Journal of Antimicrobial Stewardship Practices and Infectious diseases

JASPI

December 2024 / Volume 2 / Issue 4

Editorial

Nontuberculous Mycobacterial (NTM) Disease in Indian Settings

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INTRODUCTION

The prevalence of nontuberculous mycobacterial (NTM) disease is increasing worldwide and is an emerging public health problem in India.[1-3] NTM are ubiquitous in our environment, including air, water, dust, soil, terrestrial and aquatic animals, and man-made infrastructure.[1,4] Nearly 200 NTM species/subspecies have been reported.[5] Based on their growth rate in the culture media, NTM are classified into slowly growing mycobacteria (SGM; >7 days) and rapidly growing mycobacteria (RGM; <7 days).[6] *Mycobacterium avium* complex (MAC), *M. abscessus*, and *M. kansasii* are major pathogenic NTM species isolated globally.[3,7] Like tuberculosis (TB), NTM causes both pulmonary (80-85%) and extrapulmonary diseases (15-20%).[3,8,9] Unlike TB, person-to-person transmission of NTM does not occur. Still, it has been rarely reported due to *M. abscessus* among cystic fibrosis (CF) patients (rare in India, involves 1 in 40,000-1,00,000 population).[10,11] Risk factors for developing NTM-pulmonary disease (NTM-PD) include previously damaged lungs due to TB, bronchiectasis, CF, and chronic obstructive pulmonary disease.[3,7] Lymph nodes, skin and soft tissues, bones, non-healing post-operative suture sites, and other surgical wounds are favourite sites for extrapulmonary-NTM (EP-NTM) disease.[3,8,9] Disseminated NTM disease due to congenital deficiency of interferon-γ is rare in India; however, disseminated MAC infection occurs in HIV/AIDS patients with verylow CD4+ lymphocytes.[3] NTM disease is not a notifiable disease in several countries, including India.[2,3,12] The prevalence of NTM disease is variably reported across several countries.[1,12] In a few Western countries, South Korea and Japan from Asia, the NTM disease prevalence is regularly estimated to know the time trend.[1,12] In a high TB burden and resource-limited countries such as India, the exact incidence and prevalence of NTM disease are unknown.[2,3] While NTM prevalence is estimated among 1,00,000 individuals in low TB-burden countries, in high TB-burden countries, it is estimated among TB suspects.[3] NTM disease is frequently misdiagnosed as drug-sensitive and drug-resistant TB or is often overlooked due to a lack of awareness among clinicians and microbiologists and inadequate laboratory infrastructure.[3]

STATUS OF NTM DISEASES IN INDIA

Studies on NTM began in India in the late 1970s. With the emergence of human immunodeficiency virus/acquired immunodeficiency virus syndrome (HIV/AIDS) in the early 1980s, MAC was the most common opportunistic infection, especially among patients presenting with low CD4+ cell counts.[2,12] In

Citation: Upadhyay V, Sharma SK. Nontuberculous Mycobacterial (NTM) Disease in Indian Settings. *JASPI.* 2024;2(4):5-9. 10.62541/jaspi062

