

Management of Multidrug Resistant Tuberculosis (MDR-TB)

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Abstract: Tuberculosis has been a scourge of the mankind from times immemorial and is still an important health problem. The developments in pharmacotherapy and health programmes indicated the tuberculosis could be contained and probably eradicated. But the present day reality is a stunning contradiction to optimism of the earlier days tuberculosis seems to have struck back with a vengeance. Today, multi drug resistant tuberculosis (MDR-TB) is a dreadful reality and advancing its march to destroy the national programmes to control tuberculosis.

Current prevalence of primary and acquired multidrug resistance in India is 3.4% and 13.3% respectively. Susceptibility testing is the 'Gold-standard' for the diagnosis of MDR-TB which is not the 'absolute' parameter to dictate therapy but should be used to guide therapy along with complete clinical profile. The treatment of MDR-TB is difficult, complicated, much costlier, less frequently affordable, challenging needs experience and skill and individualized for the needs of the particular patient. The therapy once instituted should be carried out despite all discomfort to prevent morbidity, mortality and transmission of MDR-TB as this is, probably the last chance between life and imminent death.

The WHO-programme of 'DOTS-PLUS' highlights the comprehensive management strategy to control MDR-TB optimal treatment of MDR-TB, alone, will not curb or control the epidemic but 'prevention' of ultimate emergence of MDR-TB should be focussed therapy by effective use of firstline drug is absolutely essential.

Diagnosis of MDR-TB

Early diagnosis and treatment of MDR-TB is of paramount importance not only from the patients perspective but also for the community at large. Consideration of the following are generally contributory to the diagnosis of MDR-TB^{1,2,3}.

High Risk population^{4,5} :

- 1 History of contact with known case of MDR-TB.
- 1 History of previous or many irregular or regular treatment of Tuberculosis.
- 1 Cavitory pulmonary tuberculosis.
- 1 Presence of infection with HIV-positive patients are not more prone to MDR-TB than to drug susceptible TB. Rather, epidemiological association of HIV-positive status and MDR-TB reflects nosocomial transmission of TB (some being MDR-TB) and propensity of HIV-positive patients to progress rapidly to active disease⁶.
- 1 Clinical presentation with, interstitial infiltrate, hilar or mediastinal adenopathy, cavitation on chest radiograph has been suggested to be more typical of drug-resistant rather than drug-susceptible disease in HIV-positive patients. There is no convincing evidence for these assertions. Some have found higher rate of cavitation among HIV-positive patients with MDR-TB while others have actually documented fewer cavitory lesions in such patients⁷.
- 1 History of contact with family members and health care professionals of MDR/TB.

Clinical diagnosis

(a) High suspicion :

- 1 *Fall and rise phenomenon* : on antitubercular therapy, sputum

smear initially becomes negative (or less positive) and later becomes persistently positive. This indicates failure usually due to either the patient having ceased to take the drugs or to the development of resistance to all the drugs, patient is receiving.

- 1 *Persistently positive sputum smear* for AFB even after 5 months of WHO or other retreatment regimens.
 - 1 Development of *distant complications* of pulmonary tuberculosis during therapy.
 - 1 Presence of *extensive multicavitory disease*.
- (b) Relative Suspicion -**
- 1 History of *contracted infection* from a known source.
 - 1 *Radiological deterioration* : Even after regular and adequate chemotherapy for 3 months change in size of cavities, increase in existing lesion and appearance of new lesion is an indication of disease progression. However, radiological worsening in addition to, positive sputum-smear for AFB and/or clinical worsening may indicate MDR-TB.
 - 1 *Clinical deterioration*: This is the least reliable evidence of MDR-TB, if not associated with bacteriological or radiological deterioration. Failure to defervesce after 2 weeks of treatment with a standard four drug regimen is an independent marker of MDR-TB. In areas with a high prevalence of MDR-TB, broader empirical treatment may be indicated for patients who fail to defervesce⁸.

However, this approach has several limitations. For example, not all patients with TB present with fever. Persistent fever can also be caused by severe miliary disease or another concomitant infection, and is therefore not a specific sign of MDR-TB.

