Diagnosis and treatment of multidrug-resistant tuberculosis

Jong Geol Jang, Jin Hong Chung

Department of Internal Medicine, Yeungnam University College of Medicine, Daegu, Korea

Introduction

Tuberculosis (TB) is still a major health problem worldwide. Especially, multidrug-resistant TB (MDR-TB), which is defined as TB that shows resistance to both isoniazid and rifampicin, is a barrier in the treatment of TB. Globally, approximately 3.4% of new TB patients and 20% of the patients with a history of previous treatment for TB were diagnosed with MDR-TB. The treatment of MDR-TB requires medications for a long duration (up to 20–24 months) with less effective and toxic second-line drugs and has unfavorable outcomes. However, treatment outcomes are expected to improve due to the introduction of a new agent (bedaquiline), repurposed drugs (linezolid, clofazimine, and cycloserine), and technological advancement in rapid drug sensitivity testing. The World Health Organization (WHO) released a rapid communication in 2018, followed by consolidated guidelines for the treatment of MDR-TB in 2019 based on clinical trials and an individual patient data meta-analysis. In these guidelines, the WHO suggested reclassification of second-line anti-TB drugs and recommended oral treatment regimens that included the new and repurposed agents. The aims of this article are to review the treatment strategies of MDR-TB based on the 2019 WHO guidelines regarding the management of MDR-TB and the diagnostic techniques for detecting resistance, including phenotypic and molecular drug sensitivity tests.

Keywords: Diagnosis; Multidrug-resistant tuberculosis; Treatment

Definitions of tuberculosis drug resistance

- Mono-resistant TB is defined as TB caused by an isolate that shows resistance to a single first-line anti-TB drug (isoniazid, rifampicin, ethambutol, or pyrazinamide) [5].

[4]. Treatment of MDR-TB lasts for a long duration of approximately 2 years and consists of a combination of multiple second-line drugs, which are more expensive, less effective, and more toxic than the first-line drugs. Therefore, treatment outcomes for MDR-TB are poor, with a success rate of approximately 54% [2]. WHO published new guidelines for MDR-TB treatment in 2019. This article reviews the treatment of MDR-TB according to the most recent updated WHO guidelines and diagnosis of MDR-TB [2].
• Isoniazid-resistant TB is defined as TB caused by an isolate that shows resistance to isoniazid, but is susceptible to rifampicin.
• Rifampicin-resistant TB is defined as TB caused by an isolate that shows resistance to rifampicin, but is susceptible to isoniazid.
• Poly-resistant TB is defined as TB caused by an isolate that is resistant to more than one anti-TB drug, but not resistant to both isoniazid and rifampicin simultaneously.
• MDR-TB is defined as TB caused by an isolate that shows resistance to at least isoniazid and rifampicin.
• Pre-extensively drug-resistant TB is defined as TB caused by an isolate that shows resistance to isoniazid, rifampicin, and either fluoroquinolones or injectable agents (amikacin, kanamycin, or capreomycin), but not both.
• Extensively drug-resistant TB is a rare type of MDR-TB that is resistant to isoniazid and rifampicin as well as to any fluoroquinolone and at least one out of the three injectable agents (amikacin, kanamycin, or capreomycin). Approximately 9% of the MDR-TB patients have extensively drug-resistant TB.

**Mechanism of drug resistance**

Drug resistance to *Mycobacterium tuberculosis* (MTB) results from spontaneous and random chromosomal mutations that result in reduced susceptibility to specific agents [6]. The mechanism leading to the development of drug resistance includes activation of the efflux pump at the surface of the bacteria, drug target alteration, production of drug inactivating enzymes, and disruption of drug activation [7]. The incidence of MDR-TB is low, as the rate of mutation is \(10^{-7}\) for isoniazid and \(10^{-5}\) for rifampicin [8]. Drug resistance can occur in two ways (primary or secondary resistance). Primary resistance develops when patients are exposed to and infected with an already drug-resistant strain. Secondary resistance or acquired resistance develops due to poor adherence to medication, drug malabsorption, and inadequate regimen among patients taking TB medication. Although most cases of MDR-TB arise from acquired resistance, a previous study reported that most of the incidences of MDR-TB resulted from transmission rather than acquisition of resistance during treatment in most high-burden settings [9].

