

Review on Drug Resistant Tuberculosis

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Date of Submission: 15/02/2022

Date of Review: 21/04/2022

Date of Acceptance: 20/05/2022

ABSTRACT

Introduction: An estimated 9.9 million people fell ill with tuberculosis globally in 2020 with India and China contributing a major percentage to the burden of TB. India is grouped under high TB, high HIV associated TB and MDR TB burden countries and 1.24 lakh fell ill with drug resistant TB out of which 56000 were started on second line treatment in 2020. Annually India accounts for 27% of missing TB cases. **Diagnosis:** The major forms of drug resistant TB that are of clinical importance are INH mono-resistant TB, multidrug resistant TB, pre-XDR TB and XDR TB. WHO approved newer molecular tests for MTB detection and drug susceptibility tests. **Treatment:** Few newer drugs and few previously used drugs are showing promise when used in combination which have come up in recent years. Bedaquiline based regimens are showing improved cure rates. **Conclusion:** Guidelines based regimens should be strictly adhered to by both public and private TB case treating physicians.

KEYWORDS: Multi drug resistant tuberculosis (MDR TB), Molecular tests for tuberculosis, Programmatic management of Drug resistant tuberculosis (PMDT), Bedaquiline.

INTRODUCTION:

An estimated 9.9 million people fell ill with tuberculosis globally in 2020 with India and China contributing a major percentage to the burden of TB. ^[1]The number of people treated with drug resistant TB was 1.5 lakh globally in 2020 with treatment success rate being 59%. ^[2]

Globally in 2020, 71% of people diagnosed with bacteriologically confirmed TB were tested for Rifampicin resistance. 1,32,222 of 3 million cases were MDR TB and 25681 were pre-XDR or XDR cases. ^[2]

According to an estimation, worldwide, drug resistant cases have doubled between 2013-2018. ^[3]India accounted for 26.4 lakh TB cases in 2019 with 82% successfully completing the treatment and an estimated 1.24 lakh fell ill

with drug resistant TB out of which 56000 were started on second line treatment. ^[1]India is grouped under high TB, high HIV associated TB and MDR TB burden countries. ^[2]

The drug resistant TB accounts for 25% of the TB related deaths annually. ^[3]Deaths due to MDR TB cases after treatment initiation & completion is 25% and for XDR TB more than 35% ^[3]as reported from selected study trials but overall mortality remains at 45% for MDR TB and 60% for XDR TB annually.

The global incidence of tuberculosis is declining only at 1.5% per year. ^[4]In high burden TB countries less than 50% of estimated TB patients have documented treatment success, with only 45% being permanently cured ^[4], hence the risk of drug resistance can be as high as 55% in the annual estimated cases worldwide.

INDIAN SCENARIO :

Globally 4.1% of new TB patients and 19% of previously treated patients have multidrug resistance TB whereas a national survey in India showed 2.84% of new cases and 11.6% of previously treated cases in India have MDR TB. ^[5] Among MDR TB cases additional resistance to any Fluoroquinolone was 21.82% and 3.58% to any second line injectable in India. This survey was done on sputum smear positive cases only, collected from RNTCP run centres and overall intake has 5320 samples across the country. According to the survey, males contributed to 72% of all the cases taken in the study, XDR detected was 1.3% among all patients, Mono-resistance observed was 2.22% among new cases and 2.48% among previously treated cases. For Isoniazid it was 3.85% among new cases and 7.6% among previously treated cases, Pyrazinamide resistance similarly was 4.11% and 4.07%, Levofloxacin resistance was 0.1% and 0% which was also seen with Moxifloxacin.

The MDR in Telangana was 0% among new cases and 15% among previously treated cases. Drug resistance other than MDR was 30% among new cases and 21.2% among

previously treated cases. [5]

Missing Cases:

In many countries, there is a high ratio of prevalent to notified TB cases, suggesting many unreported TB cases. Nearly 4 million TB cases (40% of incident cases) are not reported to national programmes. [4] The high burden countries for drug resistant TB cases, account for 92% of missing cases in the world. About 60% of all TB patients, initiate care in private sector but they report only 10% of these cases. [4] India which has 23% of global TB cases also has 27% of world's missing patients (nearly 1 million). [6]

Areas Requiring Attention:

One study estimated that 37.6% of patients with new smear negative TB remained undiagnosed despite evaluation at Government facilities whereas the estimates for smear positive cases (new and retreatment) who were lost to follow up were at 11%. [6] In an Indian study, Rifampicin resistance of 5.3% was detected among confirmed cases in sputum scarce suspected Pulmonary TB cases through Bronchial washings. [7] TB care in the private sector is often of poor quality due to lack of standardisation and regulations. [8] Prudent approach to tackle drug sensitive TB and drug resistant TB is to strengthen the public private mix (PPM) in all aspects of TB care.

