REVIEW

http://dx.doi.org/10.4046/trd.2015.78.3.168
ISSN: 1738-3536(Print)/2005-6184(Online) • Tuberc Respir Dis 2015;78:168-174

TRD
Tuberculosis and Respiratory Diseases

Medical Management of Drug-Resistant Tuberculosis

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Drug-resistant tuberculosis (TB) is still a major threat worldwide. However, recent scientific advances in diagnostic and therapeutic tools have improved the management of drug-resistant TB. The development of rapid molecular testing methods allows for the early detection of drug resistance and prompt initiation of an appropriate treatment. In addition, there has been growing supportive evidence for shorter treatment regimens in multidrug-resistant TB; and for the first time in over 50 years, new anti-TB drugs have been developed. The World Health Organization has recently revised their guidelines, primarily based on evidence from a meta-analysis of individual patient data (n=9,153) derived from 32 observational studies, and outlined the recommended combination and correct use of available anti-TB drugs. This review summarizes the updated guidelines with a focus on the medical management of drug-resistant TB.

Keywords: Tuberculosis; Drug Resistance; Tuberculosis, Multidrug-Resistant; Extensively Drug-Resistant Tuberculosis

Introduction

The prevalence of tuberculosis (TB) has decreased markedly in Korea since the establishment of the National Tuberculosis Control Program in 1962. However, in recent years, the rate of decrease has slowed[1] and multidrug-resistant TB (MDR-TB) has emerged as a significant threat to public health. The proportion of MDR-TB among new cases of TB increased from 1.6% in 1994 to 2.7% in 2004[2]. In addition, according to data from the 2008 Health Insurance Review and Assessment Service, 4.6% of patients (n=2,472) were MDR-TB[3]. Of these cases, 2.9% were new cases of TB while 9.3% were patients with prior TB treatment history.

Treatment of MDR-TB, compared to drug-sensitive TB, is more difficult given the higher cost, longer treatment period, and more adverse events. Meta-analysis data indicate that the MDR-TB treatment success rate is about 62% worldwide[4,5]. In Korea, the treatment success rate varies depending on the study site and ranges from 37.1% to 66.0%[6-12]. However, the largest retrospective multicenter cohort study in Korea (n=1,407 MDR-TB patients) showed a treatment success rate of 45.3% and a default rate of 32.3%[10].

Recently, the World Health Organization (WHO) revised the MDR-TB management guidelines[13,14]. The revisions incorporate advancements in the diagnosis of drug-resistant TB and the development of new anti-TB drugs. The recommendations are primarily based on evidence from a meta-analysis of individual MDR-TB patient data (n=9,153) from 32 observational studies[15]. Although few prospective randomized trials have been conducted to support the new recommendations, these guidelines were based on the best evidence available to date. In 2014, the Korean guidelines regarding MDR-TB management were updated in accordance with the WHO guidelines[16]. This review summarizes the WHO and Korean guidelines for the medical management for drug-resistant TB.

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Received: Jan. 31, 2015
Revised: Mar. 15, 2015
Accepted: Mar. 19, 2015

Advances in the Diagnosis of Drug-Resistant TB

For decades, the laboratory diagnosis of drug-resistant TB has depended on phenotypic, culture-based methods. Diagnostic delays are a major disadvantage of these methods and could result in ineffective treatment, poor outcomes, and the spread of drug-resistant TB. Although other phenotypic methods (e.g., the microscopic observation drug susceptibility assay and the thin layer agar technique) have shortened the delay[17], their use is still limited.

