REVIEW

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Respiratory Review of 2014: Tuberculosis and Nontuberculous Mycobacterial Pulmonary Disease

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Since tuberculosis (TB) remains a major global health concern and the incidence of multi-drug resistant (MDR)-TB is increasing globally, new modalities for the detection of TB and drug resistant TB are needed to improve TB control. The Xpert MTB/RIF test can be a valuable new tool for early detection of TB and rifampicin resistance, with a high sensitivity and specificity. Late-generation fluoroquinolones, levofloxacin, and moxifloxacin, which are the principal drugs for the treatment of MDR-TB, show equally high efficacy and safety. Systemic steroids may reduce the overall TB mortality attributable to all forms of TB across all organ systems, although inhaled corticosteroids can increase the risk of TB development. Although fixed dose combinations were expected to reduce the risk of drug resistance and increase drug compliance, a recent meta-analysis found that they might actually increase the risk of relapse and treatment failure. Regarding treatment duration, patients with cavitation and culture positivity at 2 months of TB treatment may require more than 6 months of standard treatment. New anti-TB drugs, such as linezolid, bedaquiline, and delamanid, could improve the outcomes in drug-resistant TB. Nontuberculous mycobacterial lung disease has typical clinical and immunological phenotypes. Mycobacterial genotyping may predict disease progression, and whole genome sequencing may reveal the transmission of *Mycobacterium abscessus*. In refractory *Mycobacterium avium* complex lung disease, a moxifloxacin-containing regimen was expected to improve the treatment outcome.

Keywords: Tuberculosis; Nontuberculous Mycobacteria; Tuberculosis, Multidrug-Resistant; Diagnosis; Antitubercular Agents

Introduction

Tuberculosis (TB) remains a major global health concern, with 8.6 million incident cases and 1.3 million deaths in 2012[1]. The emergence of multidrug resistant-TB (MDR-TB) and extensively drug resistant-TB (XDR-TB) pose a global risk to patients. MDR-TB is widespread, with an estimated 450,000 incident cases and 170,000 deaths, while XDR-TB has been reported in 92 countries during 2012[1]. In Korea, the prevalence of bacteriologically or radiologically active TB (>5 years old) had decreased dramatically from 5,168/100,000 persons in 1965 to 767/100,000 persons in 1995[2]. However, TB remains a current major health concern, since new cases have plateaued at approximately 100/100,000 persons over the past decade[3]. One possible explanation for the steady rate of new TB cases in Korea is that the aging population may have a higher risk

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for TB development[3].

Nontuberculous mycobacteria (NTM) are any mycobacterium other than *Mycobacterium tuberculosis* and *M. leprae*. NTM infection can cause 4 specific clinical manifestations, which are pulmonary disease, lymphadenitis, soft tissue and bone infections, and disseminated disease[4]. Among them, NTM pulmonary disease is the most common, comprising more than 90% of all NTM infections[4]. The incidence of chronic pulmonary disease, caused by NTM in human immunodeficiency virus (HIV)-negative patients, has also been increasing worldwide[5]. In Korea, NTM isolation in clinical specimens has been increasing, and has recently reached 47%–70% of positive mycobacterial cultures. The incidence of NTM lung disease has also increased[6-9].

This review covers important, recent clinical studies, especially those focused on diagnosis and treatment of drug-resistant TB, and the clinical manifestations and treatment for NTM pulmonary disease.

Tuberculosis

1. Xpert MTB/RIF test

Early detection and proper treatment can improve the outcomes of TB treatment, and are crucial for TB control programs. However, mycobacterial culture, which has the highest sensitivity and confirmative tool for diagnosis of active TB, requires 6 to 8 weeks for interpretation[10,11]. Sputum smear microscopy is a rapid, simple, and inexpensive tool for diagnosis of active TB, and is highly specific in endemic areas. Unfortunately, it has low and variable sensitivity ranging between 20 and 60%[12,13].