Of the patients who are initially smear-positive, 75% will become

smear-negative after 2 months of treatment with a regimen containing isoniazid and rifampicin, and over 95% will have converted by 5 to 6 months. Smear positivity at 2 months may be caused by nonadherence with treatment, cavitation and heavy initial bacillary load or presence of drug resistance^{9,10,11}.

1. **Inadequate and irregular therapy:** In a drug-o-gram (listing of all drugs taken in the past) evidence of inadequate dosage or monotherapy, adequate therapy but for shorter duration is present. At the same time a list of drug 'never' used in therapy and drugs with cross-resistance may also be prepared.

c Unreliable suspicion :

1. Past history of antitubercular therapy and has come with fresh relapse.
1. Not gaining weight.
1. No radiological improvement.
1. Radiological deterioration without clinical deterioration.
1. Development of a cavity in exudative lesion on treatment.
1. New shadows may not, necessarily, be tuberculosis.

Bacteriological diagnosis

Laboratory evidence of resistance to rifampicin and INH is a gold standard for the diagnosis of MDR-TB. There are limitations of these highly specific test-as the technique is complex and difficult to perform accurately even when skilled personnel are available and laboratory facilities are of high standard. One must also consider that sampling of different population of bacilli, and laboratories varying in reliability, errors occurring in laboratory, may be the factors for the different sensitivity reports obtained of the same patient from different laboratories. There is lack of standardization, coordination and cross checking with national laboratories in our country. The conservative approach is to assume that any drug resistance that has been reported is real irrespective of the reputation of the testing laboratory. However the results of sensitivity should not be accepted uncritically. Correlation with history, smear results and radiology should be used as a guide for future therapy and therapy should not be changed if the patient is improving satisfactorily. Newer techniques have greatly shortened the time of obtaining the reports with increased "sensitivity and specificity. Previous therapy with a drug, which has been associated with a reduced clinical response to that drug, despite apparent "Susceptibility" in in-vitro laboratory tests has also to be considered. The presence of dead bacilli can also produce "false positive" smear early in treatment. Patients who were initially smear and culture positive may have culture conversions, but may continue to have positive smears 4 to 20 weeks after commencing treatment. This "Smear positive/culture negative reaction" was more common among patients with cavitory disease and also in those treated with rifampicin containing regimens. WHO recommends extending the intensive four drug treatment phase, for a further month in patients with positive smear at 2 months. However drug treatment is only changed if smear remains positive at 5 months.

Assessment of patients with MDR-TB

Planning drug therapy for a patient with MDR-TB requires experience, skill and time. The treatment history of the patient must be thoroughly chronicled listing the previous treatments (including preparations that might have been obtained privately from the pharmacists), the patients adherence with these regimens, and the bacteriological response. Clinical and radiological changes should also be recorded. However, these changes can be affected by intercurrent conditions (pneumonia, emolism) and are, therefore, less reliable parameters of progress. The patient's previous drug susceptibility results should also be recorded including those performed at other hospitals.

Treatment of MDR-TB

The management of MDR-TB is an area that has been shrouded in lot of myths and misconceptions, and therefore, utterly chaotic. Though, WHO guidelines are useful in managing MDR-TB patients but they may not be applicable to every patient. Therefore, therapy should be individually tailored to the needs of a particular patient.

Basic Principles of Chemotherapy with MDR-TB

- 1.(a) *When sensitivity tests are not available :* A likely resistance pattern can be inferred from the patients history and previous susceptibility results. A patient, who had drug susceptible TB and adhered to a satisfactory treatment regimen, presenting with a relapse years later, is likely to have drug-susceptible disease and will respond to the WHO-retreatment regimen. In contrast, a patient who has failed therapy, is likely to have drug resistant tuberculosis. In this circumstance, a "Retreatment regimen" is used comprising a minimum of 4 to 5 drugs in the "initial phase" and at least 3 of the most active and best tolerated drugs, in the "continuation phase". this regimen should contain drugs to which the bacilli are certainly sensitive i.e. not received previously as the bacilli are unlikely to be resistant to the drugs. A "first line" drug that the patient has received previously may be added to this regimen, if resistance appears unlikely, based on patients previous treatment history. However, such additional drugs must not be relied upon until results of new susceptibility tests are available².