All non-NTEP controlled institutes/groups come under PPM including public hospitals, medical colleges, corporate sector medical services, mission hospitals, non-governmental organisations. Among the various strategies being advocated, ensuring of patient-centred care and effective PPM mechanism for DR TB will help in tackling DR TB. [8]

Extrapulmonary Drug Resistance:

Extrapulmonary drug resistant TB forms a diagnostic and therapeutic dilemma. An Indian study reported 4.4% of drug resistant TB cases as having EPDR TB. 51% of them were lymph node TB cases followed by 19.7% spine TB, 12% Pleural TB and disseminated EP DRTB were 6.5%.

Among the DR cases of EPTB, MDR formed 54% of cases with Pre XDR seen in 40% and XDR in 6% of cases. [9] In 2015, the MDR EPTB among DR EPTB was 19% and XDR was 1% with Mono-resistance seen to INH was 1.6% and to Ofloxacin was 4.8%. [10]

Diagnosis Of Drug Resistance:

Detection of drug resistance requires bacteriological confirmation of TB and testing for drug resistance. In 2015, only one third of new bacteriologically confirmed TB and previously treated TB underwent drug sensitivity testing. [11] which was 33% of all bacteriologically confirmed cases in 2020. [2] Inappropriate treatments based on non-DST tests could result in highly drug resistant TB Strains. [11] Standard conventional method for drug susceptibility testing is proportional agar method on LJ medium but is time-consuming (3-8 weeks for culture). The propor-

tion method for DST in M7H10 agar has a faster turnaround time of 10-12 days. [12] Other solid culture method of Middle brook agar gives result in 10-12 days. [13] Liquid culture methods have higher sensitivity for detecting drug resistance, with shorter mean time of detection. [14] BACTEC Mycobacterium growth indicator tube (MGIT), a liquid culture method has a turnaround time of 10-30 days. [15] The limitations of liquid culture methods include prohibitive expenditure. [16]

Mutation Sites:

In MTB strains, drug resistance is mainly acquired by spontaneous mutation (single nucleotide polymorphisms SNPs). [11] 97% of resistance to Rifampicin is due to mutation in rpo B gene at 81bp hotspot region. Isoniazid resistance is acquired through mutations in the Kat G, Inh A genes. Kat G is seen in 50-90% of the cases. Emb B gene mutation leads to ethambutol resistance (47-62%). [11] Among aminoglycosides 60% of resistance is due to rrs-A mutation. Quinolone resistance occurs at gyr A region (60-70%). [11] However in 10-40% of drug resistant cases the mutation of development of resistance is not clear. [17]

Line Probe Assays:

Line probe assays involve DNA extraction, target amplification followed by hybridization of amplifications with specific probes. These amplification probe hybrids appear as coloured bands. [11] The turnaround time is 5-7 hours. [18] LPAs recommended by WHO include Genotype MTBDR plus, Genotype MTBDR sl and Nipro NTM+ MDR TB.

MTB DR plus detects Rifampicin and INH resistance (rpoB and Kat G) whereas MTBDR plus version 2.0 detects inhA promoter gene mutation as well. [7]

Genotype MTBDR sl version 1.0 & 2.0 also detect resistance to Ethambutol, Aminoglycosides and Fluoroquinolones. Nipro NTM+ MDRTB also has ability to detect important Mycobacterial and NTM species of M.avium, M.intracellulare, M.Kansasii. [19] In a multicentre study, sensitivity for MTB DR plus version 1.0 was 90.3% and specificity was 98.5%. The sensitivity for MTB DR plus version 2.0 was 90.3% and specificity was 98.5%. The Nipro NTM+ MDRTB showed sensitivity of 92% and specificity of 98.5% for Rifampicin resistance detection and for INH detection MTB DR plus & MTB DR plus version 2.0 showed sensitivity of 89% and specificity of 99.4% compared to sensitivity of 89.6% and specificity of 100% by Nipro NTM+ MDRTB LPA test. [19]

