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Diagnosis and treatment of multidrug-resistant tuberculosis

Jong Geol Jang, Jin Hong Chung

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

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Corresponding author:
Jin Hong Chung
Department of Internal Medicine, Yeungnam University College of Medicine, 170 Hyeonchung-ro, Nam-gu, Daegu 42415, Korea
Tel: +82-53-640-6682
Fax: +82-53-620-3849
E-mail: jhchn@med.yu.ac.kr

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

Introduction

Tuberculosis (TB) is the tenth leading cause of death worldwide and a major global health problem [1]. The World Health Organization (WHO) reported that 10.4 million patients developed TB and 1.6 million patients died from TB worldwide in 2017 [2]. Drug resistance is one of the major threats to the treatment of TB. The WHO has defined multidrug-resistant TB (MDR-TB) as TB that shows resistance to isoniazid as well as rifampicin, the most effective anti-TB drugs [3]. In 2018, a total of 186,772 cases were diagnosed with MDR-TB and rifampicin-resistant TB, and 156,071 patients began treatment worldwide [4]. Approximately 3.4% of the new TB patients and 20% of the patients with a history of previous treatment for TB were diagnosed with MDR-TB worldwide [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].

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].

- 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^{-5} for isoniazid and 10^{-7} 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 anti-TB drug-free and drug-containing media and molecular tests that detect genes related to drug resistance [7]. Conventional phenotypic DST is a solid culture-based method that uses egg-based or agar-based media. There are three different methods, namely: the proportion method, the resistance ratio method, and the absolute concentration method [10,11]. The proportion method is the most commonly used method. It is the reference method for phenotypic testing, which provides a measure of the susceptibility of the bacteria to a drug [11,12]. The absolute concentration method is also commonly used due to its technical convenience [7]. These methods are sensitive, have good clinical correlation, and enable the determination of minimal inhibitory concentration. However, it takes a relatively long time as long as 2 to 3 months to confirm the DST results due to the long turnaround time for MTB culture [13]. Liquid culture and DST have a higher rate of MTB isolation and require less time for detection than solid culture and DST. However, it is more expensive and carries a risk of increased bacterial contamination and cross infection by nontuberculous mycobacterial isolation [14]. In order to shorten the turnaround time for mycobacterial culture and DST, a variable rapid culture technique has been developed that usually utilizes liquid media (BACTEC 460, Becton Dickinson, Sparks, MD, USA; Mycobacteria Growth Indicator Tube [MGIT], Becton Dickinson; Septi-Check, Becton Dickinson; Myco-ESP Culture System II, Trek Diagnostic Systems, Westlake, OH, USA; BacT/ALERT MB susceptibility kit, bioMérieux Inc., Durham, NC, USA). This technique can provide DST results within a month [15]. Among the liquid-based culture systems, the most commonly used systems are BACTEC 460 that detects carbon dioxide production and MGIT that detects oxygen consumption [14].

Molecular DSTs have been developed to offer an advantage over conventional phenotypic tests that are more time-consuming. These tests can be used to diagnose TB through amplification of nucleic acids. They detect drug resistance by identifying genetic mutations in specific genes. These genotypic tests are more rapid and accurate than the phenotypic DSTs [16]. Molecular DSTs are divided broadly into two types; probe-based assays and sequence-based assays.

The probe-based DSTs include line probe assays (LPA) and GeneXpert (Cepheid Inc., Sunnyvale, CA, USA). In 2008, WHO approved the use of commercial LPAs (the INNO-LiPA Rif.TB assay [Innogenetics, Ghent, Belgium] and the GenoType MTBDR*plus* version 1 [MTBDRplus; Hain Lifescience GmbH, Nehren, Germany]) for detecting MTB and drug resistance [17]. In 2015, WHO performed a systemic review of the accuracy of commercial LPAs (MTBDR*plus* version 1, version 2, and Nipro NTM+MTBDR [NIPRO Corp., Osaka, Japan]) for detecting MTB

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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 MTBDR*plus* 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 *rpo*B gene for rifampicin resistance and in the *kat*G gene and the *inh*A promoter region for isoniazid resistance [20,21]. Although MTBDR*plus* 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 MTBDR*sl* (Hain Lifescience GmbH) that was developed to detect resistance to ethambutol (mutation in *emb*B), fluoroquinolones (mutations in *gyr*A and *gyr*B), 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 clofazimine. 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-

Table 1. Classification of medication for multidrug-resistant tuberculosis in 2016

Group	Classification	Medicine
A	Fluoroquinolones	Levofloxacin
		Moxifloxacin
		Gatifloxacin
B	Second-line injectable agents	Amikacin
		Capreomycin
		Kanamycin
		Streptomycin
C	Other core second-line agents	Ethionamide or prothionamide
		Cycloserine or terizidone
		Linezolid
		Clofazimine
D	Add-on agents	
D1		Pyrazinamide
		Ethabutol
		High-dose isoniazid
D2		Bedaquiline
		Delamanid
D3		*Para*-aminosalicylic acid
		Imipenem/cilastatin
		Meropenem
		Amoxicillin/clavulanate

Modified from World Health Organization treatment guidelines for drug-resistant tuberculosis [5].

