

Conference Paper

The Increase of *nontuberculous mycobacteria* Infection: Emphasis on Epidemiology, Risk Factors and Diagnostic Tools

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Abstract

Nontuberculous mycobacterium (NTM) is the species of mycobacteria other than *Mycobacterium tuberculosis*. In recent years, there is a significant increase in infection due to NTM species and disease caused by NTM infection increasingly becomes a health problem in countries with high prevalence or with a low prevalence of tuberculosis. NTM can cause various disease manifestations, but mainly it causes chronic pulmonary infections. Despite the rise of NTM infection, there is still limited information about NTM. This paper aims to elucidate the epidemiology of NTM, the risk factors of NTM infection, and the diagnostic methods used for the detection of NTM. Factors that have been identified for NTM infection including age, the presence of pulmonary diseases, immune-compromised conditions, and frequent exposure to NTM from the environment. Various techniques have been used to identify NTM from samples. The development of diagnostic tools such as the used of the mass-spectrometry assay and molecular techniques have enabled the detection of NTM worldwide and enable to identify into species level. However, in developing countries diagnosis of NTM is still challenging because of the limited diagnostic tools. In high prevalence tuberculosis countries, there is a growing concern that NTM has been diagnosed as tuberculosis. In addition, the possibility of co-infection of MTB and NTM in tuberculosis patients has also not been properly examined. These factors lead to misdiagnosis and inappropriate treatment for NTM infection. The knowledge about the species distribution of NTM, the risk factors, and the diagnostic methods is important to prevent the infection and provide accurate treatment of NTM infection.

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1. Introduction

Nontuberculous mycobacteria (NTM) can cause opportunistic infections with various clinical manifestations but mostly it caused chronic pulmonary infection [1]. Recently, there is an increase of NTM infection in many countries and it has been reported that

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infection by NTM is becoming a public health problem worldwide that burden the health care system [2, 3].

NTM infection is one of the neglected infectious diseases, especially in a high-burden country of tuberculosis. Since the past few years, there is a significant increase of multidrug resistant (MDR) tuberculosis globally. Besides the effort to treat and to prevent the spread of MDR tuberculosis, there is also a growing concern that some of the MDR tuberculosis patients are may be infected with NTM. The development of the diagnostic method for NTM diagnosis showed that NTM infections might be misdiagnosed as tuberculosis [4]. The clinical manifestations of NTM infection are varied, so to establish the diagnosis of NTM infection based on clinical manifestations only is difficult. Therefore, clinical and microbiologic criteria are needed for the diagnosis of disease caused by NTM [1]. The diagnosis of NTM lung disease is established if the suspected patient meets all clinical and microbiologic criteria. In addition, the drugs for NTM treatment are species-specific, so the identification of NTM into species level is crucial for the success of the treatment. The development of new techniques, such as molecular-based methods leads to the identification of NTM at a species level and the characterization of new species. The identification of NTM at a species level will increase the success of the treatment of NTM infection [1]. However, despite the increase of NTM infection, there is limited information about the risk factors of NTM infection. Identification the risk factors are important to prevent the infection and the morbidity rate of NTM infection.

This review paper will discuss the increase of NTM infection, with emphasis on the epidemiology of NTM, risk factors of NTM infection, and the diagnostic method for the detection of NTM.

2. Methods

Article search was conducted through the following databases PubMed, Springer Link, and Google Scholar. The keywords used for searching articles were nontuberculous, mycobacteria, diagnostic, and risk factor. Articles were selected based on title and abstract.

3. Discussions

3.1. Epidemiology of Nontuberculous mycobacteria

NTM are ubiquitous in nature, and this bacterium can be found in the soil and aquatic environment [5]. It has been reported that NTM can be isolated from various equipment and environment such as drinking water pipelines, water tanks, hospital faucets and ice machines, diagnostic laboratories, bottled and municipal water, commercial and hospital ice, potting soil, house dust, water damaged building materials, showerheads, shower aerosols, hot-tub aerosols, livestock, and seawater [6]. NTM generally is not infectious pathogen for most individuals; however, this bacterium can cause opportunistic infection and causes diseases in an individual with immunosuppressive conditions or in individuals who have underlying lung diseases [7].

