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Public Health Significance of Non-Tuberculous Mycobacterial Infections

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Introduction

Mycobacteria are extremely diverse species of bacteria that cause disease both in animals and humans. According to medical classification, mycobacteria are divided into two categories, namely, *Mycobacterium tuberculosis* complex (MTBC) and non-tuberculous mycobacteria (NTM). MTBC causes tuberculosis (TB) in animals and humans, whereas NTM species are also responsible for infections in humans and animals as well. It is well recognised that NTM are ubiquitous free-living microbes that are abundant in soil, natural water sources, and domestic water. NTM can afflict immunocompromised individuals and people who already have lung disorders; HIV patients are most susceptible to this infection. Humans typically acquire NTM infections from aerosols in contaminated environments; on the other hand, human-to-human transmission is uncommon. However, the precise route of transmission is understudied. There are four major clinical syndromes associated with NTM-related infections, such as chronic pulmonary infection, cutaneous disease, lymphadenitis, and disseminated disease, and among them, chronic pulmonary disease is more prevalent. The majority of lung infections among the NTM species are caused by *Mycobacterium avium* complex (MAC), *Mycobacterium kansasii*, and *Mycobacterium abscessus*. In most cases, NTM are misdiagnosed as pulmonary TB because they are not identified up to the species level. Furthermore, NTM are naturally resistant to anti-tuberculosis drugs, thus may lead to prolonged treatment and patient recovery. Several studies showed an increase in the prevalence of NTM cases, which often exceeds the worldwide incidence of new TB infections.

Microbiology:

NTM are aerobic, acid-fast, non-motile and non-spore forming bacteria. Most of the NTM are able to make biofilms, which confers resistance to disinfectants and anti-microbial resistance. The family of NTM consists of almost 200 species and not all species are pathogenic. According to traditional Runyon classification NTM is divided into two broad categories based on their growth rate and colony morphology: rapid-growing NTM and slow-growing NTM. Slow growers are further separated into three types: Type I termed photochromogens (e.g. *M. kansasii*), as they produce pigment in the presence of light, Type II termed Scotochromogens (e.g. *M. gordonae*) produce pigment in the dark and Type III NTM known as non-photochromogens (e.g. *M. avium* complex), they are non-pigmented in nature. Type IV (e.g. *M. abscessus*) is rapid growing NTM that produces mature colonies on media within 7 days. Nowadays this classification is less relevant due to advancements in culturing and molecular techniques.

Prevalence:

For proper disease management, the prevalence of disease plays a significant role. The defined prevalence of NTM is challenging to estimate because, in most countries, there are no proper guidelines for NTM infections. Moreover, countries with high rates of TB burden misdiagnose NTM infections as TB due to a lack of awareness and resources, which leads to underestimation of NTM infections. Studies conducted in India reported that the prevalence of NTM ranges from 0.5% to 8.6%. In the UK, NTM lung infection prevalence increases from 4 cases/100,000 to 6.1/100,000 person and similarly in the USA it increases from 5.2 - 7.5% between the year 2008 and 2015. These data show that the prevalence of NTM is rising. This could be due to advancements in detection methods. Therefore, further investigation is required to determine the precise NTM prevalence.

Symptoms:

The signs and symptoms of NTM diseases are highly variable and insidious. Cough with hemoptysis, dyspnea, fever, weight loss, fatigue, and lymphadenitis are frequent symptoms of chronic pulmonary disease. Lymphadenitis is characterised by lymph enlargement, painless swelling, and rarely fluctuant swelling with pus formation. Disseminated disease is commonly found in HIV-positive patients with night sweats, diarrhoea, fever, weight loss as frequently reported symptoms and in cutaneous disease skin lesions are the common symptom.

Diagnosis:

Since mycobacteria are slow-growing bacteria, it requires more time to effectively diagnose the NTM up to the species level. Furthermore, it could be misidentified as other acid-fast bacilli. The

diagnosis of pulmonary NTM disease is based on clinical, radiological, and microbiologic criteria, according to recommendations issued by the American Thoracic Society.

Acid-fast staining is the most common method to screen for the presence of acid-fast bacilli from the clinical samples. However, it cannot differentiate NTM from *Mycobacterium tuberculosis* (*M. tb*). The nucleic acid amplification test (NAA) is widely used for the detection of *M. tb* whereas NTM are negative for the NAA test. Moreover, for rapid identification nucleic acid probes can be used. The U.S. Food and Drug Administration (FDA) has approved acridium ester-labeled DNA probes specific for *M. kansasii,* MAC, and *M. gordonae* and it has been used in several laboratories for NTM diagnosis. The PRA method, PCR-based gene sequencing and the highly species-specific High-performance liquid chromatography approaches are frequently employed for precise NTM identification up to the species level. However, for laboratory confirmation of NTM infection, culture remains the gold standard.

Treatment:

Before initiating the treatment, the prospective risks of a prolonged course of medication for the patient should be taken into consideration, along with their age and disease type. Once the decision has been made, the prescribed course of therapy must adhere to the established guidelines and evaluate the drugs toxicity at regular intervals of time. The recent antibiotic therapies that are effective against the majority of NTM species are liposomal amikacin for inhalation, linezolid, and tigecyline in combination with clarithromycin, clofazimine, and bedaquiline. Moreover, the treatments approaches are employed based on the NTM isolated and usually require a combination of drugs for a period of 6 months to one year or even longer.

Control:

To overcome NTM infections effective actions should be taken such as

a) Avoid the exposure of surgical wounds, catheters and endoscopes with tap water.
b) Do not use tap or ice water in the operating room, especially during surgery.
c) As benzalkonium chloride promotes the growth of mycobacteria like *M. abscessus*, it should not be used as a skin disinfectant.
d) Avoid using unfiltered tap water in humidifiers.
e) Ascertain that indoor pools are cleaned properly and regular replacement of shower heads.
f) Proper surveillance for NTM infections and adequate funding.

Conclusion:

The prevalence of NTM infection is increasing worldwide both in immunocompromised and immunocompetent individuals. NTM disease poses a global health concern due to a lack of knowledge about immune susceptibility to the infection, difficult diagnostic procedures, expensive treatments and multi-drug therapy regimens. These microbes can cause a wide range of clinical infections from minor cutaneous infections to potentially fatal diseases that may have no effective treatment. Hence, a deeper comprehension of the disease pathogenesis and the discovery of novel therapeutic targets are required. More effective and less toxic new combinations of therapy or novel drugs like ketolides, and peptide deformylase should be considered in the quest for future therapeutics.

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