For second line drugs Genotype MTBDR sl version 2.0 has sensitivity and specificity between 91-100% for detection of fluoroquinolone resistance but shows variable rates for aminoglycoside resistance. LPAs, thus are rapid, simple and easy to perform but require complex laboratory infrastructure and expensive equipment. [11]

Indian studies have shown the sensitivity and specificity of MDR TB genotype to be 97.6% and 94.4% respectively

for detection of Rifampicin resistance against the gold standard of BACTEC MGIT-960 culture. The sensitivity for INH resistance has 83.3% and specificity was 93.8%.^[16]

PCR ASSAYS: Xpert MTB/ RIF (Cepheid US):

This test is recommended by WHO for diagnosis of Tuberculosis (Pulmonary and Extra-Pulmonary) and detection of Rifampicin resistance in adults and children. The Xpert MTB/RIF assay uses semi quantitative nested real time PCR for amplification and followed by hybridization to fine molecular beacon probes. Sensitivity and specificity among smear positive cases were 99% and 100% respectively and for smear negative cases 67% and 99% respectively. The detection time for Rifampicin resistance is as low as 2 hours with this test. INH resistance is not detected by this test. The newer updated version of Xpert MTB/RIF ultra system has a larger amplification chamber and two additional targets for detection of MTB. The MTB detection sensitivity is 16 bacilli/ml compared to 131 bacilli/ml with Xpert MTB/RIF system. Hence, it can be used in sputum scarce, sputum negative and extra pulmonary samples such as CSF, Lymph node and tissue samples.^[7] Among sputum scarce suspected TB cases Gene Xpert MTB/RIF could detect 56% pulmonary tuberculosis cases from bronchial washings where in 5.35% of these cases showed Rifampicin resistance.^[7] Gene Xpert OMNI is smaller, lighter and cheaper than Xpert systems and has a 4-hour battery and can be a point of care test.^[11]

Gene drive MTB/RIF ID kit (Epstein, UK) is a portable, low power requiring system and has an overall sensitivity for rpoB gene mutation of 72.3%. The fast-reporting time of 75 minutes makes it an excellent point of care test. The overall sensitivity of the Gene-drive system compared with culture was 90.8% for MTB detection and 72.3% for Rifampicin resistance whereas specificity for both was 100%.^[20]

GENE SEQUENCING:

Whole genome sequencing (WGS) and the new generation gene sequencing (NGS) generate sequences of unique DNA fragments followed by amplification, clustering (clonal amplification of simple DNA fragments) and automated single or paired end sequencing.^[21] However NGS has poor sensitivity while using sputum rather than culture isolate.^[22]

Pyrazinamide which shows sterilizing activity on MTB colonies, also has good penetration into lung tissues of MDR TB patients. Pyrazinamide resistance evaluation which is not done routinely confounds the MDR TB management because of which identification of Pyrazinamide resistance in a pre-requisite before starting MDR treatment regimen.^[23] Adding Pyrazinamide for MDR cases with PZA resistance increases the duration of treatment. The specific sites of mutation for Pyrazinamide are pncA gene and rpsA gene.^[23]

ANYPLEX MTB/MDR AND MTB/XDR:

A semi automated multiplex real time PCR method which can detect MTB, MDR-TB and XDR-TB from sputum, bronchial wash, culture isolates and fresh tissues.^[11] The

accuracy for detection of MTB is 83% in all samples, with specificity ranging from 94-100% in resistance detection and sensitivity between 50-100%.^[11]

TREATMENT FOR DRUG RESISTANT TB:

Treatment of drug resistant TB is challenging because of prolonged duration of treatment, toxicity, costs and sub-optimal outcomes.^[24]

DEFINITIONS

Multidrug resistant TB is defined as resistance to Isoniazid and Rifampicin with or without resistance for other anti-TB drugs.

Pre XDR (Pre-Extensively drug resistance) is defined as drug resistance to a Fluoroquinolone or an injectable (aminoglycoside) in a MDR TB patient.

XDR (Extensively drug resistance) is defined as MDR TB with resistance to Fluoroquinolones and to second-line injectables.

Mono-resistance (as in INH-mono resistance) is resistance seen with any one anti-tubercular drug.

Primary anti TB drug resistance occurs when a person develops infection after exposure to a drug resistant TB patient and acquired or secondary resistance due to poor adherence, drug malabsorption, inadequate regimen among patients taking TB medication, the latter being the most common.^[22]

The major forms of drug resistant TB that are of clinical importance are INH mono-resistant TB, multidrug resistant TB, pre XDR TB and XDR TB.

