Review Article

Current Treatment of Multidrug Resistant and Rifampicin Resistant Tuberculosis

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Abstract

Multidrug- and rifampicin-resistant tuberculosis (MDR-TB/RR-TB) has been an area of growing concern to human health worldwide and posing a threat to the control of tuberculosis (TB). Proper treatment of every diagnosed case of MDR-TB/RR-TB is of paramount importance. For the treatment of MDR-TB/RR-TB, standardised, empirical and individualised approaches have been laid down. There can be two types of treatment regimen — conventional and shorter regimen. A conventional regimen of at least five effective anti-TB drugs (ATDs) during the intensive phase is recommended, including pyrazinamide and four core second-line ATDs. Intensive phase including injectables should be given for atleast eight months. The total duration of the treatment is atleast 20 months which can be prolonged upto 24 months depending upon the response of the patient. Shorter regimen for the treatment for subset of MDR-TB/RR-TB patients who have not been previously treated with second-line drugs and in whom resistance to flouroquinolones and second-line injectable agents has been excluded can given for 9-11 months. The intensive phase of 4 to 6 months consists of kanamycin, high dose moxifloxacin, ethionamide, clofazimine, pyrazinamide, high-dose isoniazid and ethambutol, followed by the continuation phase of five months that consist of high dose moxifloxacin clofazimine, pyrazinamide and ethambutol. Extra-pulmonary MDR-TB/RR-TB including TB meningitis is treated with a longer regimen with same duration as pulmonary MDR-TB/RR-TB. All patients initiated on treatment and their family members should be intensively counselled prior to the treatment initiation and during all the follow-up visits. Surgery may be considered with recommended MDR-TB/RR-TB regimen only with good surgical facilities, trained and experienced surgeons and with careful selection of the patients. The treatment outcomes varied from 50% to 80% in different studies.
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Key words: Multidrug/Rifampicin resistant tuberculosis, Conventional regimen, Shorter regimen, Lung resection, Surgery.

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) is defined as resistance to rifampicin detected using genotypic or phenotypic methods with or without resistance to other first-line anti-TB drugs. Multidrug- and rifampicin-resistant TB (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 Tuberculosis Report 2018[1] estimated that 558,000 cases of RR-TB and 82% out of them had MDR-TB globally in 2017. Out of 558,000 cases of MDR-TB/RR-TB, only 139,114 (25%) cases were given treatment in 2017. In India, it is estimated that 135,000 cases of MDR-TB/RR-TB emerge every year of which only 35950 (30%) were on treatment in 2017 with a success rate of 46%.[1] Early diagnosis and subsequently proper treatment of every diagnosed case of MDR-TB/RR-TB is of paramount importance. The present write up aims to give an overview of the treatment of MDR-TB/RR-TB.

Treatment of MDR-TB/RR-TB

For the treatment of MDR-TB/RR-TB, standardised, empirical and individualised approaches have been laid down.[2,3] Individualised treatment based on individual drug susceptibility testing (DST) and prior treatment history is costly and needs skilled professionals and quality assured bacteriological and molecular diagnostic labs, whereas standardised treatment is simple, less costly and same treatment is given to all patients. There can be two types of treatment regimens — conventional and shorter regimen, according to recent update from World Health Organization (WHO) in which they have also reclassified anti-tuberculosis drugs (ATDs) for MDR-TB/RR-TB.[4] Drugs and doses according to new classification is given in table 1.

Conventional Regimen for MDR-TB/RR-TB. In patients with MDR-TB/RR-TB, a conventional regimen of atleast five effective ATDs during the intensive phase is recommended, including pyrazinamide and four core second-line ATDs – one from group A (flouroquinolones: levofloxacin, moxifloxacin and gatifloxacin), one from group B (second-line injectable drugs: kanamycin, amikacin, capreomycin),

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Table 1. Drugs and doses recommended for the treatment of MDR/RR-TB (WHO 2016)

Groups	Drugs	Average Daily Dose	Daily Dosage (mg)	
			Minimum	Maximum
Flouroquinolones	Levofloxacin	7.5-10mg/kg	750	1000
	Moxifloxacin	7.5-10mg/kg	400	400
	Gatifloxacin	7.5-10mg/kg	400	400
Second-line injectable agents	Amikacin	15mg/kg	500	1000
	Kanamycin	15mg/kg	500	1000
	Capreomycin	15mg/kg	500	1000
	Streptomycin	15mg/kg	500	1000
Other core second-line agents	Ethionamide/Prothionamide	15-20mg/kg	500	1000
	Cycloserine/Terizadone	10-20mg/kg	500	1000
	Linezolid	600mg	600	600
	Clofazimine	4-5mg/kg	100	300
Add on agents				
D1	Pyrazinamide	25mg/kg	750	2000
	Ethambutol	15mg/kg	600	1200
	High dose isoniazid	16-20mg/kg	600	1500
D2	Bedaquiline	400mg OD for 2 weeks and then 200mg 3 times per week		
	Delamanid	100mg BD		
	PAS	200-300mg/kg	10g	12g
D3	Imipenem-Cilastatin	1000mg – 1000mg BD		
	Meropenem	1000mg TDS		
	Amoxicillin-Clavulanate	80mg/kg/day	500/125mg BD	1000/250mg BD
	Thioacetazone	150mg OD		