Happily, recent advances in TB diagnosis have given hope for rapid detection of this disease. The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) (hereafter referred to as Xpert MTB/RIF) is a novel, rapid, automated, and cartridge-based nucleic acid amplification test which can detect TB, along with rifampicin resistance, directly from sputum within 2 hours[14]. The cartridges, named GeneXpert, are pre-loaded with all the necessary reagents for sample processing, DNA extraction, amplification, and laser detection of the amplified *rpo*B gene target[14]. The sensitivity and specificity of this test has been reported to be acceptable for TB detection. In a Cochrane database review of diagnostic accuracy, 27 studies were assessed, and the Xpert MTB/RIF pooled sensitivity was found to be 89% (95% confidence interval [CI], 85%–92%) and pooled specificity 99% (95% CI, 98%–99%)[15]. As an follow-up test for specimens with negative smear microscopy results, Xpert MTB/RIF pooled sensitivity was 67% (95% CI, 60%–74%), and pooled specificity was 99% (95% CI, 98%–99%)[15]. For rifampicin resistance detection, Xpert MTB/RIF showed an excellent pooled sensitivity of 97% (95% CI, 90%–97%), and pooled specificity of 98% (95% CI, 97%–99%)[15].

A major advantage of this test is that it can be accurately administrated by unskilled nurses in primary-care clinics. In an African study of randomly assigned 758 TB patients, 'point-of-care' Xpert MTB/RIF testing administered by nurses had a higher sensitivity, and a similar specificity, compared to microscopy. Point-of care Xpert MTB/RIF test also had similar sensitivity, and higher specificity, compared to laboratory-based Xpert MTB/RIF testing[16].

In a study conducted in South Korea, the Xpert MTB/RIF assay also showed similar results, with sensitivity of 79.5% and specificity of 100.0% in culture among 681 patients with suspected pulmonary TB[17]. Furthermore, the test decreased the median time to treatment, after initial evaluation, to 7 days (interquartile range [IQR], 4–9 days) vs. 21 days (IQR, 7–33.5 days)[17]. Therefore, Xpert MTB/RIF is a useful method for rapid detection of TB cases, as well as rifampin resistance, even in primary-care settings. The Xpert MTB/RIF also shortens the time to initiation of TB treatment.

2. Fluoroquinolones

Fluoroquinolones are the mainstay drugs for treatment of MDR-TB, and their efficacy has been established in many clinical studies[18]. They also have a potential role in reducing treatment duration in drug-susceptible TB[19]. Therefore, MDR-TB patients with additional resistance to fluoroquinolones have a worse prognosis. According to a meta-analysis by Falzon et al.[20], treatment success was lower in MDR-TB patients with resistance to fluoroquinolones alone (48%; 95% CI, 36%–60%) than in MDR-TB patients without additional resistance (64%; 95% CI, 57%–72%) or those with resistance to injectables alone (56%; 95% CI, 45%–66%).

Late-generation fluoroquinolones, such as levofloxacin and moxifloxacin, have been recommended in guidelines for the treatment of MDR-TB[21]. However, the superiority of these drugs for MDR-TB treatment is still unknown. Some experimental and animal studies have shown that moxifloxacin had lower minimal inhibitory concentrations, and higher bactericidal activity, compared to levofloxacin[22,23]. However, high-dose levofloxacin (1,000 mg/day) showed an excellent early bactericidal activity, equivalent to that of moxifloxacin[24]. Recently, the results of a prospective multicenter randomized trial in South Korea were published, in which moxifloxacin and levofloxacin (750 mg/day) were compared in the treatment of MDR-TB[25]. According to this study, there was no difference in sputum cultures conversion (88.3% in levofloxacin group vs. 90.5% in moxifloxacin group, p>0.05) or adverse drug events[25]. Thus, these 2 drugs have been shown to have equivalently high efficacy and safety in the treatment of MDR-TB.

3. Steroids

Oral corticosteroids are well-known immunosuppressants, which can increase the risk of developing TB[26]. However, whether inhaled corticosteroids (ICS) affect TB development remains unclear. Recently, 2 studies were published in South Korea examining this topic. First, a retrospective cohort study examined 616 patients with chronic obstructive pulmonary disease[27]. Of all patients, 20 patients developed TB, and ICS users with suspicious radiologic sequelae (from prior pulmonary TB) in their chest radiographs had the highest risk for pulmonary TB (hazard ratio [HR], 24.95; 95% CI, 3.09–201.37; p=0.003)[27]. Moreover, ICS users with normal chest radiographs also had increased an risk of pulmonary TB (HR, 9.08; 95% CI, 1.01–81.43; p=0.049)[27].