There are more than 150 species of NTM that has been identified worldwide. The distribution of NTM species shows that this group is specific geographically. The geographic diversity of NTM species has been reported previously. *Mycobacterium avium* complex (MAC), *M. abscessus* complex (MABC), and *M. kansasii* are species of NTM frequently found and are the important etiologic organisms of NTM diseases [8]. Generally, in various areas, MAC species is the most common NTM found [9] followed by *M. gordonae*, *M. xenopi*, and *M. kansasii*. In addition, MABC and *M. fortuitum* are the most species identified worldwide [8]. It is reported that *M. avium* and *M. intracellulare* (MAC group) are the most frequent species that cause NTM lung diseases [10].

The distribution of NTM is varied, every region or country shows a different pattern of NTM species [8]. It has been reported that in Brazil, NTM species that frequently as the cause of lung disease are *Mycobacterium kansasii* and *Mycobacterium avium* [4, 11, 12]. On the other hand, in the United States the most frequent species causing NTM diseases are *Mycobacterium kansasii* and *Mycobacterium marinum* [2]. Other species commonly cause infection in other geographic areas are *Mycobacterium malmoense*, *Mycobacterium xenopi*, *Mycobacterium scrofulaceum*, and *Mycobacterium ulcerans* [2]. The difference of bacterial species among regions and the difference in the prevalence of infection may be caused by various factors including the environmental, host immune response, and behavioral factors.

NTM infection is one of the emerging diseases that cause a health problem in various countries. The increase of the incidence and prevalence of NTM infection has been reported in many countries, including the United States, Canada, and the United Kingdom, Japan and Taiwan [8]. NTM are mostly associated with pulmonary infections [13]. NTM infection can manifest in a various condition such as pulmonary infection, disseminated infection, skin disease, and lymphadenitis [7]. The clinical manifestations of lung

diseases caused by NTM may be indistinguishable from those of tuberculosis [10]. It has been reported that the failure to recognize NTM infection leads to misdiagnosis to tuberculosis since tuberculosis is usually endemic and patients are presumptively treated for tuberculosis [4]. A study in Zambia showed that of the individuals with presumptive tuberculosis infection, 15.1% were found to have NTM and 0.2% was tuberculosis and NTM co-infected [14]. It is reported that 18% of chronic TB cases has NTM infection and all of these patients were diagnosed as MDR TB and receiving MDR regimen or were the candidates for MDR-TB treatment [4].

Since the treatment of NTM infection is species specific, treatment of patients with NTM pulmonary disease is individualized since the treatment is dependent on the species of mycobacteria isolated. In addition, the individualized treatment also depends on where the infection occurred, the severity of the diseases, the antimicrobial resistant strains, and the underlying diseases [10]. Therefore, the diagnosis of NTM infection is very important not only for effective treatment but also to avoid the high cost of treatment which causes the treatment ineffective and increase bacterial resistance [15].

Even though NTM has been known can cause disease with manifestation similar to TB infection or other diseases, there is very limited information about the role of NTM in countries with high prevalence of tuberculosis infection rate [4]. This is mainly due to the lack of diagnostic facilities to identify the mycobacteria. The knowledge about the species that is present and cause infection in certain geographic areas is important, therefore accurate identification of NTM species is required.

3.2. Risk factors for Nontuberculous mycobacteria infection

Patient commonly gets NTM infections from the environment. The infection can be required from ingestion, inhalation, and dermal contact; this infection can manifest as lymphadenitis, pulmonary disease, skin infection, and soft tissue infection [16]. Unlike infection by *M. tuberculosis*, infection by NTM is not transmitted by person-to-person; it is presumed that most people get NTM infection from the environment [10]. In NTM respiratory diseases, the infection may be acquired from airborne NTM, whereas in children with cervical lymphadenitis NTM and in majority HIV-infected patients the infection mostly from NTM ingestion [10]. In addition, it has also been reported that soft tissue infection by NTM is acquired from the direct inoculation of NTM species from water [10].