Definition of abbreviations: PAS= Para-amino salicylic acid; OD=Once daily; BD=Two times per day; TDS=Three times per day

and at least two from group C (other core second-line drugs: ethionamide/prothionamide, cycloserine/terizidone, linezolid and clofazimine). If the minimum of effective ATDs cannot be composed as above, one drug from group D2 (bedaquiline and delamanid) and other drugs from D3 (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/RR-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 human immunodeficiency virus (HIV) seropositive.[4] Intensive phase including injectable ATDs should be given for atleast for eight months for most of the patients, which can be modified depending upon the response of the patient. The total duration of treatment is atleast 20 months which can be prolonged upto 24 months depending upon the response of the patient. Pyrazinamide is usually continued for the entire treatment period, 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 may be used for six months in intensive phase and are presently not recommended for complete duration of the treatment.

It is important to remember 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.

Shorter Regimen for MDR-TB/RR-TB. In 2016, WHO approved the use of a shorter regimen for the treatment of subset of MDR-TB/RR-TB patients who have not been previously treated with second-line drugs and in whom resistance to flouroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB/RR-TB regimen of 9-11 months may be used instead of a conventional regimen of 20-24 months. The intensive phase of four months which may be extended to six months in case of lack of sputum smear conversion consists of kanamycin, high dose moxifloxacin, ethionamide, clofazimine, pyrazinamide, high-dose isoniazid, ethambutol, followed by the continuation phase of five months which consist of high dose moxifloxacin, clofazimine, pyrazinamide, ethambutol.[4-6] Doses of drugs given in shorter regimen is given in table 2.

Care and Support for Adherence for Patients of MDR-TB/RR-TB

All patients initiated on treatment and their family members should be intensively counselled prior to the initiation of the treatment and during all follow-up visits. To reduce the risk of development of resistance to second-line ATDs and for optimal treatment outcomes, all efforts should be made to administer the treatment under direct observation over the entire period of treatment. If treatment under observation is not possible, attempts should be made to ensure treatment adherence by checking empty blister packs during follow-up visits every month.[7] Prevention of treatment interruptions is important to increase the likelihood of the treatment success, measures to support the adherence, either by patients visit to health-care facilities or home visit by health-care staff or by using digital technologies (daily reminder) may be very important.[8] All possible 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.

Future Direction for Treatment of MDR-TB/RR-TB

World Health Organization has recently in 2018 revised the grouping of ATDs for use in MDR-TB/RR-TB patients into three groups based on individual patient data meta-analysis of more than 13000 patients depending on their individual efficacy, risk of relapse, treatment failure and death.[9-12] Drugs and their doses according to recent classification and weight bands are given in table 3. WHO consolidated guidelines recently in the year 2019 and suggested that MDR-TB/RR-TB patients on longer regimens should have all three Group A agents and at least one Group B agent initially at the start of anti-TB therapy to ensure treatment efficacy and that at least three agents are included for the rest of the treatment after bedaquiline is stopped. However, if only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Group A and B alone, Group C agents can be added to complete the regimen. Kanamycin and capreomycin are not to be included for the treatment of MDR-TB/RR-TB patients on longer regimens.[12] Government of India is in the process of adopting the changes based on this recent WHO guidelines.

Treatment of Extra-pulmonary and TB Miningitis MDR-TB/RR-TB

Extra-pulmonary MDR-TB/RR-TB including TB meningitis is treated with the longer regimen with same 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.[12] 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 flouroquinolones have variable CSF penetration, with better penetration seen in the later generations. Levofloxacin and moxifloxacin penetrates central nervous system well. Linezolid is believed to penetrate the central nervous system, and has been used in meningitis treatment. Imipenem has 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.[13-18] There is no data available on central nervous system penetration of clofazimine, clarithromycin, bedaquiline and delamanid.

Table 2. Drugs and doses used in shorter MDR regimen

Product	Weight Group		
	<33 Kg	**33 to 50 Kg**	**>50 Kg**
Moxifloxacin	400mg	600mg	800mg
Clofazimine	50mg	100mg	100mg
Ethambutol	800mg	800mg	1200mg
Pyrazinamide	1000mg	1500mg	2000mg
Isoniazid	300mg	400mg	600mg
Prothionamide/Ethionamide	250mg	500mg	750mg
Kanamycin	15mg/Kg body weight (maximum 1 g)		

Table 3. Drugs and doses recommended for the treatment of MDR-TB/RR-TB (WHO 2018)