Second, Lee et al.[28] performed a nested case-control study, which included 4,139 matched patients with TB, and 20,583 control subjects among a total of 853,439 adults who had recently used inhaled respiratory medications, based on the database of the Health Insurance Review and Assessment Service (HIRA, Seoul, Korea). In their study, ICS use significantly increased the occurrence of TB (adjusted odds ratio, 1.20; 95% CI, 1.08–1.34), and a dose dependent relationship was also found (p<0.001 for trend)[28].

The effects of systemic steroids on TB have been described in TB meningitis and pericarditis[29,30]. However, it has been unclear whether corticosteroid use can affect the mortality in patients with TB involving other organ. According to a recent meta-analysis of 41 trials, systemic steroids reduced overall mortality by 17% (risk ratio, 0.83; 95% CI, 0.74–0.92) across all organs[31]. However, it is worth noting that most trials took place before the era of the more effective rifampin-containing regimen. Therefore, HIV and MDR-TB infections, and the adverse events associated with corticosteroid treatment, cannot be ignored, and more convincing evidence is required to support the use of steroids to treat all forms of TB.

4. Fixed dose combination

Tablets of fixed-dose combination (FDC) are composed of 2 or more anti-TB drugs, and have been manufactured since the 1980s in order to improve medication compliance[32]. Since FDCs were also expected to reduce the risk of drug-resistant TB, by preventing inappropriate drug selection and monotherapy, the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) recommended the use of these drugs in 1994[33,34]. However, their efficacy is still controversial, due to the decreased bioavailability of rifampicin in FDCs[35]. Recently, a systemic review and meta-analysis was performed to determine whether FDCs are effective in treating TB, and the results showed a trend toward higher risk of treatment failure or relapse with FDC use (pooled relative risk, 1.28; 95% CI, 0.99–1.7)[36]. Given the possible risks, additional studies examining the effectiveness of FDCs are required.

5. Positive culture at 2 months of treatment and cavitation on baseline chest radiography

Although current TB drugs have existed for more than 40 years, and their high efficacy have been demonstrate in many studies, relapse rates for standard 6-month treatment of pulmonary TB were 1%–2% at 24 months after treatment[37]. Unfortunately, there are no defined criteria for prolonging treatment to prevent a relapse of TB. In a recent study, the combination of cavitation on initial chest radiograph, and positive culture after 2 months, was associated with an increased risk of 1-year relapse, and the authors suggested an extension of treatment in these patients[38]. However, this study was a single center retrospective study that included only 6 patients with TB relapse, and there was no proven efficacy of prolonged TB treatment in these patients. Further studies are needed to evaluate the efficacy of extending standard treatments.

Nontuberculous Mycobacterial Infection

1. Phenotypes of nontuberculous mycobacterial infection

NTM lung disease has 2 different radiographical manifestations: fibrocavitary and nodular bronchiectatic forms[4]. Fibrocavitary forms of NTM lung disease have cavitary lesions that typically involve the upper lobes, and have radiographic features similar to pulmonary TB[4]. There are some distinct characteristics of fibrocavitary NTM lung disease compared to pulmonary TB, including thin walled cavities with reduced surrounding parenchymal opacity, less bronchogenic with greater contiguous spread of disease, and a more marked involvement of pleura over the involved areas of the lungs. However, these were not sufficiently specific to NTM lung disease to be of diagnostic use[4].

For patients with nodular bronchiectatic forms, both multifocal bronchiectasis and clusters of small nodules and branching linear structures are present in the mid and lower lung field[4]. In a study examining the frequency of NTM lung disease in 105 patients with bilateral bronchiectasis and bronchiolitis in their chest computed tomography, these characteristics were very specific for NTM lung disease, especially *Mycobacterium avium* complex (MAC) and *M. abscessus* infections. Bronchiolitis in more than 5 lobes with bronchiectasis, lobular consolidation, and cavitation were also related to NTM lung disease[39]. However, it is important to note that there is considerable overlap in the radiographical manifestations of pulmonary TB and NTM lung disease, and radiographic findings alone could not differentiate the 2 diseases.

