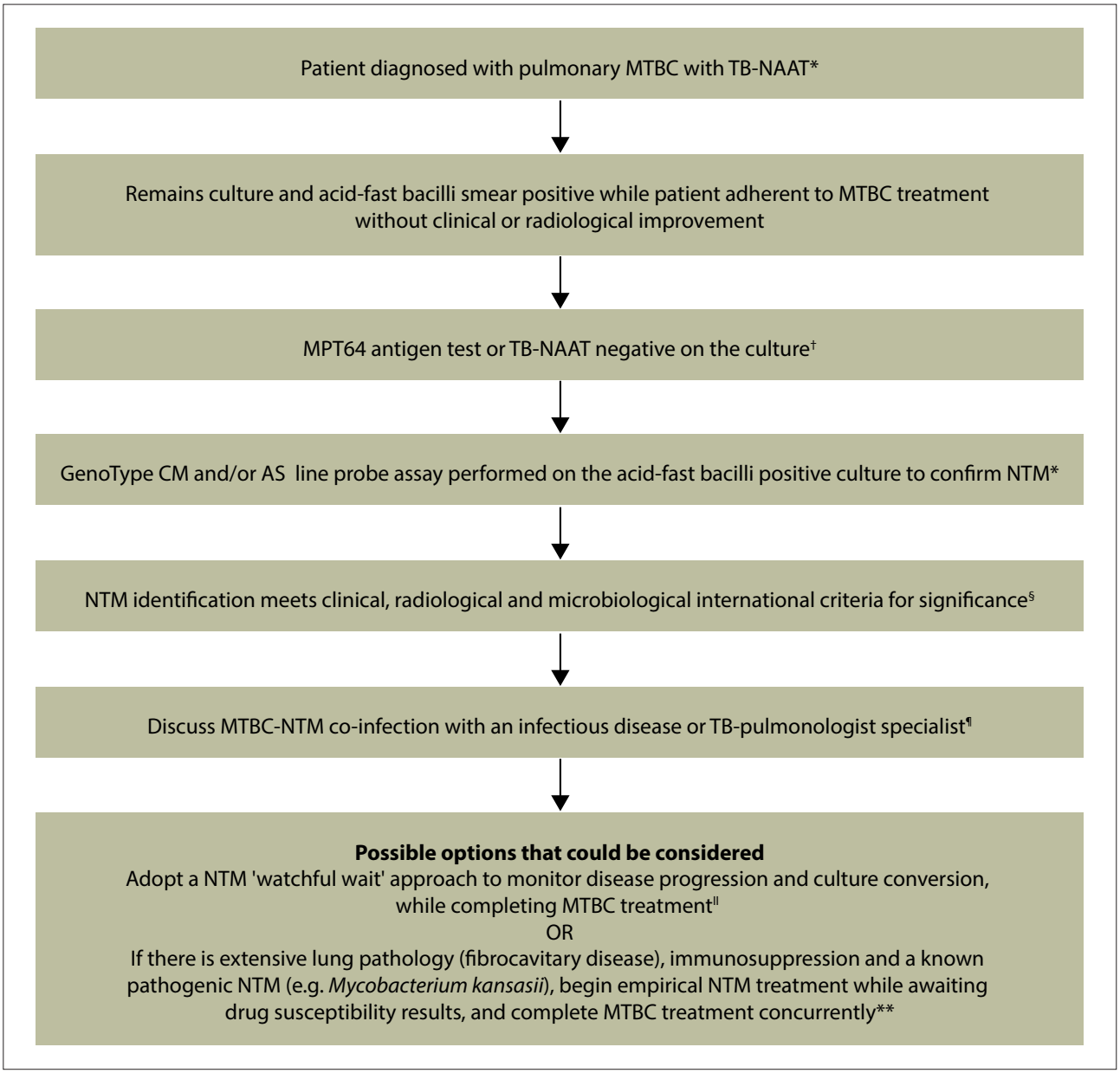

Fig. 1. The management of NTM and MTBC co-infections should be approached using anecdotal evidence and established international guidelines. Management of mycobacterial co-infections must be tailored on a case-by-case basis and overseen by a consultant with expertise in NTM infections. Suspected NTM cases are identified using diagnostics specific to these organisms. Treatment of MTBC should be initiated, followed by rigorous culture monitoring of the NTM (watchful wait approach). Alternatively, based on the severity of the disease, the extent of lung damage and the virulence potential of the NTM, concurrent treatment of both NTM and MTBC may be warranted.

*TB-NAAT platforms in SA can include the GeneXpert MTB/RIF Ultra, BD MAX MDR-TB assay, or Roche cobas MTB platform.

†MPT64, also known as protein Rv1980c, is a protein secreted by actively growing *Mycobacterium tuberculosis* strains. This antigen is not present in (BCG) strains, *Mycobacterium bovis*, *Mycobacterium leprae*, or other mycobacterial (NTM) species.[4]

‡The DNA-DNA reverse hybridisation GenoType *Mycobacterium* CM and AS line probe assays are not part of routine reflex testing in SA. Acid-fast bacilli can be confirmed with a Ziehl-Neelsen or an auramine stain.

