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Commentary

Diagnosis & management of infections due to non-tuberculous mycobacteria in developing countries: Looking ahead

The study by Sharma *et al*[1] in this issue is a prospective study of 42 patients with non-tuberculous mycobacteria (NTM) disease among 5409 tuberculosis (TB) suspects who presented to a tertiary care centre in north India, during 2014-2016. This was an interesting study with a critical analysis of the importance of observations recorded in these cases. Disease confirmation was by internationally used criteria developed by the American Thoracic Society (ATS)[2]. Bronchiectasis as a sequel of pulmonary TB was the most common predisposing cause. Only one patient in the extrapulmonary NTM group had HIV/AIDS. As such, the data presented and discussion provided a lot of useful material with clinical relevance. However, one wonders what it means for developing countries like India. While treatment guidelines such as that developed by the ATS will be useful for diagnosis and treatment, it is expected that these will have some limitations as susceptibility profiles will have differences due to varying environmental factors. What more needs to be done before we can have evidence-based guidelines for treating different NTM infections in India or other similarly placed developing countries? Such countries/regions will have varying levels of infrastructure and expertise ranging from the optimal or ideal to below suboptimum.

It is well known that of the 212 (species/subspecies) mycobacteria described so far[3], about one-fourth have been known to cause disease in humans and other animals[4]. Besides well-known mycobacterial pathogens such as *Mycobacterium tuberculosis* and *M. leprae*, others have been lumped together and given various nomenclatures such as atypical mycobacteria, anonymous mycobacteria, mycobacteria other than *M. tuberculosis* complex (MOTT) and NTM. Most of such mycobacteria have been thought to be saprophytes or not established as pathogens. However, their pathogenic potential has been known for a long time. Incidentally, the first such *Mycobacterium* was recognized as a cause of human disease in 1908[5].

In the study by Sharma *et a1*[1], *M. intracellulare* was the most common NTM isolate followed by *M. abscessus* among pulmonary patients; other species were *M. kansasii*, *M. simiae*, *M. gordonae*, *M. chimaera*, *M. senegalense* and *M. abscessus.* NTMs isolated from extrapulmonary specimens included *M. abscessus, M. intracellulare* and *M. parascrofulaceum.* The first available report from India on NTMs was in 1964 by Kaur and Chitkara[6], this was 56 years after the 1908 report of Duval[5]. For the next 20 years after that, possibly, there was no report. Several reports on NTM disease were published in the next 20-25 years. Besides 10 species isolated in this study[1] published in this issue, other NTM species reported from patients from India include *M. chelonae*, *M. fortuitum*, *M. mucogenicum*, *M. avium*, *M. triviale*, *M. celatum*, *M. porcinum*, *M. massiliense*, *M. phlei* and *M. genavense*. Thus, of the nearly 50 NTM species known to be opportunistic pathogens in humans across the world, only half have been reported from India[4]. Does it mean that others do not exist in India? or they do not cause disease in Indians? Perhaps, the real answer may turn out to be that we have ignored the diseases caused by them and/or a major part of India lacked the expertise and/or infrastructure to diagnose such cases.

The magnitude of NTM disease in India is not known with certainty. There are very few studies with sufficient numbers such as the one published in this issue. It would be realistic to state that this study may also not represent the situation from this tertiary care institution itself. Many patients would have gone to other clinicians and departments depending on predominant organ involvement. Other reports with smaller numbers will have lesser epidemiological

significance. However, 0.8 or one per cent prevalence or frequency of NTM for a country like India means huge numbers. Morbidity and mortality associated with many NTM infections, costs of treating such patients and disability-adjusted life years lost will tell the importance of such numbers. Developing registries from institutions with centralized electronic registration and good follow up can provide realistic estimates. Such information will also be relevant in understanding the gaps in knowledge, infrastructure, expertise and trends.