NATIONAL GUIDELINES:

DOTS plus introduced in 2000 was the first attempt by WHO in initiating treatment guidelines against Drug resistant TB. Programmatic management of drug resistant TB (PMDT) from 2006 saw integration of MDR TB treatment with national TB control programmes.

The 2011 PMDT guidelines advised 20 months regimen (with 8 months intensive phase), with use of at least four or possibly five effective drugs. The newer 2019 WHO guidelines classified the second line drugs into ABC groups Table 1 and recommended a longer regimen (18-20 months) and a shorter regimen (9-12 months) for MDR TB.^[25]

The longer Oral MDR/XDR-TB regimen includes 18-20 months with no separate IP or CP.[18-20 months LFX, BDQ(6 months or longer), LZD, CFZ, CS].^[26] Table 2

The shorter MDR regimen includes 4-6 months intensive phase with Kanamycin, Moxifloxacin, Prothionamide, Clofazamine, Pyrazinamide, High dose Isoniazid and Ethambutol followed by 5 months of Moxifloxacin, Clofazamine, Pyrazinamide and Ethambutol. Table 3

Cases which showed resistance or suspected having resistance to any of these drugs used or exposure to

GROUPS	DRUGS
Group A Include all three medicines	Levofloxacin (Lfx) or Moxifloxacin (Mfx) Bedaquiline (Bdq) Linezolid (Lzd)
Group B Add one or both medicines	Clofazimine (Cfz) Cycloserine(Cs) or Terizidone (Trd)
Group C Add to complete the regimen and when medicines from Group A and B cannot be used	Ethambutol (E) Delamanid (Dlm) Pyrazinamide (Z) Imipenem-cilastatin (Ipm-Cln) or Meropenem (Mpm) Amikacin (Am) or Streptomycin (S) Ethionamide (Eto) or Prothionamide (Pto) p-aminosalicylic acid (PAS)

Table 1: ABC groups of second line TB drugs

DRUGS	16-29 Kg	30-45 Kg	46-69 Kg	>70 Kg
Levofloxacin (Lfx)	250 mg	750 mg	1000mg	1000mg
Moxifloxacin (Mfx)	200mg	400mg	400mg	400mg
High dose Mfx (Mfxh)	400mg	600mg	800mg	800mg
Clofazimine (Cfz)	50mg	100mg	100mg	200mg
Cycloserine (Cs)	250mg	500mg	750mg	1000mg
Linezolid (Lzd)	300mg	600mg	600mg	600mg
Amikacin (Am)	500mg	750mg	750mg	1000mg
Pyrazinamide (Z)	750mg	1250mg	1750mg	2000mg
Ethionamide (Eto)	375mg	500mg	750mg	1000mg
Ethambutol (E)	400mg	800mg	1200mg	1600mg
Pyridoxine (Pdx)	50mg	100mg	100mg	100mg
Delamanid (Dlm)	50 mg twice daily (100 mg) for 24 weeks in 6-11 years of age 100 mg twice daily (200 mg) for 24 weeks for ≥ 12 years of age			
Bedaquiline (Bdq)	Week 0–2: Bdq 400 mg daily. Week 3–24: Bdq 200 mg 3 times per week			

Table 2: Dosage of drugs for longer regimen

DRUGS	16-29Kg	30-45Kg	46-70Kg	>70 Kg
High dose H	300mg	600mg	900mg	900mg
Ethambutol	400mg	800mg	1200mg	1600mg
Pyrazinamide	750mg	1250mg	1750mg	2000mg
Levofloxacin	250mg	750mg	1000mg	1000mg
Clofazimine	50mg	100mg	100mg	200mg
Ethionamide	375mg	500mg	750mg	1000mg
Pyridoxine	50mg	100mg	100mg	100mg
Bedaquiline	Week 0–2: Bdq 400 mg daily Week 3–24: Bdq 200 mg 3 times per week			

Table 3: Dosage of drugs in shorter regimen

these drugs for more than one month, or intolerance for any drug or extrapulmonary TB cases or pregnancy were not recommended for the shorter regimen. This regimen showed a favourable outcome in 78.8% of the MDR TB cases.^[27]

NEWER DRUGS:

