Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis: Principles of management

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ABSTRACT

Multidrug-resistant tuberculosis (MDR-TB)/rifampicin-resistant TB (RR-TB) is human-made problem and emerging due to poor management of TB and is a threat to control of TB. Early suspicion and diagnosis are important. Culture and drug susceptibility testing are gold standards, but newer molecular methods help in rapid diagnosis. Once diagnosed, prompt treatment should be started, preferably under direct observation. Treatment can be standardized or individualized. Conventional regimen takes up to 24 months but recently shorter regimen of up to 12 months was introduced in specific subset of MDR-TB/RR-TB patients. Management of MDR-TB/RR-TB is complicated, costlier, and challenging and is a concern for human health worldwide. It must be emphasized that optimal treatment of MDR-TB/RR-TB alone is not sufficient. Efforts must be made to ensure effective use of first- and second-line anti-TB drugs.

KEY WORDS: GeneXpert, line probe assays, multidrug-resistant tuberculosis, rifampicin-resistant tuberculosis, shorter regimen

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INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is defined as disease due to *Mycobacterium tuberculosis* that is resistant to isoniazid (H) and rifampicin (R) with or without resistance to other drugs. Rifampicin-resistant TB (RR-TB) defined as resistance to rifampicin detected using genotypic or phenotypic methods with or without resistance to other first-line anti-TB drugs. MDR-TB/RR-TB has been an area of growing concern to human health worldwide and posing a threat to the control of TB. The Global TB Report 2016 estimated that of 3.9% newly diagnosed and 21% of previously treated TB cases had MDR-TB. It has been estimated that 580,000 cases of TB resistant to at least rifampicin (RR-TB) globally in 2015, of whom, 480,000 were having resistant to both rifampicin and isoniazid (MDR-TB), and 250,000 deaths occurred due to MDR-TB/RR-TB in 2015 globally. Out of estimated 580,000 MDR-TB/RR-TB cases, only 132,120 (23%) were detected, and even fewer 124,990 (20%) started treatment, and only 52% of them were treated successfully.[1] In India, estimates showed that the prevalence of MDR-TB among new and previously treated patients was 2.5% and 16%, respectively. It is estimated that 130,000 cases of MDR-TB/RR-TB emerged in India, of which, 79,000 were among notified cases of TB in 2015. Out of 79000 MDR-TB/RR-TB cases, only 28876 (36%) were diagnosed, 26988 (34%) were started on treatment, and treatment success rate was only 46%.[1] MDR-TB/RR-TB is emerging as major problem due to poor management of drug sensitive as well as drug resistance TB. MDR-TB/RR-TB is treatable but is very expensive and requires long duration of treatment and contains potentially toxic drugs. This write-up aims to discuss the principles of diagnosis and treatment of MDR-TB/RR-TB.

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PRINCIPLES OF DIAGNOSIS OF MULTIDRUG-RESISTANT TUBERCULOSIS/RIFAMPICIN-RESISTANT TUBERCULOSIS

Early suspicion, diagnosis, and appropriate treatment of MDR-TB/RR-TB are essential to prevent morbidity, mortality, and transmission of MDR-TB/RR-TB. A "presumptive case of MDR-TB" is defined as a TB patient who fails new treatment regimen and retreatment regimens with first-line anti-TB drugs who is sputum smear positive at the end of the 4th month of treatment or later and close contacts of drug-resistant TB cases.[2] Diagnosis of MDR-TB/RR-TB is based on clinical, radiological, and bacteriological evidence. Clinical evidence comprises of the symptoms and signs suggestive of TB and past history of antitubercular treatment. History of prior treatment with antitubercular drugs is most important. The main predictor of resistance to a particular drug is the demonstration of its prior use in monotherapy for more than 1 month. To obtain evidence of possible inadvertent or direct monotherapy, it is essential to be meticulous in obtaining the history of anti-TB treatment in all presumptive cases of MDR-TB. There should be a detailed evaluation into the drugs used, the drug dosages if previous drug prescriptions are available, whether the drugs were fixed dose combinations or separate drugs, their reliability in terms of WHO approved bioavailability, whether the patients were compliant to these drugs, supervised or unsupervised treatment and any drug intolerance that included partial or complete drug defaulting. Any real masked monotherapy previously received by the patient can be identified with reasonably good accuracy, and one can accurately predict resistance to specific drugs and prevent their inclusion in the retreatment plan.[3,4] The other important aspects of history include contacts with known case of resistant TB and patient's place of residence which may have a high prevalence of drug resistance. Although radiological worsening is not a very reliable indicator for predicting drug resistance, it serves to compliment the clinical and bacteriological evidence of the patient. Change in size of cavities and increase in the size of existing lesions and appearance of new lesions are signs of disease progression and activity.

