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Determination of the Diagnosis of Non-Tuberculous Mycobacterial Infections by Metagenomic Next-Generation Sequencing

He Zhu and Limin Zhao*

Department of Respiratory and Critical Care Medicine, Henan Provincial People's Hospital, Zhengzhou, China

***Corresponding author:** Dr. Limin Zhao, Respiratory and Critical Care Medicine, Henan Provincial People's Hospital, Zhengzhou, China, E-mail: zlm9898@126.com

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Abstract

Non-Tuberculous *Mycobacteria* (NTM) is ubiquitousin the environment and is conditional pathogen. Due to NTM and *Mycobacterium tuberculosis* belong to the genus *Mycobacterium*, their pathogenic mechanisms and clinical manifestations are similar. Therefore, NTM can cause tuberculosis-like lesions and lead to misdiagnosis. Early diagnosis and treatment greatly improve prognosis. However, traditional pathogenic microorganism detection has limitations, and it is difficult to accurately identify strains in clinical practice. In this editorial, We summarize the diagnosis and treatment of NTM, and the unique advantages of metagenomic next-generation sequencing in the identification of pathogenic microorganisms.

Keywords: Non-Tuberculous *Mycobacteria*; Metagenomic next-generation sequencing; Diagnosis

Editorial Note

Non-Tuberculous *Mycobacteria* (NTM) refers to a general term for a large group of *mycobacteria* other than *Mycobacterium tuberculosis* complex (Including tuberculosis, cattle in Africa, vole, goat, *Mycobacterium pinnipedii*, *Mycobacterium suricattae* and *Mycobacterium mungi*) and *Mycobacterium leprae*. According to statistics, more than 190 species of NTM strains and 14 subspecies have been discovered so far, of which only a few are pathogenic to humans and belong to conditional pathogens [1,2]. Among pathogenic bacteria, the *Mycobacterium avium* complex (*M. avium* Complex, MAC) is the *mycobacterium* with the most new species or subspecies [3]. NTM disease means that the human body is infected with NTM and causes the disease of related tissues and organs, most commonly in the lungs. The epidemiological study of NTM disease is difficult, and the exact information and data in different countries or regions are difficult to obtain, because the reporting of NTM disease is not mandatory in most countries, and it is also difficult to identify NTM infection and incidence. The incidence and prevalence of infection vary significantly. However, from the existing data, the incidence and prevalence of NTM disease are increasing in some countries and regions, and even exceed the incidence and prevalence of tuberculosis [4-7].

In recent years, as the infection rate of NTM has increased year by year, NTM Pulmonary Disease (NTM-PD) has become a common clinical disease, accounting for about 70%-80% in the United States, while China currently has no specific information data in this area [5,8]. Because the clinical characteristics of the disease are similar to those of tuberculosis, it often leads to misdiagnosis and missed diagnosis, which delays treatment and seriously threatens human life and health.

NTM-PD often occurs in patients with original underlying diseases, especially chronic respiratory diseases, such as chronic obstructive pulmonary disease, bronchiectasis, and cystic pulmonary fibrosis. Due to the weakened autoimmune function, NTM infection cannot be effectively controlled, and eventually it progresses to NTM-PD [9,10]. The main clinical symptoms of NTM-PD are fever, cough and sputum. Due to the atypical clinical manifestations, it often needs to be differentiated from other diseases of the respiratory system. In the case of sterile species identification results, it can be misdiagnosed as Mycobacterium tuberculosis infection for a long time. In this review, we will review the diagnosis and treatment of nontuberculous mycobacteriosis, with particular emphasis on the unique advantages of mNGS in the identification of pathogenic microorganisms.

Diagnosis of Non-Tuberculous Mycobacteriosis

Respiratory symptoms and systemic symptoms, cavitary shadows, multifocal bronchiectasis, and multiple small nodular lesions were found by chest imaging examination, and others have been excluded Pulmonary disease, on the premise of ensuring that the specimen is free of exogenous contamination, one of the following conditions can be diagnosed as NTM lung disease: (a) 2 sputum specimens submitted separately for NTM culture were positive and identified as the same pathogen, and (or) NTM molecular biology test is the same pathogen; (b) NTM culture and (or) molecular biology test in bronchial lavage fluid or bronchoalveolar lavage fluid is positive once; (c) pulmonary by bronchoscopy or other means Biopsy found histopathologically characteristic changes of mycobacterial disease (granulomatous inflammation or positive acid-fast staining), and positive NTM culture and/or molecular biological tests; (d) pulmonary biopsy by bronchoscopy or other means Histopathologically characteristic changes of mycobacterial disease (granulomatous inflammation or positive acid-fast staining) were found on histological examination, and NTM culture and NTM in 1 or more sputum specimens, bronchoalveolar lavage fluid or bronchoalveolar lavage fluid molecular biology test was positive.