Group	Medicine	Weight Based Patients for Older Than 14 Years				
	Weight Groups	30-35 Kg	36-45 Kg	46-55 Kg	56-70 Kg	>70 Kg
A	Levofloxacin	750 mg	750 mg	1000 mg	1000 mg	1000 mg
	Moxifloxacin					
	Standard dose	400 mg	400 mg	400 mg	400 mg	400 mg
	High dose	400/600 mg	600 mg	600/800 mg	800 mg	800 mg
	Bedaquilline	400mg OD for 1st 2 Weeks;				
		Then 200mg OD on MON/WED/FRI for 22 weeks				
	Linezolid	600 mg	600 mg	600 mg	600 mg	600 mg
B	Clofazimine	100 mg	100 mg	100 mg	100 mg	100 mg
	Cycloserine or Teridone	500 mg	500 mg	750 mg	750 mg	750 mg
C	Ethambutol	800 mg	800 mg	1200 mg	1200 mg	1200 mg
	Delamanid	100mg BD	100mg BD	100mg BD	100mg BD	100mg BD
	Pyrazinamide	1000mg	1500mg	1500mg	1500mg	2000mg
	Imipenem Cilastatin	2 Vials (1g + 1g) BD				
	Meropenem	1 Vial TDS or 2 Vials BD				
	Amikacin (500 mg/2mL vial)	2.5mL	3mL	3 - 4mL	4mL	5mL
	Streptomycin	500mg	500mg	750mg	750mg	1000mg
	Ethionamaide or Prothionamide	500mg	500mg	750mg	750mg	1000mg
	Para-amino salicylic acid	4g BD	4g BD	4g BD	4g BD	4-6g BD

Definition of abbreviations: OD=Once daily; BD=Two times per day; TDS=Three times per day

Treatment of MDR-TB/RR-TB in Pregnancy

Use of kanamycin, capreomycin, amikacin, streptomycin, prothionamide and ethionamide are usually contraindicated during pregnancy. Following these changes have been made in the recent WHO guidelines,[12] update, these agents are expected to be used less frequently in future. Knowledge about the safety of bedaquiline and delamanid during pregnancy and during breast feeding is sparse. It is recommended that in such cases, a longer regimen be individualised to include the components with a safety profile that is better established.[12]

Role of Surgery

Surgery has been in use for treating TB patients before the advent of chemotherapy and it remains one of the treatment options. With inadequate regimens to treat MDR-TB/RR-TB and the risk of serious sequelae, the role of pulmonary surgery is being re-evaluated as a means to reduce the amount of lung tissue with intractable pathology, reduce bacterial load, and thus, improves the prognosis. Individual patient data meta-analysis and systematic review[19,20] evaluated the effectiveness of different forms of elective surgery as an adjunct to multidrug medical therapy for MDR-TB/RR-TB and concluded that there was a statistically significant improvement in cure and successful treatment outcomes. However, when the patients who underwent partial lung resection and those who had a more radical pneumonectomy *versus* patients who did not undergo surgery, those who underwent partial lung resection had statistically significantly higher rates of treatment success. Prognosis appeared to be better when partial lung resection was performed after culture conversion. This effect was not observed in patients who underwent pneumonectomy.[21] Partial lung resection for patients with MDR-TB/RR-TB is to be considered with recommended MDR-TB/RR-TB regimen only under conditions of good surgical facilities, trained and experienced surgeons, and with careful selection of the candidates.

Role of Steroids and Immunomodulators

Adjuvant use of corticosteroids can be beneficial in conditions, like 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.[22] The immunomodulators may have the potential to improve the outcomes in all TB cases including MDR-TB/RR-TB as observed in a evidence-based review by an expert group in 2007[23] but still evaluation of efficacy and safety of such therapy is needed before any recommendation is made.

Monitoring and Evaluation of Treatment in MDR-TB/RR-TB

Monitoring of the treatment should be done with bacteriological, radiological and clinical methods. Sputum specimens should be obtained for semi quantitative smear and culture every month from the third month onwards

during the intensive phase of the therapy. After sputum conversion, smear and culture examinations may be done once in three months until the end of the therapy.[3,12] If such a large number of smears and cultures for follow-up are not possible, then at least five smears and cultures must be done for follow up (4, 6, 12, 18 and 24 months), radiographs should be taken every six months whereas clinical monitoring preferably should be done every month.[7,24-28]

Monitoring adverse drug reactions should be done to ensure appropriate action for prompt response along with monitoring of the treatment outcome.[27] Electrocardiography audiometry and specific biochemical tests should also be monitored when certain drugs, such as bedaquilline, clofazimine and amikacin are included in the regimen.

Outcome of Treatment

The outcome of the treatment of MDR-TB/RR-TB is not very favourable and varied from 50% to 80% in different studies.[28-34]

Conclusions

Treatment of MDR-TB/RR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. With the advent of newer drugs and repurposed drugs to treat MDR-TB/RR-TB, new and better efficacious regimens are available. As MDR-TB/RR-TB is a man-made problem, its emergence can be prevented by prompt diagnosis and effective treatment of all TB cases. Effective use of first-line anti-tuberculosis drugs in every new patient of tuberculosis to prevent the MDR-TB/RR-TB and proper use of second-line drugs to treat patients with MDR-TB/RR-TB are the top priorities for the effective control of MDR-TB/RR-TB.

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