**Diagnosis of multidrug-resistant tuberculosis**

Successful diagnosis and treatment of MDR-TB are based on a rapid and precise drug sensitivity test (DST), which provides evidence for selecting an effective drug [4]. DST is divided into phenotypic tests that observe growth or metabolic inhibition in an-
and resistance to isoniazid and rifampicin, and later in 2016, WHO recommended the use of LPAs in patients with culture-positive (direct testing) or a sputum smear-positive specimens (indirect testing) [18,19]. The MTBDRplus is a semi-automated genotypic method that consists of three steps, namely DNA extraction, multiplex polymerase chain reaction (PCR) amplification, and reverse hybridization. This method can detect mutations in the rpoB gene for rifampicin resistance and in the katG gene and the inhA promoter region for isoniazid resistance [20,21]. Although MTBDRplus has shown high accuracy for rifampicin resistance (98.7%), its accuracy for isoniazid is variable and has relatively low sensitivity (84.3%) [22]. Recently, the WHO recommended the GenoType MTBDRsl (Hain Lifescience GmbH) that was developed to detect resistance to ethambutol (mutation in embB), fluoroquinolones (mutations in gyrA and gyrB), and injectable agents (mutation in rrs, leading to resistance to kanamycin, amikacin, and capreomycin) [23].

In 2020, the updated WHO guidelines recommended the use of molecular assays (Xpert MTB/RIF and Xpert MTB/RIF [Xpert Ultra]; GeneXpert) as the initial test for the diagnosis of pulmonary and extrapulmonary TB and rifampicin resistance in adults and children [19,24]. The Xpert MTB/RIF is a fully automated real-time PCR based molecular assay for detecting MTB and resistance to rifampicin [25], which provides results within 2 hours. In a large clinical trial, the Xpert MTB/RIF showed an MTB detection accuracy of 98.2% in smear-positive and culture-positive patients, but the accuracy was 72.5% in smear-negative and culture-positive patients. The specificity of the Xpert MTB/RIF was 99.2%. In the same study, the Xpert MTB/RIF showed 97.6% sensitivity for detecting rifampicin resistance [22]. The WHO also recommends Xpert MTB/RIF for the diagnosis of extrapulmonary TB (e.g., tuberculous lymphadenitis and tuberculous meningitis) based on a systematic review [26]. The Xpert Ultra was developed to improve the sensitivity of TB diagnosis (especially in smear-negative, human immunodeficiency virus [HIV]-infected patients and in case of extrapulmonary TB such as tuberculous meningitis and tuberculous lymphadenitis) and rifampicin resistance identification. For TB detection, the sensitivity of Xpert Ultra was higher than that of Xpert in smear-negative patients and in patients with HIV, but the specificity was lower than that of Xpert in all patients [27]. A recent study reported that Xpert Ultra was not superior to Xpert in diagnosing tuberculous meningitis [26]. Further evaluation of the diagnostic accuracy of Xpert Ultra is required. To date, there have been no fully automated molecular assays that can detect resistance to second-line agents. In Korea, rapid DST using LPA and Xpert can be used.

Probe-based DSTs are not able to detect resistance profiles when mutations occur outside the target genetic region [28]. Next-generation sequencing (NGS) is a technique that can compensate for this weakness. NGS provides rapid and detailed sequence information of a part of the genome (targeted NGS) or the whole genome (whole genome sequencing). It can identify genotypes that predict drug-resistant phenotypes. It can also provide genetic information that can detect transmission in potential outbreak situation [29]. This technique can provide drug susceptibility profiles not only for the first-line drugs but also for many second-line drugs [30]. Whole genome sequencing was well correlated with phenotypic DST as well as with culture conversion rate and treatment outcome [31]. However, NGS has several disadvantages, such as poor sensitivity while using sputum rather than culture isolate as a specimen and the need for specialized staff [32].