The clinical and immunological phenotypes of NTM lung

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disease have recently been reported. Kartalija et al.[40] measured body morphotype, serum leptin, serum adiponectin, and several whole-blood cytokines in 103 patients with NTM lung disease, as well as 101 control subjects. Patients with NTM lung disease had significantly lower body mass index (BMI) and body fat, more prevalent scoliosis and pectus excavatum, and were taller stature than control subjects. Serum leptin and adiponectin less corresponded to body fat in patients with NTM lung disease, and interferon-γ and interleukin-10 levels were significantly suppressed in stimulated whole blood of these patients[40]. These findings warrant further studies to clarify how specific morphotypes and immunophenotypes of NTM patients are responsible for developing disease. In a study reported by Lee et al.[41], 84 patients with nodular bronchiectatic NTM lung disease were examined to evaluate morphotype, immunologic, and clinical characteristics. Similar to the findings of Kartalija et al.[40], Lee et al.[41] found that patients with NTM had lower BMI and more scoliosis, compared to non-NTM bronchiectatic patients.

In addition to clinical and immunological phenotypes, mycobacterial genotyping may be capable of predicting clinical characteristics and prognoses in NTM lung disease. According to a study by Shin et al.[42], patients with NTM lung disease caused by *M. abscessus* and *M. massiliense* were classified to 3 clusters on their variable number tandem gait genotyping. In each cluster, patients had similar clinical courses and prognoses; a stable nodular bronchiectatic form which had no NTM treatment >24 months after diagnosis, a progressive nodular bronchiectatic form which had NTM treatment within 24 months, and a fibrocavitary form which had NTM treatment immediately after diagnosis[42]. Furthermore, in a study using whole-genome sequencing for *M. abscessus* isolates from patients with cystic fibrosis, it was found that the route of transmission was inter-patient, confirmed by less diverse variation in phylogenic analysis among patients. These findings were confirmed by the fact that multidrug-resistant species were isolated from several patients who had been never previously exposed to drugs, indicating cross-infection[43].

2. Treatment of refractory MAC pulmonary disease

For the treatment of MAC infection, macrolide antibiotics, such as clarithromycin and azithromycin, are crucial treatments, and clinical outcomes are significantly correlated with *in vitro* susceptibility to clarithromycin[4]. Therefore, American Thoracic Society (ATS)/Infectious Diseases. Society of America (IDSA) guidelines recommend regimens consist of clarithromycin or azithromycin, ethambutol, and rifampin for treatment of this disease[4]. The efficacy of this regimen has shown up to 80% of negative culture conversion[44,45].

However, if patients have are resistant to macrolide, or have failed to respond to treatments including macrolide in the previous 6 months, the treatment is very difficult[46]. Risk factors for macrolide-resistant infection include macrolide monotherapy or regimens containing 2 drugs[46], and poor physician adherence to NTM treatment guidelines may also contribute[47]. In a recent study by Koh et al.[48], 41 patients with persistent positive culture after at least 6 months of macrolide-based standardized therapy were recruited to evaluate the clinical efficacy of a moxifloxacin-containing regimen. All 41 patients were treated with a moxifloxacin-containing regimen, and the overall treatment success rate was 29% (12/41), indicating that moxifloxacin may improve treatment outcomes for refractory MAC lung disease[48]. However, this was a single-center, retrospective study with small number of enrolled patients. Prospective randomized control studies are required to clarify the clinical efficacy of moxifloxacin for refractory MAC lung disease.

Conclusion

The emergence of drug-resistant TB is an increasing global health concern. Early detection of TB and drug resistance is important for TB control programs, and the Xpert MTB/RIF test could be a useful tool in this field. Levofloxacin and moxifloxacin are equally safe and efficacious in the treatment of MDR-TB. ICS could be a risk factor of the development of active TB, and systemic administration of corticosteroids may decrease mortality in all forms of active TB. Positive culture at 2 months of treatment, and cavitation on baseline chest radiography, could indicate a risk of TB relapse, and may require prolonged treatment. NTM pulmonary disease has typical clinical phenotypes, and moxifloxacin may improve treatment outcomes in refractory MAC pulmonary disease.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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