The bacteriological evidence serve as the gold standard in the detection of MDR–TB/RR-TB. This is based on sputum smear microscopy and culture of *M. tuberculosis* and drug susceptibility testing (DST). Sputum smear microscopy after starting standard chemotherapy can show a positive, negative, or suboptimal response. While positive response is characterized by sputum conversion at 2/3 months of chemotherapy, a negative response could mean persistent smear positivity at the end of 3 months of adequate chemotherapy and a suboptimal response by an initial fall in the sputum grade followed by a gradual rise - the so-called "fall and rise" phenomenon while the patient is on antitubercular treatment. The last two patterns increase the probability of drug-resistant TB.

Diagnosis is confirmed by DST from reliable and reputed laboratories under constant quality control. However, one has to keep in mind, the limitation of highly specific DST because the technique is complex, difficult to perform accurately even when skilled personnel is available, and laboratory facilities are of high standard.[5] Further, one should realize that laboratories vary in reliability; errors may occur in laboratories, different DST reports are obtained from the same patient from different laboratories. There is often lack of standardization, coordination, and cross-checking by national and supranational reference laboratories. Susceptibility testing for isoniazid, rifampicin, fluoroquinolones, and the injectable drugs (kanamycin, amikacin, capreomycin) is very reliable. For other drugs, it is less reliable, and basing individualized treatments on DST for these drugs should be avoided. The effectiveness or ineffectiveness of a drug cannot be predicted by DST with 100% certainty.[6] Furthermore, the DST to second-line drugs (SLDs) is very variable. Keeping above facts in mind, it is pertinent that DST should not be accepted uncritically.

Molecular techniques have been used for identification of resistance-associated mutation. WHO with stop TB partnership endorsed line probe assays (LPAs) in low-resource countries in 2008. LPAs can do rapid screening of patients with MDR-TB/RR-TB risk within 2 days.[7,8] The Xpert MTB RIF assay endorsed by WHO in 2010 enables simultaneous detection of *M. tuberculosis* and rifampicin resistance (reliable proxy for MDR-TB) directly from sputum and other extrapulmonary specimen except blood in <2 h.[8-10] The assay is robust enough to be performed outside of conventional laboratories at district and subdistrict level of health system but requires uninterrupted power supply. It provides accurate results and can allow rapid initiation of MDR-TB/RR-TB treatment pending results from conventional culture and DST.[11,12] WHO recently recommended second LPA, a rapid diagnostic test MTBDRsL that identifies genetic mutation in MDR strains that detect resistance to fluoroquinolones and injectable second-line anti-TB drugs.[13]

PRINCIPLES OF TREATMENT OF MULTIDRUG-RESISTANT TUBERCULOSIS/RIFAMPICIN-RESISTANT TUBERCULOSIS

For treatment of MDR-TB/RR-TB, standardized, empirical, and individualized approaches have been laid down.[2,14-17] Individualized treatment based on individual DST and prior treatment history is costly and needs skilled professionals; standardized treatment is simple, less costly, and same treatment is given to all patients. Designing an individualized appropriate regimen needs skill, and treatment of MDR-TB/RR-TB is very difficult in the hands of many physicians with restricted knowledge who dare to treat these patients and create worsening problems. Therefore, individualized treatment needs specialized physicians experienced in dealing with such cases since this treatment represents the patient's last chance of a cure.

Ideally, an appropriate treatment regimen should consist of pyrazinamide and at least four new drugs selected from five groups of anti-TB drugs in hierarchical order which the patient has not taken previously or to which bacilli is considered to be sensitive[2] but WHO has reclassified the anti-TB drugs used for MDR-TB in 2016 in four groups-A, B, C, and D [Table 1]. In patients with MDR-TB/RR-TB, a regimen with at least five effective anti-TB drugs during the intensive phase is recommended, including pyrazinamide and four core second-line anti-TB drugs - one chosen from Group A (fluoroquinolones: levofloxacin, moxifloxacin, and gatifloxacin), one from Group B (second-line injectable drugs: kanamycin, amikacin, capreomycin), and at least two from Group C (other core second-line drugs: ethionamide/prothionamide, cycloserine/terizidone, linezolid, and clofazimine). If the minimum of effective anti-TB cannot be composed as above, one drug from Group D2 (bedaquiline and delamanid) and other drugs from D3 (para-aminosalicylic acid [PAS], imipenem-cilastatin, meropenem, amoxicillin-clavulanate, and thioacetazone) may be added to bring the total number of drugs to five. The regimen may be further strengthened with rest of Group D1 (high-dose isoniazid and/or ethambutol). While streptomycin is not usually included with the second-line drugs, it can be used as the injectable drug of the core MDR-TB regimen if none of the three other injectable drugs can be used and if the strain can be reliably shown not to be resistant. Thioacetazone should not be used if the patient is HIV seropositive.[18] Intensive phase including injectables should be given for at least 8 months for most patients which can be modified depending on the response of the patient, and the total duration of treatment is at least 20 months which can be prolonged up to 24 months depending on the response of the patient. Pyrazinamide is usually continued for the entire treatment especially if there is extensive disease. If the patient has minimal disease, pyrazinamide can be stopped with injectables at the end of intensive phase. Bedaquiline or delamanid are used for 6 months in intensive phase and are presently not recommended for whole treatment duration.