### Treatment of multidrug-resistant tuberculosis

The goal of treatment for MDR-TB is to cure the individual patient and to avoid the transmission of MDR-TB to other people. The WHO developed guidelines for the programmatic management of drug-resistant TB in 2006 and updated these guidelines in 2011. These updated guidelines recommend the use of rapid diagnosis of rifampicin resistance and a combination of four effective drugs, including pyrazinamide, an injectable agent, and a later generation fluoroquinolone for the treatment of patients with MDR-TB [33]. In the updated guidelines of 2016, the WHO suggested MDR-TB regimens with at least five effective TB drugs, including pyrazinamide and four second-line TB drugs [5]. Drugs to be included in the regimen are fluoroquinolone, an injectable agent, ethionamide or prothionamide, pyrazinamide, and either cycloserine or para-aminosalicylic acid (Table 1). Rapid DST for isoniazid and rifampicin or rifampicin alone is recommended. The WHO released a rapid communication in 2018 [34] and updated the consolidated guidelines in 2019 [2]. These guidelines include a new drug classification, guidelines for building regimens, enhanced monitoring strategies, and a feasible implementation plan based on clinical trials and individual patient data meta-analysis (IPD-MA) [2,35,36]. A recent IPD-MA including 12,030 patients from 25 countries involved analysis of anti-MDR-TB drugs associated with favorable outcomes. Treatment success was positively associated with the use of linezolid, levofloxacin, carbapenems, moxifloxacin, bedaquiline, and clofazidine. Reduced mortality was significantly associated with the use of linezolid, levofloxacin, moxifloxacin, and bedaquiline.

Streptomycin and amikacin provided modest benefits when compared with regimens without injectable agents [35]. Accord-
During the treatment, misclassification of treatment outcomes, and their selective use in severe clinical cases [35]. Although Korean guidelines also excluded kanamycin in classification of MDR-TB drug, they recommended that kanamycin can be used as a substitute for amikacin until additional data are available [37].

1. Classification of drugs

In 2018, the WHO rapid communication classified the drugs for the longer MDR-TB regimen into three groups (Table 2) [34]. Agents in group A include fluoroquinolones, bedaquiline, and linezolid, which are highly effective and strongly recommended in the MDR-TB regimen unless contraindicated. Clofazimine and either cycloserine or terizidone are included in group B. These drugs are conditionally recommended as the second choice. Group C drugs can be used when an adequate regimen cannot be formulated with agents from group A or group B. Agents in group C are ranked by the balance of benefits to toxicities. It includes all other drugs except high-dose isoniazid, amoxicillin-clavulanate, kanamycin, and capreomycin.

Fluoroquinolones are effective against growing as well as non-growing tuberculous bacilli and are well tolerated over the long treatment period. Fluoroquinolones inhibit DNA transcription and bacterial replication of MTB by interfering with DNA gyrase, which is a tetramer composed of two α and two β subunits encoded by gyrA and gyrB genes [38]. Fluoroquinolone resistance in MTB is usually caused by mutations in the gyrA gene [39]. Fluoroquinolones have become a mainstay of regimens used to treat MDR-TB, as their mechanism of action is distinct from both isoniazid and rifampicin [40].
Levofloxacin and moxifloxacin are the two most frequently recommended agents, and the WHO has recommended the use of these drugs for the treatment of MDR-TB. The optimal dose of levofloxacin is 750 mg once daily and that of moxifloxacin is 400 mg once daily. The study from South Korea reported that levofloxacin and moxifloxacin have similar effectiveness and side effects [41]. Adverse effects of fluoroquinolones include gastrointestinal trouble, problems related to the central nervous system, and QT interval prolongation. However permanent discontinuation of fluoroquinolones due to side effects was uncommon [42].