With advances in rapid molecular technologies, drug-resistant TB can be diagnosed by a using a molecular (genotypic) or conventional (phenotypic) drug susceptibility test (DST). The new molecular tests significantly reduce diagnostic delays allowing for the prompt initiation of MDR-TB treatment. The WHO endorsed two line probe assays (LPAs) in 2008[18], the INNO-LiPA Rif.TB (Fujirebio, Ghent, Belgium) and the GenoType MTBDRplus (Hain Lifescience GmbH, Nehren, Germany), and the Xpert MTB/RIF system (Cepheid, Sunnyvale, CA, USA) in 2010[19]. The WHO currently recommends using rapid DSTs over conventional testing or no testing at the time of TB diagnosis[13,14]. Recently several molecular assays for the detection of rifampicin resistance have been developed. In Korea, new commercial molecular assays, REBA MTB-Rifa (YD Diagnostics, Yongin, Korea)[20,21] and AdvanSureMDR-TB GenoBlot assay (LG Life Sciences, Seoul, Korea)[22], are currently available.

Revisions to the Case Definition

In 2013, the WHO revised the case definition of TB and drug-resistant TB in order to incorporate advances in the new molecular DSTs[23]. "A bacteriologically confirmed case" is now defined as a biologic specimen that is positive by molecular methods as well as smear or culture methods. "Rifampicin resistance" was newly introduced and could be detected using phenotypic or genotypic methods. The revised definitions of drug-resistant TB are included in Table 1.

The WHO recommended against labeling TB cases as "totally drug-resistant" or "extremely drug-resistant" given the concerns about the reliability and reproducibility of DSTs for many anti-TB drugs and insufficient evidence regarding the impact of such results on treatment outcomes. The term "resistance beyond extensively drug-resistant TB (XDR-TB)" is preferred[24]. Patients with additional resistance beyond XDR-TB showed poorer outcomes[25].

Interpretation of Results from Molecular Tests

WHO-recommended molecular testing methods have a high sensitivity and specificity for the detection of rifampicin resistance. A negative result generally excludes rifampicin resistance and no further confirmatory test is required. However, although a positive result is a reliable indicator for MDR-TB, a false positive is also possible. Molecular methods have a positive predictive value for MDR-TB of only about 60% when the prevalence of rifampicin resistance is 3% (the proportion of MDR-TB among new TB cases in Korea)[26,27].

When a molecular method detects rifampicin resistance, further treatment or testing depends on the patient's risk of MDR-TB. For patients with a high risk of MDR-TB, an MDR-TB treatment regimen should be initiated. For patients with a low risk of MDR-TB, further confirmatory tests (such as a phenotypic DST, LPA, or sequencing) are required prior to initiation of treatment[14,28,29].

Mono- and Poly-Resistant TB

The choice of drugs should be based on the DST pattern; however, when interpreting the results, the possibility of resistance amplification should be considered given that conventional DSTs often take several months, i.e., the results do not reflect the bacterial population at the time of regimen design. If a particular drug was included in a failing or an ineffective regimen for over a month while waiting DST result, acquisition of additional resistance to that drug should be considered. The WHO recently emphasized monitoring for possible

Table 1. Definitions of drug-resistance[23]

Drug-resistance	Definition
Monoresistance	Resistance to one first-line anti-tuberculosis drug only
Polydrug resistance	Resistance to more than one first-line anti-tuberculosis drug (other than both isoniazid and rifampicin)
Multidrug resistance	Resistance to at least both isoniazid and rifampicin
Extensive drug resistance	Resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance
Rifampicin resistance	Resistance to rifampicin detected using phenotypic or genotypic methods. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance

http://dx.doi.org/10.4046/trd.2015.78.3.168

amplification of rifampicin resistance during treatment, using the Xpert MTB/RIF[14]. The feasibility and effectiveness of this approach are to be verified by further studies. However, it should be kept in mind that the risk of amplification to MDR is high in the treatment of polyresistant TB and close monitoring is necessary.

The WHO-suggested regimens for mono- and poly-resistant TB are shown in Table 2[14]. Rifampicin resistance is a reliable indicator of MDR-TB. For patients who are diagnosed with rifampicin resistance using Xpert MTB/RIF, they should be managed in the same way as MDR-TB. Justification of adding isoniazid to the MDR regimen depends on drug resistance data of each country. In Korea, rifampicin monoresistance is rare; therefore, routine addition of isoniazid to the MDR regimen is not recommended[16]. Isoniazid can be added to the regimen until DST results to isoniazid are available, but it should not be counted as an effective drug.