Thus, treatment regimen should ideally contain multiple drugs with "bactericidal activity (a) injectable agent, a quinolone, pyrazinamide, or ethionamide) with the "bacteriostatic" drugs (cycloserine, para-aminosalicylic acid (PAS) added to prevent the development of furter resistance. The initial phase of at least 6 months and continuation phase of 12-18 months, after the sputum has become negative is usually needed.

- (b) *When sensitivity tests are available :* the treatment regimens are straight forward (Table 1).
 - (c) Depending upon the *history of antituberculosis drugs used previously and non availability of sensitivity tests, various combinations, of resistance may be anticipated.*
2. Drugs must be given in adequate dosage (corrected according to weight and duration).

Table 1 : Standard treatment regimen considered suitable if sensitivity lists are available

Resistance to	Initial phase		Continuation Phase	
	Drugs	Minimum duration in months	Drugs months	Duration in
Isoniazid (streptomycin, thioacetazone)	Rifampicin	2-3	rifampicin	6
	Aminoglycoside ^c	2-3	ethambutol	6
	Pyrazinamide	2-3		
	Ethambutol	2-3		
Isoniazid and ethambutol (streptomycin)	Rifampicin	3	rifampicin	6
	Aminoglycoside ^c	3	Ethionamide ^d	6
	Pyrazinamide	3		
	Ethionamide ^d	3		
Isoniazid rifampicin	Aminoglycoside ^c	6	ethionamide	12-18
	ethionamide	6	fluoroquinolone ^f	12-18
	fluoroquinolone	6	pyrazinamide	12-18
	pyrazinamide	6	ethambutol +/-	12-18
	ethambutol +/-	6		
Isoniazid, rifampicin, streptomycin and ethambutol	Aminoglycoside ^c	6	ethionamide	18
	Ethionamide	6	fluoroquinolone ^f	18
	Pyrazinamide	6	Cycloserine	18
	Cycloserine ^g	6		
Resistance to all drugs	Aminoglycoside ^c	6	fluoroquinolone ^f	18
	fluoroquinolone ^f	6	2 of these Ethionamide	18
	2 of these Ethionamide	6	PAS	18
	PAS	6	Cycloserine ^g	18
	Cycloserine ^g	6		
Susceptibility test to reserve drugs available	Tailor regimen according to susceptibility pattern ^h			

1. Streptomycin, if still active, if resistance to streptomycin, use kanamycin or capreomycin.

1. If ethionamide is not available or poorly tolerated (even at a dose of 500 mg day) use ofloxacin.

1. Kanamycin or mikacin, or capreomycin

1. Ciprofloxacin or Ofloxacin.

1. PAS if cycloserine is not available or too toxic.

1. Individualized regimen is feasible in designated centers of excellence.

3. Use of first line drugs is preferred because they are most effective and less toxic. INH should be included in all regimens, unless it can not be used due to resistance to it.

4. A previous history of treatment with a particular drug, leads to reduced efficacy of that drug, regardless of "in-vitro" sensitivity.

Table 2 : The regimen is modified as recommended in table 2.

5. Never add a single drug to a failing regimen.

6. It is ineffective to combine two drugs of the same group or to combine a drug, potentially ineffective because of cross-resistance. Cross resistance occurs between thioamides and thioacetazone; kanamycin/amikacin with streptomycin; rifampicin with rifapentine and rifabutin (> 70% strains) and among various derivatives of fluoroquinolones. Cross resistance has also been reported between ethionamide and INH; Viomycin and kanamycin; viomycin^f and capreomycin. Strains resistant to streptomycin/kanamycin and amikacin are still sensitive to capreomycin.

7. All the drugs should preferably be given in a single daily

dose, except PAS which is usually given in two divided doses in order to avoid problems of intolerance.