§Refer to main text for the international criteria for diagnosis of NTM pulmonary disease.[5,6]

¶Both the current and previous versions of the international criteria for NTM pulmonary disease have referenced the concept of co-infections and the importance of seeking expert consultation for case-by-case management.[5,6]

‖It is imperative to acknowledge that fulfilling diagnostic criteria for NTM pulmonary disease does not inherently mandate antibiotic intervention. Rather, a comprehensive evaluation is essential, encompassing factors such as the organism's pathogenic potential, the risk-to-benefit ratio of therapeutic interventions, the patient's willingness and capacity to adhere to treatment, and the overarching therapeutic objectives. In certain scenarios, the adoption of a 'watchful waiting' strategy may emerge as the preferred course of action.[6] Many NTM species may not cause significant pulmonary disease due to their low pathogenic potential. Examples include *M. flavescens*, *M. gastri*, *M. gordonae*, *M. haemophilum*, *M. mucogenicum*, *M. nonchromogenicum*, *M. terrae* and *M. triviale*.[1]

**Factors indicating a relatively poor prognosis encompass diminished albumin levels, cavitary disease, elevated inflammatory markers and a low BMI. The isolation of a more virulent organism with a heightened responsiveness to antimicrobial therapy (e.g. *M. kansasii*), and underlying immunosuppression further tilt the scale towards antimicrobial intervention.[6]

(NTM = non-tuberculous mycobacteria; MTBC = Mycobacterium tuberculosis *complex; TB-NAAT = tuberculosis nucleic acid amplification test; MDR-TB = multidrug-resistant tuberculosis; BCG = Bacillus Calmette-Guérin; CM = common* Mycobacterium; *AS = additional species; SA = South Africa; BMI = body mass index.)*

S Singh
National Health Laboratory Service, Green Point TB Laboratory, Cape Town, South Africa; SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Cape Town, South Africa

Y Ghebrekristos
National Health Laboratory Service, Green Point TB Laboratory, Cape Town, South Africa; SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Cape Town, South Africa

R Warren
SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Cape Town, South Africa

W Goosen
SAMRC Centre for Tuberculosis Research, Division of Molecular Biology and Human Genetics, Stellenbosch University, Cape Town, South Africa

Author contributions. CO drafted the first version of the manuscript. CO, SS, YG, RW, and WG contributed to the editing, provided critical revisions, and approved the final version of the manuscript for submission.

Conflicts of interest. None.

S Afr Med J 2024;114(9):2313. https://doi.org/10.7196/SAMJ.2024.v114i9.2313

1. Opperman CJ, Singh S, Goosen W, Cox H, Warren R, Esmail A. Incorporating direct molecular diagnostics in management algorithms for nontuberculous mycobacteria: Is it high time? IJID Reg 2023;10:140-145. https://doi.org/10.1016/j.ijregi.2023.12.003
2. Sharma SK, Upadhyay V. Epidemiology, diagnosis and treatment of nontuberculous mycobacterial diseases. Indian J Med Res 2020;152(3):185-226. https://doi.org/10.4103/ijmr.IJMR_902_20
3. Lange C, Böttger EC, Cambau E, et al. Consensus management recommendations for less common nontuberculous mycobacterial pulmonary diseases. Lancet Infect Dis 2022;22(7):e178-e190. https://doi.org/10.1016/S1473-3099(21)00586-7
4. Kumar VG, Urs TA, Ranganath RR. MPT 64 antigen detection for rapid confirmation of *M. tuberculosis* isolates. BMC Res Notes 2011;4:79. https://doi.org/10.1186/1756-0500-4-79
5. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. Am J Respir Crit Care Med 2007;175(4):367-416. https://doi.org/10.1164/rccm.200604-571ST
6. Daley CL, Iaccarino JM, Lange C, et al. Treatment of nontuberculous mycobacterial pulmonary disease: An official ATS/ERS/ESCMID/IDSA clinical practice guideline. Eur Respir J 2020;56:2000535. https://doi.org/10.1183/13993003.00535-2020
7. Joao I, Bujdáková H, Jordao L. Opportunist coinfections by nontuberculous mycobacteria and fungi in immunocompromised patients. Antibiotics 2020;9(11):771. https://doi.org/10.3390/antibiotics9110771
8. Thangavelu K, Krishnakumariamma K, Pallam G, et al. Prevalence and speciation of non-tuberculous mycobacteria among pulmonary and extrapulmonary tuberculosis suspects in South India. J Infect Public Health 2021;14(3):320-323. https://doi.org/10.1016/j.jiph.2020.12.027
9. Yılmaz N, Uçar EY, Sağlam L. *Mycobacterium tuberculosis* and nontuberculous mycobacteria coinfection of the lungs. Turk Thorac J 2017;18(1):23-26. https://doi.org/10.5152/TurkThoracJ.2017.16034
10. Brink AJ, Centner CM, Opperman C. Microbiology assessments in critically ill patients. Semin Respir Crit Care Med 2022;43(1):75-96. https://doi.org/10.1055/s-0041-1741018
11. Wang L, Liu D, Yung L, et al. Co-infection with 4 species of *Mycobacteria* identified by using next-generation sequencing. Emerg Infect Dis 2021;27(11):2948-2950. https://doi.org/10.3201/eid2711.203458