NTM disease is one of the important agents causing disease in an immunocompromised individual, included patients infected with human immunodeficiency virus, malignancy, and patient with autoimmune disease [10]. In addition, genetic factors, immune disorder, and lung disease, environmental factors (such as humidity and altitude) may contribute to the development of NTM infection [8, 10]. It has been reported that the increasing prevalence of NTM pulmonary disease is as the results of the increasing of immunocompetent patients with or without pre-existing pulmonary disease [10]. It has also been shown that extrapulmonary NTM infection was found in rheumatoid arthritis patients. In addition, most of the NTM strains associated with extrapulmonary infection were isolated from skin or pus [17].

Disseminated disease due to NTM is primarily found in acute immunodeficiency syndrome (AIDS) and other conditions with severe immunosuppression [12]. Bronchiectasis was common among patients with pulmonary isolation of any NTM [18]. NTM also has been reported as the cause of iatrogenic infection in skin and soft tissue [19]. In addition, NTM is increasingly found to cause skin and soft tissue infections, such as in patients post underwent surgery [20, 21]. It has also been reported that the increase of medical tourism among US citizens has led to the increase of NTM infections from cosmetic surgery performed in other countries [22]. Multi-drug resistant *Mycobacterium abscessus complex* has become a concern as the cause of infection in Cystic Fibrosis [23].

3.3. Diagnostic tools for the detection of Nontuberculous mycobacteria

NTM infection showed various clinical manifestations and difficult to be differentiated with tuberculosis infection or other pulmonary infection. Therefore diagnostic method to identify NTM infection is very crucial to establish the diagnosis of NTM. The treatment for NTM infection specifically depends on the species, therefore, species-level identification of NTM is recommended [8, 24]. In developing countries, there is a limited method available for the detection of NTM; the conventional methods such as smear microscopy are cheap and simple for rapid detection of mycobacteria [8]. Two types of smear microscopic staining for Acid Fast Bacilli (AFB) detection that are commonly used are carbol fuchsin stain (such as Ziehl-Neelsen or Kinyoun staining) and the fluorochrome staining (using auramine O alone or in combination with rhodamine B) [8]. However, these techniques cannot see the differences between NTM and *M. tuberculosis* [8].

To diagnose NTM lung diseases, there are two types of cultures, liquid and solid media cultures that are recommended to increase the growth detection of NTM [8, 10]. Definitive diagnosis of NTM lung diseases requires the growth culture identification, even though *Mycobacterium* needs several weeks to grow in culture medium. In addition, it is suggested that the presence of NTM in a single sputum sample is not proof of NTM infection, especially when the AFB smear is negative and NTMs are cultured in small numbers [10], because of the possibility of contamination. However, until now, mycobacterium culture is still as the gold standard for laboratory confirmation of NTM; in addition, genotypic typing and drug susceptibility tests are required [10].

Various new technologies have greatly improved particularly in detection, identification, bacterial strain typing, and drug susceptibility testing of NTM [25]. For example, multiplex PCR has been used to identify the cause of tuberculosis infection and to identify NTM strain [11]. This PCR method can also identify new species which previously cannot be characterized by conventional biochemical and phenotypic techniques [11]. Species of NTM can be identified using PCR by examining the specific sequence such as hsp65 sequence and 16S rRNA [26]. Recently, a new method that is matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) can be used to identify NTM to species level. This technique can perform an accurate, rapid, cost-effective, and simple to identify species of NTM [27]. However, despite the advantages of this method, it is reported that this test is not as fast as to identify other bacteria. To identify NTM, it needs more time than to identify other bacterial strains [28].

4. Conclusion

NTM infection is increasing and becoming a major health problem worldwide. Recognising and minimising the risk factors for NTM infection can prevent and reduce the morbidity of NTM infection. Since the clinical manifestations of NTM infection are not specific and differ between species that infect the human, diagnostic tools to identify NTM species are crucial to establish a definite diagnosis and to determine the appropriate treatment. The knowledge about the species distribution of NTM, the risk factors, and the diagnostic methods is important to prevent the infection and provide accurate treatment of NTM infection.

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