Multidrug-Resistant Tuberculosis

1. General principles for regimen design

1) Perform rapid DSTs for all patients with a risk of drug resistance prior to treatment: Early MDR-TB detection and the prompt initiation of an effective treatment regimen are important factors for successful outcomes. The benefits of rapid DSTs for patient and public health include better prognosis, prevention of further drug resistance, and a reduction in the spread of drug-resistant strains.

2) Design regimens based on DST results, patient TB treatment history, and contact history: The results of DSTs are essential for designing the appropriate treatment regimen. However, DSTs for drugs such as ethambutol, streptomycin, and those in group 4 and 5 do not have high reproducibility or reliability. Therefore, the DST results should be interpreted along with a detailed clinical history. If a patient has used a drug as part of a failing regimen for over a month, the strain should be considered "probably resistant," even if the results of the DST indicated susceptibility.

3) Include anti-TB drugs from each group in a hierarchical order based on potency: Fluoroquinolones and injectable drugs are two groups of second-line core drugs with potent bactericidal activity. Other second-line drugs are accompanying drugs that are responsible for protecting the core drugs against resistance. To build a MDR-TB treatment regimen, begin with two core drugs (a fluoroquinolone and an injectable drug) and then add oral second-line drugs in the following order: ethionamide or protionamide, cycloserine, and p-aminosalicylic acid (PAS)[14,28,29]. If the preceding drugs are not sufficient to make a regimen, group 1 and then group 5 drugs could also be added.

The recent WHO guidelines have changed the priority of first-line drugs[14]. Although first-line drugs were previously given the highest priority for inclusion in treatment regimens (if the strain showed susceptibility to the drugs)[30,31], the meta-analysis have shown only a slight benefit or no benefit for successful outcomes[15]. Similarly, group 5 drugs showed no association with successful outcomes. Based on such clinical evidence, first-line drugs and group 5 drugs may be included in a regimen but should not to be considered as active drugs.

4) The intensive phase of treatment should consist of pyrazinamide and at least four second-line drugs: The optimal number of drugs required to cure MDR-TB is not known. The meta-analysis showed that the use of at least four active drugs in the intensive phase and three active drugs in the continuation phase was likely to be effective[15]. There was no evidence to support the use of more than four second-line drugs in patients with extensive disease. Increasing the number of second-line drugs is permissible if the effectiveness of some drugs is uncertain. As opposed to this recommendation, several retrospective cohort studies showed that an aggressive regimen of at least 5 likely effective drugs during the intensive phase was associated with a reduced risk of treatment failure, death or relapse[32-34].

Based on clinical evidence from the meta-analysis, the intensive phase of treatment should consist of at least pyrazinamide, a fluoroquinolone, an injectable drug, protionamide (or ethionamide), and cycloserine (or PAS if cycloserine cannot be used).

Table 2. Suggested regimens for mono and polyresistant TB[14]

Resistance pattern	Suggested regimens	Minimum duration (mo)
H	R, Z and E (±FQ)	6–9
H and E	R, Z, and FQ	9–12
H, E, and Z	R, FQ, PTH, and the injectables*	18
R mono or polyresistance	Full MDR regimen plus H	20

*For the first 2–3 months.
TB: tuberculosis; H: isoniazid; R: rifampicin; Z: pyrazinamide; E: ethambutol; FQ: fluoroquinolone; PTH: pyrazinamide; MDR: multidrug resistance.

5) An intensive phase of 8 months and total treatment duration of 20 months are recommended: There have been controversies concerning the optimal duration for injectable drug use and total treatment. The American Thoracic Society guidelines from 2003 recommended a maximum cumulative streptomycin dose of 120 g (due to its cumulative toxic effects) but did not mention any other injectable drugs[35]. The WHO had suggested the time following sputum conversion in the recommendation of treatment duration. In 1997, the WHO recommended a minimum intensive phase of 3 months or until after culture conversion[36]. The 2006 and 2008 WHO guidelines recommended an intensive phase of at least 6 months or at least 4 months after culture conversion[30,31]. However, in the 2011 and 2014 guidelines, the time for the intensive phase was increased to a minimum of 8 months and bacteriological conversion was not considered[13,14]. This recommendation was based on clinical evidence from the meta-analysis, which did not determine the optimal time following culture conversion[15]. Therefore, the injectable drugs are recommended to use for at least eight months, but the duration can be modified based upon severity of disease, prior therapy, drug resistance patterns, response to therapy, and timing of sputum conversion.