Submit a Manuscript: https://journal.saspi.in/
SASPI: https://saspi.in/

ISSN: 3048-4510 (Online)
DOI: 10.62541/jaspi062

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1985, Paramasivan et al. published the first comprehensive study on NTM from India.[14] Since then, most Indian studies have reported NTM species isolation from microbiology laboratories without establishing their clinical relevance.[2,3] In the 1980s, NTM isolation was 5.6% among pulmonary TB suspects in India. Between 2001 and 2010, the NTM isolation rate from pulmonary and extrapulmonary specimens was 0.93%, increasing to 1.6% in the decade between 2011 and 2020.[2,3] These differences in NTM isolation can be attributed to the use of culture-based biochemical methods for speciation in the 1980s, which may be frequently inaccurate and spuriously high due to contamination at various steps, from specimen collection to laboratory processing.[2,3] In the Revised National Tuberculosis Control Program [(RNTCP), now known as National TB Elimination Program (NTEP)] of India, sputum smear microscopy was considered sufficient to diagnose and treat TB as culture facilities were not widely available in India, making diagnosis of NTM disease further difficult. Since 2000, the widespread availability of culture facilities, the advent of new rapid molecular techniques, and the publication of various NTM diagnosis and treatment guidelines have accurately streamlined the isolation and reporting of NTM species/subspecies.[15-19] Different study objectives and designs could have also contributed to differences in NTM isolation rates.[2,3] However, these isolation rates do not define true NTM disease prevalence as these data are laboratory findings without establishing the clinical relevance of isolated organisms.[2,3] Only a handful of Indian studies reported NTM disease prevalence ranging from 0.2%-0.8% among TB suspects.[2,3,8] A history of TB is the most frequent predisposing risk factor for NTM-PD in India.[2,3,8] In EP-NTM, post-operative sites are commonly associated with NTM infections and may be attributed to unautoclaved surgical instruments and other items used in dressing wounds.[2,3,8] The most frequently isolated and clinically relevant NTM species in India include *M. avium* complex [MAC (mostly *M. avium* and *M. intracellulare)*], *M. abscessus, M. kansasii, and M. fortuitum*.[2,3] NTM-PD is frequently caused by MAC, *M. kansasii,* and *M. abscessus*. In EP-NTM, *M. abscessus* and *M. fortuitum* were frequently isolated.[2] None of the previous Indian studies has reported subspecies of *M. abscessus* isolates and their *erm* (41) [*(*erythromycin ribosomal methylase (*41)*] gene mutation status. Further, there is a paucity of data on treatment outcomes of NTM diseases in India, as most patients are left untreated because of the following reasons.[2] These include reporting of NTM data from microbiology laboratories, inappropriate treatment and frequent guidelines-based treatment (GBT) not followed, longer treatment, poor or no clinical follow-up of patients, and unwillingness of patients to pay for out-of-pocket treatment due to poor socioeconomic background and exhaustion during laboratory tests.[2,3,7]

Geographical variations in the distribution of NTM species have been described globally, including in India, which may be attributed to diverse climatic and terrestrial conditions.[1,2,12] Only a few Indian studies have reported NTM isolation from environmental samples.[2]

FUTURE PROSPECTS

The NTM isolation in India from various specimens was not considered serious, and no efforts were made to establish the clinical relevance of the isolated NTM species from the microbiology laboratories.[2,3] Various forms of TB (pulmonary, extrapulmonary, and subclinical TB) and HIV-TB were considered a priority globally, including in India. With the declining prevalence of TB, stakeholders of the Indian healthcare system must gear up to face challenges posed by NTM diseases soon. In medical colleges, the curriculum for medical students, residents, and nursing students must include up-to-date information on NTM epidemiology, diagnosis, treatment, and prevention. Cross-talk between the microbiologist and the treating doctor should take place regularly.[7] A network of clinicians, radiologists, and microbiologists should be established to diagnose NTM disease.[7] All countries, including India, should make NTM disease notifiable.[20] Appropriate precautions should be taken while collecting various specimens and during storage, and good laboratory practices should be followed while processing these specimens in microbiology laboratories.[3,7,20] Patient should not rinse their mouth with tap water before collecting sputum samples.[3] Wounds should not be washed with tap water while collecting specimens from extrapulmonary sites.[3] Transport and storage of specimens must be done at optimal temperature and sterile conditions. Contamination from various reagents, instruments, and tap water must be avoided in the laboratory.[3] Rapid molecular techniques like line probe assay should be available nationwide in all laboratories for rapid and correct NTM species/subspecies identification. Targeted and whole genome sequencing may be used to identify genetically closely related NTM species, and genotypic drug susceptibility testing should be done only in selected cases. Laboratories should report subspecies of MAC and *M. abscessus*. In MAC and *M. abscessus*, the mutation status of 23S rRNA and 16S

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rRNA genes must be reported to confirm susceptibility to macrolides and amikacin, respectively, when patients don't respond to the administered treatment. In *M. abscessus, erm* (41) gene mutations must be analysed to detect inducible macrolide resistance on days 3-5, and 14.[7,16,17] Expert consultation must be taken before initiating treatment.[15,16] Patients should be counselled regarding GBT and follow-up.[7,16,17,19] Adequate hydration, airway clearance therapy, and chest physiotherapy should be instituted.[7,16,17,19] Surgery may be considered if the disease is localised, the patient is fit and has a sufficient cardiopulmonary reserve to tolerate lung resection surgery. Special attention should be paid to treating malnutrition, including hypoalbuminemia and anaemia if present.[7,15,16,18] As the treatment duration of NTM disease is long, meticulous follow-up of patients is recommended.[7,16,17,19] Further, like TB, the Government of India should make efforts to provide free-of-cost treatment to NTM patients, and abuse of azithromycin (macrolide; backbone drug of NTM treatment regimen) must be regulated. It was pathetic to see that azithromycin was misused during the SARS-CoV-2 pandemic not only in India but globally also. Further, in India, azithromycin is available over-the-counter (OTC), and the patient can purchase it from the nearby medical store without a valid prescription and take it even for a simple throat infection without ascertaining the aetiology, which may well be due to a viral cause. Indian healthcare authorities should seriously consider a National registry for NTM diseases.