Diagnosis of disease conditions caused by different NTMs is not often easy. Expertise along with a strong clinical suspicion among clinicians, pathologists, microbiologists and radiologists is necessary. While many of the NTMs may be ignored as contaminants, there is an equal danger of missing them as they may not be cultivable on routine media used for *M. tuberculosis*. Rapid growers may be causing pyogenic infections; thus, they may be missed if microbiological protocols are not robust. Even decontamination procedures can contribute to the loss of viability. Many NTM species require low or high temperatures for growth and specific medium requirements such as mycobactin J and blood for their growth. Further, paraffin-based media have also been found to be useful for NTMs[4]. Index of suspicion and appropriate protocols with a focus on appropriate growth conditions are required to culture them or detect them by chemical, immunological and molecular tools including probes, PCR, PCR-restriction fragment length polymorphism (RFLP) and *in-situ* hybridization/immunohistochemistry without culture[4].

Identification of NTMs also requires knowledge of biochemical tests useful to differentiate them and their chemical components such as lipid patterns, antigenic profiles, enzymes/isoenzymes and genetic diversity[4]. Proteome analysis; PCR/isothermal gene amplification/real-time PCR-based methods; probe hybridization; PCR-RFLP approaches targeting 16S rRNA, 16-23S rRNA internally transcribed sequences, *rpoB* gene, *hsp65* kDa gene, *etc.*; and sequencing of rRNA/*rpoB* genes has been successfully used to identify and classify various NTM. Majority of the NTMs can be identified by biochemical tests and their lipid patterns; other techniques will have incremental value. DNA fingerprinting methods to classify various NTMs have also been published over the years[4]. During the last 30 years, vast information about these markers has become available. Depending on individual preferences, experience and convenience, different strategies to identify and subclassify the NTMs have been described. It would be necessary to determine the usefulness of various tools and strategies by multicentric studies so that it can be incorporated into clinical practice.

The medical management for NTMs is different than that for TB. For infections due to slow-growing mycobacteria, rifampin, rifabutin, clofazimine, amikacin, linezolid, new-generation macrolides (azithromycin/clarithromycin) and quinolones are recommended, whereas tetracyclines (doxycycline and minocycline), sulphonamides, cephalosporins and macrolides such as azithromycin/clarithromycin are commonly used to treat infections due to rapidly growing mycobacteria[2,4]. While there is negligible experience about drug susceptibility profiles from India, a large number of publications from other countries show that NTMs generally tend to have higher minimum inhibitory concentrations[4,7]. It is because most of the antimycobacterial drugs are from organisms present in the soil and water where NTMs may be naturally exposed to them; thus, many of these tend to be commonly resistant to drugs/doses used to treat TB[4,7]. Guidance is available from documents from well-accepted international committees about suitable methods for drug susceptibility testing (DST) for NTMs/MOTT[8]. However, research on the adaptation of these approaches will be important.

Routine DST for NTMs is not required[2,4]. For *M. avium* complex isolates, DST is recommended for clarithromycin only. Further, routine DST of *M. kansasii* is recommended for rifampicin only. In the case of rapidly growing mycobacteria (*M. fortuitum, M. chelonae* and *M. abscessus*), susceptibility profiles and levels of susceptibility are considered relevant for clarithromycin, cefoxitin, doxycycline, fluorinated quinolones, amikacin, sulphonamide or trimethoprim-sulphamethoxazole and linezolid. DST for imipenem is recommended for *M. fortuitum* only. In case of tobramycin, DST is considered necessary for *M. chelonae* only[2,4]. These recommendations are based on experience outside India. We need to generate sufficient data from different parts of India; only then, some definitive conclusions can be drawn about what is applicable to NTM strains/isolates from India.

Several gaps have been identified which need to be filled before developing robust strategies for diagnosing the NTM disease in time and treating the same effectively. In-depth epidemiological studies

are also essential for understanding the magnitude of these infections, risk factors including environmental exposures, clinical profiles in the context of locally relevant differential diagnosis, diagnostic algorithms and cost-effective diagnostic and treatment methods. Adequate knowledge about risk factors in different settings will impact the preventive approaches. After understanding the incremental value of different diagnostic and treatment methods, appropriate strategies for low-resource settings, institutions with moderate infrastructure and expertise as well as referral institutions/laboratories can be recommended[4]. It will be justified to conclude that there are no shortcuts in moving towards providing effective management and preventive services other than generating relevant information about clinical and epidemiological aspects as well as optimum techniques. Various national agencies are supporting research on these aspects, so we can have genuine expectation of developing evidence-based guidelines and strategies to combat infections due to NTMs in India in the coming future.

***Conflicts of Interest*:** None.

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