8. Intermittent therapy is usually not effective and should be avoided in the treatment of MDR-TB.

9. No drug should be kept in reserve and like most powerful drugs (bactericidal) should be used initially and in maximum combination so as to ensure that the first battle is won and won permanently.

10. Therapy should be initiated in the hospital to permit monitoring of toxicity and drug intolerance. Direct observation therapy (DOT) should be preferably for 3 to 4 months or till the sputum conversion.

11. The treatment may be initiated with a small dose of each drug and gradually increased to the planned dose over 3 to 10 days.

12. All the patients should be monitored by repeated culture and sensitivity tests, monthly during intensive phase and "once in 3 months till the end of therapy. If culture remains positive after 4 months of therapy, the strategy must be changed.

Table 2 : Suggested regimen for resistant/Multidrug Resistant Tuberculosis with Various patterns of past history of treatment.

Group	Past Treatment	Intensive Phase		Continuation Phase		
		Drugs	Duration in months	Drugs	Duration in months	Non Responders
I	Misused drugs like SHE and TZN	Rifampicin Isoniazid ethambutol Pyrazinamide+ Streptomycin	2-3*	Rifampicin Isoniazid Ethambutol+ Pyrazinamide	9	Treat as Group II or Take help of sensitivity result
I	Misused drugs like SHREZ TZN	Streptomycin Isoniazid q Rifampicin Ethambutol Pyrazinamide	2-3*	Rifampicin Isoniazid Ethambutol+ Pyrazinamide	9	Treat as Group III Or Take help of Sensitivity result.
III	Failed after adequate 5 drugs SHREZ	Aminoglycoside ^a Ethionamide Fluoro-quinolone ^b Pyrazinamide Ethambutol+ O R Kanyamycin PAS Ethionamide Cycloserine + Isoniazid	6*	Ethionamide Fluoro-quinolone ^b Pyrazinamide Ethambutol+		Treat Group IV Or Take help of Sensitivity result and consider surgery
			6*	PAS Ethionamide Cycloserine Pyrazinamide + Isoniazid		
IV	Failed on group III treatment	Aminoglycoside ^a Fluoro-quinolone ^b Clofazimine Ethio/PAS/Cyclo + Newer ATT ^c	6*	Fluro-quinolone ^b Clofazimine Ethio/Cycle/ PAS + Newer ATT ^c	18	Consider surgery

* Amikacin/Kanamycin/Capreomycin

* Ciprofloxacin/Ofloxacin/Sparfloxacin

* Clarithro/Azithro/Rifabutol/Coamoxyclav

* Depending on sputum conversion can be used for 3-6 months if toxicity does not intervene.

Abbreviation - are as followed - R- rifampicin, H-isoniazid, E-thambutol, Z-pyrazinamide, S-streptomycin, K-kanamycin, C-0capreomycin, TZN-thiacetazone.

13. All measures should be taken to persuade and encourage patients not to stop treatment, despite all its discomforts, as it is the last chance that stands between life and death.
14. The bioavailability of the anti tuberculous drugs may be altered in presence of AIDS (as malabsorption is frequent in them). Serum levels may become necessary to optimize therapy and ensure bioavailability.
15. WHO recommend of ATT drugs in fixed dose combinations of proven bioavailabilities adjusted to body-weight. Reduced bioavailability may lead to difference in choice.
16. Among fluoroquinolones, most active agents are levofloxacin, ofloxacin, sparfloxacin and moxifloxacin^{13,14}. Ofloxacin

has a bactericidal action and capable of increasing level of activity of isoniazid - rifampicin in three drug combinations during the exponential growth phase. In contrast, ofloxacin has little bactericidal activity against stationary phase and less active than isoniazid or rifampicin alone. Sparfloxacin is 8 times more potent than ciprofloxacin and almost as potent as rifampicin. Unfortunately, sparfloxacin appears less useful because of relatively high rate of photosensitization. Moxifloxacin, while demonstrating very favourable "in vitro"¹⁵ activity does not have the same extended clinical safety as levofloxacin and ofloxacin¹⁶. Although fluoroquinolones are usually well-absorbed orally, absorption is reduced by concomitant administration of

Table 3 : Second line drugs used for treatment of resistant/MDR Tuberculosis.