Currently, the WHO recommends a total treatment duration of 20 months for patients who had no previous MDR-TB treatment. Patients who have had previous treatment for MDR-TB may need longer treatment. The duration may be modified depending on bacteriological status and other indicators of treatment progress.

A non-randomized study conducted in Bangladesh reported very promising results with a 9-month regimen[37], and a randomized controlled trial is ongoing to test a shorter regimen[38]. However, until sufficient evidence is available, a shorter treatment regimen is not recommended as a standard. In addition, treatment with new drugs, such as bedaquiline[39] and delamanid[40], may allow for shorter MDR-TB therapy; however, optimization studies of these drugs are needed.

2. Choice of anti-TB drugs

1) Group 1: first-line drugs: One of the major changes in the revised WHO guidelines is how to include ethambutol and pyrazinamide in the MDR regimen. In the previous guidelines, ethambutol and pyraziamide were recommended as the first option in the drug selection (as part of four active drugs) if susceptibility was shown[30,31]. However, in the meta-analysis, pyrazinamide showed only a slightly added benefit and ethambutol was associated with a marginal but statistically significant reduction in the likelihood of cure[15]. Therefore, based on clinical evidence, ethambutol and pyrazinamide may be included in MDR-TB treatment regimens but should not be considered active drugs.

Pyrazinamide has poor bactericidal activity, but it has potent sterilizing activity that contributes to a shorter treatment duration. Given its promising potential, pyrazinamide is routinely added to MDR-TB treatment regimens if susceptibility is documented or unknown[29]. Although the WHO has recently recommended routine use of pyrazinamide even if the strain shows resistance[14], this recommendation should be verified by further studies. A recent retrospective study showed that the WHO-recommended regimen in which pyrazinamide was not likely effective was associated with higher mortality rates[41].

Pyrazinamide can be used for the entire treatment or at least for the intensive phase. Pyrazinamide is generally used with companion rifampicin for the treatment of susceptible TB. Given that rifampicin also has a potent sterilizing action, pyrazinamide is recommended to be used during the first 2 months of treatment only. While rifampicin is no longer active in MDR-TB treatment, pyrazinamide may continue working after the first few months of treatment[42]. In addition, many MDR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment where pyrazinamide is active[14].

In contrast, ethambutol is not routinely added to MDR-TB treatment regimens. Although ethambutol can be added in the regimen, it is never considered an active drug, even if the strain shows susceptibility[14].

2) Group 2: injectable drugs: Among the injectable drugs, there is currently no strong evidence to indicate which drugs are superior in terms of efficacy or adverse effects. The meta-analysis did not show any injectable to be superior to any other[15]. Therefore, the choice of injectable drug depends on the availability and resistance in each country. In Korea, capreomycin is not readily available and amikacin is usually injected intravenously; thus, kanamycin is the recommended first choice of injectable drugs[16].

In contrast, streptomycin is not recommended because of high rates of resistance in patients with MDR-TB. However, streptomycin should be considered in cases where the strain is resistant to all other second-line injectable drugs given that there is little cross-resistance between streptomycin and the other injectable drugs[14].

3) Group 3: fluoroquinolones: Fluoroquinolones, especially later-generation fluoroquinolones, have been shown to be significantly associated with cure[15]. Consequently, fluoroquinolones should always be used in MDR-TB treatment. Moxifloxacin or levofloxacin is preferred while ciprofloxacin and ofloxacin are not recommended given their weaker efficacy. The dosage recommendation for levofloxacin is 750–1,000 mg/day. Although moxifloxacin has better in vitro activity against TB compared to levofloxacin, a recent randomized trial conducted in Korea revealed that moxifloxacin and levofloxacin have comparable efficacy in terms of 3-month

culture conversion rates and adverse events[43]. The WHO recommends, despite lack of evidence, the use of moxifloxacin even if levofloxacin (or ofloxacin) resistance is documented because there is no complete cross-resistance between these fluoroquinolones[14].

