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Highlights

Time to be familiar with nontuberculous mycobacterial lung disease - An emerging disease with diverse clinical outcomes



It has been more than two decades since the first description of nontuberculous mycobacteria (NTM) clinical significance and NTM-lung disease (NTM-LD) in literature in Taiwan.¹ Over the past two decades, there has been explosive awareness of NTM, which are often neglected as clinically insignificant pathogens. Among various NTM diseases in human, NTM-LD is the most common disease entity.² Left untreated, NTM-LD, however, could lead insidious deteriorating clinical course and cause lung destruction as well as function decline.³ Meanwhile, we have experienced a decreasing incidence of pulmonary tuberculosis (TB) owing to the joint efforts of physicians and public health system.⁴ At the same time, we have also witnessed an increasing incidence of pulmonary NTM, both globally and in Taiwan.⁵ Along with the increase in number of subjects with structural lung changes due to improved care of bronchiectasis and pulmonary TB patients, NTM-LD has therefore become more and more important in Taiwan.

In view of growing importance of NTM-LD, the President of Taiwan Society of Pulmonary and Critical Care Medicine, Professor Meng-Chih Lin, has launched an NTM workgroup of panel experts and collaborated with the Taiwan Society of Tuberculosis and Lung Diseases, led by President Yi-Wen Huang. Professor Jann-Yuan Wang was later responsible for organizing this NTM work group. Besides educational seminars, this NTM workgroup wrote a series of review articles which will be published in this special issue of Journal of the Formosan Medical Association (JFMA).

This special issue includes nine articles and starts with article reviewing NTM-LD epidemiology in Taiwan.⁶ Local epidemiologic data are of great importance for primary care physicians and public health policy makers. This article summarized clinical evidence that NTM-LD is an emerging disease with rising incidence in Taiwan. Geographically, *Mycobacterium avium* complex (MAC) is the dominant species in northern Taiwan while *Mycobacterium abscessus* complex and MAC may be equally prevalent in

southern Taiwan. Also, the isolation of NTM from respiratory samples is not uncommon across different patient populations and this merit special attention.

Identifying vulnerable hosts is undoubtedly of great importance when we turned from epidemiologic data to individual patients. Unveiling the underlying immunological mechanisms then becomes the first step. The next article reviewed host factors associated with NTM-LD development.⁷ While we may be more familiar with susceptible phenotypes such as ciliary defect, structural lung abnormalities, slender body figure, and postmenopausal female, the importance of decreased host immunity to NTM especially T helper 1 cell responses should not be overlooked. In this area, much uncertainty remains and researchers from Taiwan and worldwide have work hard to elucidate the immunologic defects contributing to NTM-LD.

One major obstacle to diagnosing NTM-LD may be that isolation of NTM does not equal to clinical diagnosis. While NTM could also be mere colonizers, clinical relevance of NTM in patients with isolation of NTM from respiratory samples is always not straightforward in clinical settings. Diagnosing NTM-LD then requires criteria to be fulfilled, which relies largely on the knowledge and clinical awareness of physicians. This article by Feng et al. then summarizes current evidence and literature regarding clinical relevance and diagnosis of NTM-LD.⁸ Knowledge regarding clinical criteria is fundamental to patient management and would empower clinicians to identify NTM-LD patients.

Perhaps the most distinguished advancement in the NTM field over the past decade was the improvement in identifying NTM species and subspecies. As the number of NTM species increased along with improvement of phylogenetic classification methods, identification of NTM species became crucial and challenging for mycobacteriology laboratories. After identification, drug susceptibility results became informative for physicians in guiding therapy. Once considered very difficult to perform and unreliable in

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predicting treatment response, drug susceptibility test results for NTM are now encouraged and considered helpful. Huang et al. summarizes methods for identifying NTM species, including biochemical, molecular techniques and mass spectrometry, as well as susceptibility testing in this article.⁹

Before we came to medical treatment for NTM species, we should not forget and neglect non-pharmacologic treatment. Lan et al. reviewed two important components of non-pharmacologic therapy for NTM-LD, namely pulmonary rehabilitation and nutrition support.¹⁰ For pulmonary rehabilitation, the authors reviewed clinical practice and techniques from bronchiectasis patients including airway clearance techniques, exercise training and inspiratory muscle training. For nutrition support, the authors provided detailed guide for nutrition strategy for NTM-LD patients and suggested that an adequate protein and calorie diet with antioxidant nutrients may be the preferred approach.

Mycobacterium kansasii, while may not be the most prevalent, is probably one of the most virulent strain of NTM. Huang et al. summarizes treatment strategy and clinical outcome of *M. kansasii* NTM-LD.¹¹ This article pointed out several unresolved research questions for *M. kansasii* NTM-LD, including optimal treatment duration, effectiveness of recommended treatment regimens and emerging clarithromycin resistance. These research questions are frequently encountered by readers in treating *M. kansasii* NTM-LD and readers will certainly benefit a lot from reading this article.