Linezolid is an oxazolidinone antibiotic that inhibits bacterial protein synthesis by preventing the fusion of 30S and 50S ribosomal subunits [43]. Linezolid was categorized as a “group 5” drug in the 2011 WHO guidelines for drug-resistant TB. Agents in group 5 were not recommended for use as core drugs, as there was insufficient evidence regarding their efficacy and safety [33]. However, the 2016 WHO update reclassified linezolid into group C, which includes other core second-line agents [5]. In 2018, in the rapid communication released by the WHO regarding treatment of MDR-TB, linezolid was further elevated to group A. The effectiveness of linezolid in the treatment of drug-resistant TB has been confirmed in clinical trial and meta-analysis [35,43]. The optimal duration of linezolid use has not been established, but its long-term administration (at least 6 months) was associated with treatment success [34]. Concerns have been raised about safety and toxicity of linezolid. Critical adverse effects of linezolid include peripheral neuropathy, myelosuppression with consequent anemia and thrombocytopenia, and optic neuropathy leading to disability and blindness [44]. In a recent IPD-MA, the incidence of permanent discontinuation due to adverse effects of linezolid was 16.3% [44]. The optimal dose of linezolid is unclear. A variety of dosing strategies have been used for drug-resistant TB, which range from 300 to 1,200 mg daily, with once-daily or twice-daily administration [45,46]. The 600-mg daily dose was reported to be safer than the 1,200-mg dose without lowering its effectiveness [46]. The WHO also recommends a daily dose of 600 mg. Although some studies report that a daily dose of 300 mg is effective and reduces toxicities [45], it is associated with a risk for development of drug resistance. Moreover, there is no sufficient evidence for initiating treatment with a 300-mg daily dose.

Bedaquiline is a diarylquinoline compound that specifically inhibits the adenosine triphosphate synthase by blocking the flow of mycobacterial proton pump [47]. Bedaquiline has a concentration-dependent bactericidal effect by causing cell death in both replicating and non-replicating mycobacteria [48]. The standard regimens including bedaquiline showed a reduction in time to culture conversion and a higher cure rate at 120 weeks when compared with a placebo [49,50]. Common adverse events include QT prolongation, nausea/vomiting, and arthralgia/myalgia. Severe adverse events were reported in 2.8% of the patients [44]. Bedaquiline is well absorbed, and its absorption increases with food. According to the clinical data for safety, tolerability, and efficacy, the U.S. Food and Drug Administration approved the dose of 400 mg daily for 14 days followed by 200 mg three times weekly for 22 weeks [51].

Delamanid is a new anti-TB agent derived from the nitro-imidazooxazole class of compounds that inhibits mycolic acid synthesis of bacterial cell wall. It has shown potent in vitro and in vivo activity against both drug-susceptible and drug-resistant strains of MTB in early clinical development [52,53]. Due to the lack of data in the 2018 IPD-MA, delamanid was classified in group C, and WHO recommended conditionally that delamanid may be included in the treatment of patients with MDR-TB aged 3 years or more on the longer regimen [2,35]. However, several studies reported that delamanid-containing regimen was as effective and safe as bedaquiline [54-56]. Thus, Korean guidelines classified delamanid in group C2, and recommend that delamanid can be used as a substitute for bedaquiline (Table 3) [37].