CONCLUSION

Basic and translational research on NTM in India is still in its infancy, and there are many unanswered questions regarding biological diversity, differences and similarities in NTM species, and their pathobiology, transmission, and treatment outcomes (**Box**). Various scientific and medical organisations must support medical and basic science researchers in performing comprehensive studies on the clinical and environmental aspects of NTM. With this background, the Indian Council of Medical Research, Ministry of Health and Family Welfare, Government of India, New Delhi, has sponsored a multicentre study across various states of India from 2021 to 2025 to systematically collect data on epidemiology, diagnosis and treatment of NTM disease.[21] Results of this study are eagerly awaited, which may give further insight into NTM disease in Indian settings and help make national policies and guidelines for this neglected disease.[21]

Box: Key points for practicing clinicians and microbiologists

- The treating clinician should have a high index of suspicion for NTM disease when the patient has a positive AFB smear and MTB NAAT is negative and if the patient is not responding to the anti-tuberculosis treatment.
- Alternative diagnoses with similar manifestations must be ruled out by appropriate laboratory tests.
- Clinical, radiological, and microbiological details of patients should be carefully examined.
- Predisposing risk factors such as GERD must be investigated in patients with RGM infection.
- For NTM diagnosis, patients must not rinse their mouths with tap water before sputum sample collection.
- While collecting extrapulmonary specimens, wounds must not be washed with tap water and instruments must be autoclaved before use.
- Specimen transport and storage should be done at optimal temperature and devoid of contamination.
- The microbiology team should avoid contamination from all sources of NTM in the laboratory.
- NTM species/subspecies must be reported preferably using molecular techniques such as LPA and gene sequencing.
- For NTM isolation, 2 out of 3 sputum specimens collected at least one week apart must have a mycobacterial culture positive and the same species/subspecies must be isolated from both cultures.
- In MAC and *M. abscessus*, 23S rRNA and 16S rRNA gene mutation analysis must be done to confirm macrolides and amikacin resistance respectively if there is no response to the administered treatment.
- In *M. abscessus*, erm (41) gene mutations must be analysed to detect inducible macrolide resistance on days 3-5 and 14.
- NTM diagnosis must be established according to ATS/ERS/ESCMID/IDSA 2020 guidelines.
- Expert consultation should be taken before treatment initiation.
- Efforts should be made to administer guidelines-based treatment.
- Treatment should be continued for 12 months after culture conversion except for *M. kansasii* and
- *M. szulgai* where a total of 12 months of treatment is sufficient.
- Patients must be clinically, radiologically, and microbiologically followed up and monitored for AEs and SAEs.
- Monitoring of patients is required at regular intervals to check relapse of the disease after treatment completion

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NTM=nontuberculous mycobacteria, MTB NAAT= Mycobacterium tuberculosis nucleic amplification tests, GERD=gastroesophageal reflux disease, RGM=rapidly growing mycobacteria, LPA=line probe assay, erm gene=erythromycin resistance methylase gene ATS/ERS/ESCMID/IDSA= American Thoracic Society /European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases/Infectious Diseases Society of America, AEs =Adverse events, SAEs= severe adverse events.

ACKNOWLEDGEMENT

The authors would like to acknowledge the Indian Council of Medical Research, Ministry of Health and Family Welfare, Government of India, New Delhi, for funding a multicentre study on NTM disease (No. 5/8/5/41/ITRC/2018/ECD-I).

CONFLICTS OF INTEREST STATEMENT

The authors declare no conflict of interest

SOURCE OF FUNDING

None

ETHICS STATEMENT INCLUDING PATIENT CONSENT

Not applicable

AUTHOR'S CONTRIBUTION

Both authors are qualified for authorship as per ICMJE criteria. They approved the manuscript.

AI DECLARATION

No AI tool was used to generate research data, perform data analysis, interpret findings, formulate scientific conclusions, or make editorial decisions. All AI-assisted content was critically reviewed, verified, and revised by the authors. The authors take full responsibility for the accuracy, originality, integrity, and final content of the manuscript.

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