With local or systemic symptoms, extrapulmonary tissue and organ lesions have been found by relevant examinations, other diseases have been excluded, and under the premise of ensuring that the specimen is free from exogenous contamination, NTM culture and (or) positive molecular biology test can be diagnosed as extrapulmonary NTM disease.

The last type is disseminated NTM disease, with relevant clinical symptoms, lung or extrapulmonary tissue and organ lesions found by relevant examinations, positive blood NTM culture and/or molecular biological tests, and/or bone marrow, liver , thoracic or intra-abdominal lymph node aspirate was positive for NTM culture and (or) molecular biological testing.

It should be emphasized that, regardless of NTM lung disease, extrapulmonary NTM disease or disseminated NTM disease, NTM strain identification and drug susceptibility testing are required. In the case of sterile species identification results, NTM disease can be misdiagnosed for a long time, and the clinic should be highly vigilant [1,2,11,12].

Treatment of Non-Tuberculous Mycobacteriosis

Since most NTM diseases are resistant to commonly used anti-mycobacterial drugs, considering the uncertain clinical effect of their clinical treatment and the cost of treatment and adverse drug reactions, clinicians should weigh the pros and cons and make comprehensive judgments when deciding whether to treat. The following principles are recommended for the treatment of NTM disease [2,11-14].

First, confirmed NTM disease requires anti-mycobacterial therapy, especially NTM lung disease with positive acid-fast sputum and/or radiographic cavitation. Because the resistance pattern of NTM varies from strain to strain, mycobacterial strain identification and drug susceptibility test results before treatment are important. Although the correlation between susceptibility test results and clinical efficacy remains difficult to establish, for established correlations such as macrolide and amikacin resistance and efficacy in MAC disease and *Mycobacterium abscessus* disease, Drug selection should be based on susceptibility testing results of these drugs in the formulation of chemotherapy regimens for NTM disease. Second, the types and duration of medication for different NTM diseases are different. Experimental treatment of suspected NTM disease is not recommended. Surgery should be used with caution in patients with NTM lung disease. Finally, it is necessary to actively carry out drug safety monitoring and management of all patients included in the treatment of NTM diseases, and timely detect and deal with adverse reactions of anti-NTM drugs.

Metagenomic next generation sequencing technology

It is the highest resolution means of species identification and can also be used to track the spread of NTM in specific populations. With the increasing popularity and cost reduction of mNGS technology, it will play an increasingly important role in the diagnosis of NTM disease [15-17]. The mNGS based on next-generation sequencing technology does not rely on traditional microbial culture, does not require specific primers, and can measure all DNA/RNA genomic information in a sample in a single run, realizing the identification and typing of all pathogens. It has shown great advantages in the diagnosis and treatment of complex and mixed infectious diseases. In recent years, mNGS has been used more and more in the diagnosis of tuberculosis. In 2019, a prospective study conducted by Zhou et al. to evaluate the diagnostic performance of mNGS in the direct detection of MTBC in clinical specimens cultured direct clinical specimens such as sputum, cerebrospinal fluid, pus, etc [18]. X-pert test and mNGS were performed, among which 45 patients were clinically diagnosed with active tuberculosis (13 pulmonary tuberculosis and 32 extrapulmonary tuberculosis); the sensitivity and specificity of mNGS in diagnosing active tuberculosis was 44% and 98%, which was consistent with The sensitivity of X-pert detection (42%) is similar, much higher than that of conventional smear culture method (29%); It shows that mNGS technology can rapidly detect MTBC in various specimens with high sensitivity and specificity, and can be used for early auxiliary diagnosis of active tuberculosis.

Conclusion

mNGS is a new type of pathogenic diagnosis technology, which has shown great potential in the identification of pathogenic pathogens of infectious diseases due to its advantages of high throughput, wide coverage, fast speed, high sensitivity, independent of traditional isolation and culture, and no need for specific primers, and has the highest resolution of strain identification. With the increasing popularity and cost reduction of mNGS, it will play an increasingly important role in the diagnosis of NTM diseases. Finding and curing the source of infection in time and reducing contact with patients with NTM are the best measures to prevent NTM infection. Therefore, it is recommended to use mNGS to help clinicians improve the accuracy of identifying Mycobacterium tuberculosis and NTM.

Author Contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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