A new shorter regimen for treatment for subset of MDR-TB/RR-TB patients have been introduced recently. In patients with MDR-TB/RR-TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents have been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9–12 months may be used instead of a conventional regimen of 20–24 months. The intensive phase of 4 months which may be extended to 6 months in case of lack of sputum smear conversion consists of gatifloxacin or moxifloxacin, kanamycin, prothionamide, clofazimine, high-dose isoniazid, pyrazinamide, and ethambutol. This is followed by a continuation phase of 5 months which consist of gatifloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide.[18]

It is important that a single drug should never be added to a failing regimen, and it is ineffective to combine two drugs of the same group or to add a drug potentially ineffective because of cross-resistance. No drug should be kept in reserve, and the most powerful drugs should be used initially and in maximum combination so as to ensure that first battle is won and won permanently. All patients initiated on treatment and their family members should be intensively counseled before treatment initiation and during all follow-up visits. To reduce the risk of development of resistance to second-line anti-TB drugs and promote optimal treatment outcomes, all efforts should be made to administer treatment under directly observed treatment (DOT) over the entire course of treatment. If DOT is not possible, attempts to ensure treatment adherence should be made by checking empty blister packs during follow-up visits every month.[19,20] All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts as it is the last resort that stands between life and death.

Extrapulmonary MDR-TB/RR-TB is treated with the same regimen and duration as pulmonary MDR-TB/RR-TB. If the patient has symptoms suggestive of central nervous system involvement and is infected with MDR-TB/RR-TB, the regimen should use drugs that have adequate penetration into the central nervous system.[21] Rifampicin, isoniazid, pyrazinamide, prothionamide/ethionamide, and cycloserine have good penetration into the cerebrospinal fluid (CSF); kanamycin, amikacin, and capreomycin do so only in the presence of meningeal inflammation; PAS and ethambutol have poor or no penetration. The fluoroquinolones have variable CSF penetration, with better penetration seen in the later generations. Linezolid is believed to penetrate the central nervous system and has been used in meningitis treatment. Imipenem has

Table 1: Drugs recommended for the treatment of rifampicin-resistance tuberculosis/multidrug-resistant tuberculosis

Groups	Drugs
A. Fluoroquinolone	Levofloxacin
	Moxifloxacin
	Gatifloxacin
B. Second-line injectable agents	Amikacin
	Capreomycin
	Kanamycin
	Streptomycin
C. Other core second-line agent	Ethionamide/prothionamide
	Cycloserine/terizidone
	Linezolid
	Clofazimine
D. Add on agents	
D1	Pyrazinamide
	Ethambutol
	High-dose isoniazid
D2	Bedaquiline
	Delamanid
D3	Para-aminosalicylic acid
	Imipenem-cilastatin
	Meropenem
	Amoxicillin-clavulanate
	Thioacetazone

good central nervous system penetration, but children with meningitis treated with imipenem had high rates of seizures, and meropenem is preferred for meningitis cases and children.[21-23] There is no data on central nervous system penetration of clofazimine, clarithromycin, Bedaquiline, and delamanid.

Surgical treatment should be considered as an adjunct to chemotherapy whenever applicable and when results of chemotherapy are very unpredictable. Adjuvant use of corticosteroids can be beneficial in conditions such as severe central nervous system or pericardial involvement. Corticosteroids do not increase mortality when the patient is on effective regimen and should be used with tapering of doses over several weeks.[24] The immunomodulators may have the potential to improve outcomes in all TB including MDR-TB/RR-TB as seen in evidence reviewed by expert group in 2007,[25] but still, evaluation of efficacy and safety of such therapy is needed before any recommendation is made.

MDR-TB/RR-TB treatment should include nutritional assessment and counseling of all patients. Because of disease process, patient appetite is reduced and tends to be malnourished; in addition, second-line anti-TB drugs can further reduce appetite. Patients should be properly counseled for adequate food intake. One such step is to provide free food which is thought to improve the quality of life and may improve treatment adherence,[26] but further research is necessary. Addition of vitamins probably does not improve weight gain and also no studies have assessed their effect on quality of life;[26] but they may be added to treat specific deficiencies such as Vitamin A. Furthermore, Vitamin B6 should be given if treatment regimen consists of cycloserine, terizidone, high-dose isoniazid, or linezolid to prevent neurological side effects.

CONCLUSION

Treatment of MDR-TB/RR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. MDR-TB/RR-TB is a human-made problem, and its emergence can be prevented by prompt diagnosis and effective treatment of all TB case. Adoption of directly observed treatment, short-course to prevent the MDR-TB/RR-TB and careful introduction of SLDs to treat patients with MDR-TB/RR-TB are the top priorities for the proper management of MDR-TB/RR-TB and to prevent the development of extensively drug-resistant TB.

Conflicts of interest
There are no conflicts of interest.

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