4) Group 4: oral bacteriostatic second-line drugs: In the 2008 WHO guidelines[31], there was no preference among group 4 drugs. However, in the meta-analysis, ethionamide demonstrated a stronger association with successful outcome than cycloserine or PAS[15]. Furthermore, cycloserine demonstrated a stronger association than PAS; therefore, ethionamide or protionamide is preferred followed by cycloserine and, subsequently, PAS.

There is high cross-resistance between isoniazid and prothionamide if the *inhA* mutation is present[44]. If the *inhA* mutation is present, which can be detected by a LPA, protionamide can still be included in an MDR-TB treatment regimen; however, it may not be the best second-line drug[14].

5) Group 5: agents with limited data on efficacy and/or long-term safety: Group 5 drugs did not show an association with successful outcomes in the meta-analysis[15]; however, linezolid and high-dose isoniazid could not be analyzed due to the small number of cases. Therefore, group 5 drugs may be used if drugs from groups 2–4 are not likely to be effective; however, group 5 drugs are not included among active drugs. A recent meta-analysis showed that only linezolid was independently associated with favorable outcomes in the treatment of XDR-TB or fluoroquinolone-resistant MDR-TB[45]. There is renewed interest in the efficacy of clofazimine. A randomized controlled trial in China showed that clofazimine accelerated sputum culture conversion and improved treatment success rates in the treatment of MDR-TB[46].

There are few evidences regarding the drug selection sequence in group 5 drugs. Many experts agreed that linezolid is the first option and clofazimine and meropenem/clavulanic acid may be more effective than clarithromycin or amoxicillin/clavulanic acid[28]. Recently, bedaquiline and delamanid have been listed in group 5 as well[14].

Management of XDR-TB

The principles of XDR-TB management are similar to those of MDR-TB management. However, the design of a treatment regimen for XDR-TB is more complex and referral to an expert is strongly recommended. Although, DST for ethambutol, pyrazinamide, and second-line TB drugs do not have high reproducibility or reliability, it appears to provide clinically useful information to guide selection of treatment regimens for MDR and XDR TB[47]. Any drug that the isolate is susceptible to from group 1 and any remaining available drugs from groups 3 or 4 are added to the regimen. Group 5 drugs are often required to make a regimen as well.

The optimal number of drugs and the duration of treatment are still uncertain. In a meta-analysis conducted by Falzon et al.[48], treatment success was highest if at least six drugs were used in the intensive phase and four in the continuation phase. The odds of success were maximized when the duration of the intensive phase was 6.6–9.0 months and the total duration of treatment was 20.1–25.0 months. These results suggest that the optimal treatment of XDR-TB patients requires a similar duration but more drugs than treatment for non-XDR MDR-TB.

The use of later-generation fluoroquinolones, such as moxifloxacin, significantly improved treatment outcomes of XDR-TB even when a DST demonstrated resistance to a representative fluoroquinolone[49]. Linezolid may also represent a valuable drug to treat cases of XDR-TB[50,51]. New drugs, such as bedaquiline[52,53] and delamanid[54], and new combination regimen[55] are expected to enhance the cure rate of XDR-TB. Adjunctive surgery should be considered in localized disease cases and rigorous respiratory infection control measures are also important.

Conclusion

A rapid diagnosis of drug resistance and the subsequent initiation of an appropriate treatment are crucial in the management of drug-resistant TB. Using current recommendations, drug-resistant TB can largely be cured with the right combination and use of available anti-TB drugs. However, controlled trials are needed to improve the quality of existing evidence. In addition, further studies for optimization of new drugs and shorter treatment regimens for MDR-TB are needed.

Conflicts of Interest

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

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