Table 2. Classification of medication for multidrug-resistant tuberculosis in 2019

Group	Medicine	Step
A	Levofloxacin or moxifloxacin	Include all three medicines (unless they cannot be used)
	Bedaquiline	
	Linezolid	
B	Clofazimine	Add one or both medicines (unless they cannot be used)
	Cycloserine or terizidone	
C	Ethambutol	Add to complete a four- to five drug regimen when medicines from groups A and B cannot be used
	Delamanid	
	Pyrazinamide	
	Imipenem-cilastatin or meropenem	
	Amikacin or streptomycin	
	Ethionamide or prothionamide	
	Para-aminosalicylic acid	

Modified from World Health Organization consolidated guidelines on drug-resistant tuberculosis treatment [2].

ing to the results of this IPD-MA, the updated guidelines have developed a new drug classification that divided drugs for MDR-TB into three groups (A, B, and C) after prioritizing their effectiveness and toxicities (Table 2). Oral regimens are preferred for almost all patients. Fluoroquinolones (levofloxacin or moxifloxacin), bedaquiline, and linezolid are strongly recommended for a longer MDR-TB regimen. These three drugs should be included in the initial therapy unless there is an evidence of drug resistance or a risk of toxicity. In IPD-MA, when compared with injectable-free regimen, regimen including streptomycin or amikacin was associated with increased treatment success, while regimen including kanamycin or capreomycin showed poorer outcomes. Kanamycin treatment was associated with lower treatment success, and capreomycin was associated with lower success and higher mortality [35]. Injectable agents have critical toxicities (including hearing loss and nephrotoxicity) and poor adherence to drug. Considering the benefits and harms of injectable agents, they are not recommended in the initial MDR-TB regimen and have been downgraded to group C [35]. WHO recommended that amikacin and streptomycin be considered only when the patient's isolate is susceptible to these drugs and high-quality monitoring of hearing loss is possible. However, the poorer outcomes of injectable agents could be attributed to several confounding factors, such as drug changes 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 *gyr*A and *gyr*B genes [38]. Fluoroquinolone resistance in MTB is usually caused by mutations in the *gyr*A 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].

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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-dihydro-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

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

Group	Medicine
A	Levofloxacin or moxifloxacin
	Bedaquiline
	Linezolid
B	Clofazimine
	Cycloserine
C	
C1[a)]	Amikacin (streptomycin)[b)]
	Ethambutol
	Imipenem or meropenem
	Para-aminosalicylic acid
	Prothionamide
	Pyrazinamide
C2	Delamanid[c)]

Modified from Korean guidelines for tuberculosis, 4th ed. [37].
[a)]The order of drug in group C1 does not mean the ranking of drug selection. [b)]Amikacin is preferred over streptomycin. Kanamycin can be used as a substitute for amikacin. [c)]Delamanid can be used as a substitute for bedaquiline.

drugs) at the initiation of the treatment. If regimens cannot be built based on the optimal regimen involving drugs from groups A and B due to drug resistance and toxicity, drugs from group C can be used. If the regimen cannot include all three agents from group A, initial treatment should be started with five agents, including all available agents in groups A and B. Injectable agents (amikacin or streptomycin), delamanid, pyrazinamide, or ethambutol can be chosen preferably. Susceptibility testing for fluoroquinolones should be performed prior to initiating MDR-TB treatment. Among the group A agents, fluoroquinolones have a high rate of resistance (up to 33%) [57], and it is the only drug class for which rapid molecular tests are available. Resistance to fluoroquinolones was associated with poor outcomes (failure of treatment or relapse) in MDR-TB treatment [58]. Delamanid and second-line injectable drugs could be useful alternatives in fluoroquinolone-resistant MDR-TB. The possibility of treatment success in MDR-TB depends on patient factors (HIV infection, diabetes mellitus, low weight, large disease burden on chest radiography, genetic factors, and alcohol abuse), mycobacterial factors (resistance patterns, mycobacterial load), and optimal management (building of effective regimen and management of adverse effects and toxicities) [2,35]. American Thoracic Society, Centers for Disease Control and Prevention, European Respiratory Society, and Infectious Diseases Society of America (ATS/CDC/ERS/IDSA) published new guidelines for the treatment of drug-resistant-TB (including MDR-TB and isoniazid-resistant TB) in 2019. The WHO and ATS/CDC/ERS/IDSA guidelines were largely consistent, but there were some differences between two guidelines. ATS/CDC/ERS/IDSA recommended larger number of drugs in building regimen and focused less on shorter regimen and injectable agents. ATS/CDC/ERS/IDSA guidelines recommended that the regimens should include at least five drugs at the initiation of the treatment and four drugs in the continuation phase [42]. These guidelines recommended six steps for building regimen: step 1, choose later generation of fluoroquinolone (levofloxacin or moxifloxacin); step 2, choose both of the prioritized drugs (bedaquiline and linezolid); step 3, choose both of the two effective drugs (clofazimine and cycloserine); step 4, if a regimen cannot be built with five effective oral drugs, and the isolate is susceptible, use one of injectables (amikacin or streptomycin); step 5, if needed or if oral agents are preferred over injectable agents in step 4, injectables can be replaced by delamanid, pyrazinamide, or ethambutol; and step 6, if the options are limited, and a regimen of five effective drugs cannot be assembled, consider use of ethionamide/prothionamide, imipenem/meropenem plus clavulanate, *para*-aminosalicylic acid, or high-dose isoniazid [42].

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-

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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

Jong Geol Jang, https://orcid.org/0000-0001-8040-5363

Jin Hong Chung, https://orcid.org/0000-0003-1829-3051

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