M. abscessus complex is notorious for its multi-drug resistance and is probably the most difficult one to treat among all NTM species. Given its high prevalence in Taiwan, physicians are not unfamiliar with *M. abscessus* complex NTM-LD in clinical setting. This article by Weng et al. reviews important novel antibiotics which shows potential for *M. abscessus* complex NTM-LD.¹² Treatment regimens have substantially changed due to the introduction of new antibiotics, including clofazimine, linezolid and tigecycline. Furthermore, subspecies identification of *M. abscessus* complex has become important in providing prognostic guidance.

MAC is undoubtedly the most prevalent NTM species for NTM-LD worldwide. In the article by Pan et al., authors highlighted the importance of selecting patients who warrant initiating anti-MAC therapy.¹³ Disease severity and progression are major factors that determine the necessity of anti-MAC therapy. While randomized controlled trials may be lacking, adherence to regimens suggested by clinical guidelines is crucial to achieve favorable clinical outcome and avoiding development of macrolide resistance.

While most physicians handling NTM-LD will encounter conditions that pharmacologic treatment response is sub-optimal, surgical management is an important component of NTM-LD treatment. Guidelines have also emphasized the role of combining surgery for intractable diseases with resectable lesions. Surgical intervention requires multi-disciplinary cooperation, with surgeons being the core members. Tseng et al. extensively reviewed pre-operative assessment, operation indication, surgical approach, post-operative outcomes and prognostic factors.¹⁴ While many physicians caring NTM-LD patients may not be experienced

in referring patients for operation, this article is an important one which fills the knowledge gap and could have great impact on patient care.

While these review articles are intended for all readers of JFMA, authors of the articles have avoided jargon and used plain language in writing manuscripts, making them easy to read by physicians from all specialties. Though this series of NTM-LD articles are not intended to be clinical guidelines for physicians to follow, I believe that physicians who could possibly encounter NTM-LD in clinical practice will benefit a lot from reading this series of review articles.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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References

1. Shih JY, Hsueh PR, Lee LN, Wang HC, Yang PC, Kuo SH, et al. Nontuberculous mycobacteria isolates: clinical significance and disease spectrum. *J Formos Med Assoc* 1997;**96**:621–7.
2. Griffith DE, Aksmit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;**175**:367–416.
3. Haworth CS, Banks J, Capstick T, Fische AJ, Gorsuch T, Laurenson IF, et al. British Thoracic Society guidelines for the management of non-tuberculous mycobacterial pulmonary disease (NTM-PD). *Thorax* 2017;**72**:ii1–64.
4. Chan PC, Chen CH, Chang FY. External review of the National Tuberculosis Program and the development of strategy and targets post 2015 in Taiwan. *J Formos Med Assoc* 2014;**113**:775–7.
5. Chien JY, Lai CC, Sheng WH, Yu CJ, Hsueh PR. Pulmonary infection and colonization with nontuberculous mycobacteria, Taiwan. *Emerg Infect Dis* 2014;**20**:1382–5. 2000–2012.
6. Lee MR, Chang LY, Ko JC, Wang HC, Huang YW. Nontuberculous mycobacterial lung disease epidemiology in Taiwan: a systematic review. *J Formos Med Assoc* 2020;**119**:S4–12.
7. Shu CC, Wu MF, Pan SW, Wu TS, Lai HC, Lin MC. Host immune response against environmental nontuberculous mycobacteria and the risk populations of nontuberculous mycobacterial lung disease. *J Formos Med Assoc* 2020;**119**:S13–22.
8. Feng JY, Chen WC, Chen YY, Su WJ. Clinical relevance and diagnosis of nontuberculous mycobacterial pulmonary disease in populations at risk. *J Formos Med Assoc* 2020;**119**:S23–31.
9. Huang WC, Yu MC, Huang YW. Identification and drug susceptibility testing for non-tuberculous mycobacteria. *J Formos Med Assoc* 2020;**119**:S32–41.
10. Lan CC, Lai SR, Chien JY. Non-pharmacological treatment for patients with nontuberculous mycobacteria lung disease. *J Formos Med Assoc* 2020;**119**:S42–50.
11. Huang HL, Lu PL, Lee CH, Chong IW. Treatment of the pulmonary disease caused by *Mycobacterium kansasii*. *J Formos Med Assoc* 2020;**119**:S51–7.
12. Weng YW, Huang CK, Sy CL, Wu KS, Tsai HC, Lee SJ. Treatment for *Mycobacterium abscessus* complex lung disease. *J Formos Med Assoc* 2020;**119**:S58–66.

13. Pan SW, Shu CC, Feng JY, Su WJ. Treatment for *Mycobacterium avium* complex lung disease. *J Formos Med Assoc* 2020;119:S67–75.
14. Tseng YT, Pan CT, Yang SM, Yu SP, Huang PM. Recent advances and controversies in surgical intervention of nontuberculous mycobacterial lung disease: a literature review. *J Formos Med Assoc* 2020;119:S76–83.

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