Regimens with few 'newer' drugs and few 'old' drugs, used in combination have come up in recent years. These include Linezolid, Moxifloxacin, Bedaquiline and Clofazimine. These all being oral drugs (so no injectables as WHO recommended) showed improved outcomes, reduced mortality and shortened duration of treatment.^[24] cure rate of 63% is achieved when Bedaquiline was used for treating HIV drug resistant TB cases.^[28] NTB trial tested a novel anti TB regimen for complex forms of MDR TB (multiple resistances) and XDR TB. The regimen consists of Bedaquiline, Pretomanid and Linezolid (BPaL), which achieved a cure rate of 85-90% after a 6 months course of treatment.^[29] Nix TB trial included both MDR TB & XDR TB treatment prime cases, had high initial bacillary load, 51% HIV positive cases and fewer drugs.^[3]

Linezolid is an oxazolidinone that inhibits bacterial protein synthesis. Linezolid dose of 1200 mg was associated with better outcomes (higher Mycobactericidal effects).^[30] Linezolid toxicity and higher cost hamper the wider use of BPaL regimen. The ZeNix trial is looking at a lower dose of Linezolid based regimen in comparison with standard BPaL regimen.^[31] The Adverse effects due to various anti tubercular drugs is given in Table 4

Bedaquiline is a diaryl quinoline that inhibits ATP synthase. By the end of 2020, 109 countries were using Bedaquiline and 90 countries were using all oral longer regimens and 68 were using shorter regimen including India.^[24] Pretomanid is a nitro-imidazo-oxazine that blocks Mycobacterial cell wall production. A cohort comparison study with prospective

follow up between Nix- TB cohort (BPAL) and XDR TB cohort (where Bedaquiline and Linezolid were used) showed significant clinical benefits like Culture conversion, lower adverse effects observed with BPAL regimen.

There is also a synergistic activity between BDQ, LZD & PTM.^[30] The regimen of BPAMZ includes Bedaquiline, Pretomanid, Moxifloxacin and Pyrazinamide, which is being tested for all types of TB (Universal regimen).^[24] Overall MDR TB has a treatment success rate of 55% globally. Female gender, HIV positive subjects not taking ART (multiple drugs causing side effects), Simple MDR cases were the factors associated with treatment success among the drug resistant cases.^[32] Subjects who attained culture conversion by the end of 4 months also showed better success rates.^[32]

DRUG	ADVERSE EFFECTS
Isoniazid	Hepatitis, Peripheral neuritis
Rifampicin	Hepatitis, hypersensitivity reactions
Streptomycin	Nephrotoxicity, 8th cranial nerve involvement
Pyrazinamide	Hepatitis, Hyperuricemia
Ethambutol	Optic neuritis
Ethionamide/prothionamide	Gastroenteritis/hepatitis
Cycloserine	Personality changes/depression
Amikacin	Ototoxicity/nephrotoxicity
Levofloxacin	Tenosynovitis
Moxifloxacin	Tenosynovitis
Clofazimine	Pigmentation/eosinophilic enteritis
Linezolid	Pancytopenia/gastrointestinal disorders/polyneuritis
Bedaquiline	Gastric intolerance, hepatitis, altered QTc.

Table 4: Adverse effects of TB drugs

FUTURE APPROACHES

Individualizing the causes of drug resistance based on susceptibility reports into MDR, MDR+PZA Resistance, MDR+FQ Resistance, XDR+Bedaquiline Resistance and MDR+Bedaquiline Resistance will be the next categorization of drug resistant cases with tailored regimens.^[24]

CONCLUSIONS

Early detection and effective treatment remain the cornerstone for treating DR TB. The rapid molecular tests should

be done in all new (sputum +ve and sputum -ve) cases so as to decrease the MDR burden. Active case finding, TB chemoprevention and continuation of BCG vaccination for children are aimed at reducing the TB burden. The daily regimen of 6 months Levofloxacin is indicated for EP TB preventive therapy for contacts of MDR TB cases. Guidelines based regimens should be strictly adhered to by both public and private treating physicians. A nationwide survey which includes all regions and types of tuberculosis patients can help in framing effective strategies. Universal regimen of B Pa M Z has raised hope for increasing drug compliance without compromising treatment effectiveness.

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How to cite this article: Chenimilla NP, Pittala P, Madire R. **Review on Drug Resistant Tuberculosis.** Perspectives in Medical Research. 2022;10(2):2-8
DOI: [10.47799/pimr.1002.02](https://doi.org/10.47799/pimr.1002.02)