### 2. Building of regimen

This review will focus on building of longer MDR-TB regimens according to the WHO guidelines [2], since the shorter MDR-TB regimens are fixed. The regimens should include all three drugs from group A and at least one drug from group B. Thus, the regimens should include at least four effective drugs (ideally five

| Group | Medicine |
|-------|----------|
| A     | Levofloxacin or moxifloxacin<br>Bedaquiline<br>Linezolid |
| B     | Clofazimine<br>Cycloserine |
| C     | C1:<sup>a</sup><br>Amikacin (streptomycin)<sup>b</sup><br>Ethambutol<br>Imipenem or meropenem<br>Para-aminosalicylic acid<br>Prothionamide<br>Pyrazinamide<br>C2<br>Delamanid<sup>c</sup> |

**Table 3.** Classification of medication for multidrug-resistant tuberculosis in updated Korean guidelines

<sup>a</sup>The order of drug in group C1 does not mean the ranking of drug selection. <sup>b</sup>Amikacin is preferred over streptomycin. Kanamycin can be used as a substitute for amikacin. <sup>c</sup>Delamanid can be used as a substitute for bedaquiline.

<sup>Modified from Korean guidelines for tuberculosis, 4th ed. [37].</sup>
3. Duration of treatment
The optimal duration of therapy for MDR-TB is unclear. The WHO recommends two types of standardized MDR-TB treatment regimens (longer and shorter regimens) [2]. They differ in drug combination as well as in duration. Treatment with the longer regimen is suggested for 18 to 20 months (at least 15 to 17 months after culture conversion), and oral regimens are preferred. The intensive phase, which lasts for 6 to 7 months and includes at least four drugs, is recommended until bedaquiline is stopped. The recommended duration of treatment may be modified depending on the culture conversion status and the patient’s response to treatment [2]. The continuation phase of the treatment should include at least three drugs [2]. ATS/CDC/ERS/IDSA guidelines recommended the duration of intensive phase to be between 5 and 7 months after culture conversion [42].

The shorter regimen was originally based on the so-called Bangladesh regimen [59]. It was later tested in an international, randomized controlled trial (STREAM stage 1 trial) [60]. The recommended duration of this regimen is 9 to 11 months. The short regimen can be an alternative to the longer regimen in simple MDR-TB cases under specific conditions. This regimen includes an intensive phase lasting 4 to 6 months, which includes seven drugs (kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol). It is followed by a 5-month course with moxifloxacin, clofazimine, pyrazinamide, and ethambutol. Exclusion criteria for the shorter regimen are (1) resistance to or suspected ineffectiveness of a medicine from the shorter regimen (except isoniazid resistance); (2) exposure to one or more second-line medicines from the shorter MDR-TB regimen for greater than 1 month; (3) intolerance to medicines from the shorter MDR-TB regimen or risk of toxicity (e.g., drug-drug interactions); (4) pregnancy; (5) disseminated, meningeal, or central nervous system TB; (6) any extrapulmonary disease in patients with HIV infection; and (7) unavailability of at least one medicine from the shorter MDR-TB regimen. ATS/CDC/ERS/IDSA did not make a recommendation either for or against the standardized short-course regimen [42]. Korean guidelines also did not recommend shorter MDR-TB regimen because of the high incidence of resistance to quinolone, injectable agent, and pyrazinamide, and a lack of evidence on the effectiveness and safety of the shorter regimen when compared with the newly developed longer regimen [37].

Conclusion
MDR-TB remains a major concern in TB control. A rapid diagnosis of drug resistance and optimal treatment with effective and less toxic regimens is important in the management of MDR-TB. Re-
cently, the WHO published updated guidelines regarding the programmatic management of MDR-TB, which focused on rapid diagnosis and effective treatment via advanced rapid molecular tests and oral regimens with new and repurposed anti-TB drugs. Using these current recommendations might be helpful in the management of MDR-TB. However, well-designed clinical trials and studies for further assessment of new agents and shorter regimens are needed.

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

Author contributions
Conceptualization, Formal analysis, and Validation: JJG, CJH; Data curation, Methodology, Project administration, Visualization, Investigation, and Resources: JJG; Supervision: CJH; Writing-original draft: JJG, CJH; Writing-review & editing: JJG, CJH.

ORCID
Jin Hong Chung, https://orcid.org/0000-0001-8040-5363
Jong Geol Jang, https://orcid.org/0000-0000-1829-3051

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