Drugs	Average daily dosage	Daily Dosage (mg)		Type of antimycobacterial activity
		Minimum	Maximum	
Aminoglycosides - Kanamycin - Amikacin - Capreomycin	15mg/kg	750	1000	bactericidal against actively multiplying organisms
Thioamides - Ethionamide - Prothionamide	10-20mg/kg	500	750	bactericidal
Cycloserine	10-20mg/kg	500	750	bacteriostatic
PAS acid	200-300mg/kg	10g	12g	bacteriostatic
Fluroquinolone - Levofloxacin - Ciprofloxacin - Ofloxacin - Sparfloxacin	10-15 mg/kg 15-20 mg/kg 7.5-15 mg/kg 6-8 mg/kg	750 1000 600 400	1000 1500 800 600	weakly bactericidal
Macrolide - Clarithromycin - Azithromycin	10-15 mg/kg 10mg/kg	1000mg/kg 500 mg/day		Bactericidal (pH dependent)
Clofazimine	4-5 mg/kg	100	200	bacteriostatic
Beta Lactam - Coamoxylav		750	2 gm	weakly bactericidal

antacids. Ofloxacin is better absorbed than ciprofloxacin and has a bioavailability approaching 100%¹⁷.

17. Surgical treatment may be applied more frequently and aggressively as the overall cure-rate may be much higher (81% vs 56%). Feasibility and success appears to be substantially enhanced by nutritional support.

Second Line Drugs Used for MDR-TB

The use of the first line drugs for treatment of pulmonary tuberculosis is well established. However, some pharmacological aspects of "secondline" drugs for planning antitubercular therapy are given in Table 3.

Kanamycin, amikacin, capreomycin : Kanamycin is a glycoside of 2-deoxy-streptomycin and amikacin is a derivative of kanamycin. The aminoglycosides inhibit protein synthesis by irreversibly binding to the bacterial 30S ribosomal subunit and blocking the aminoacyl-tRNA. Cross-resistance occurs between kanamycin and amikacin because of their structural similarity, but cross-resistance between them and streptomycin is rare. Capreomycin has a similar action and adverse effects to, the aminoglycosides. However, it is a basic polypeptide antibiotic and so cross-resistance with aminoglycosides occurs occasionally. All of these injectable agents are bactericidal against actively multiplying bacilli and have, therefore, become essential agents in treatment of MDR-TB. The major adverse effects of kanamycin include hearing loss, ataxia, nystagmus nephrotoxicity, electrolyte abnormalities and are

contraindicated in pregnancy. Amikacin and capreomycin have similar adverse effects.

The usual daily dose of kanamycin and amikacin is 15 to 30 mg/kg given intramuscularly, with a maximal daily dose of 750mg to 1gm⁸. These drugs can also be given by intravenous infusion through a central line³. Following parenteral administration these drugs can be detected in body tissues and fluids. They cross the placenta but their penetration into the cerebrospinal fluid (CSF) is unreliable. Excretion is by glomerular filtration. As, with both agents ototoxicity is more common than nephrotoxicity a monthly audiometry is, therefore, recommended while patients are on treatment. If there is renal impairment, dosage adjustment and careful monitoring of renal function are required. Capreomycin is given by intramuscular injection of the daily dose of 15-30mg/kg to a maximum dose of 1. The dosage should not exceed 20 mg/kg/day for more than 40 to 120 days because of the risk of adverse effects, increases thereafter⁸. If necessary, capreomycin can be continued but given only 2 to 3 times per week. It can also be given intravenously with good tolerability. Capreomycin causes high frequency hearing loss in 3.2 to 9.4% of patients before vestibular dysfunction occurs⁹. It is, therefore, recommended to do monthly audiometry with occasional examination of vestibular function. Renal toxicity may also occur, especially in the elderly among whom total daily dose should not exceed 750mg. Electrolyte disturbances, like hypokalemia, hypocalcemia, hypomagnesaemia, possibly result from tubular damage may be observed with

capreomycin (and the aminoglycosides), particularly after 3 to 4 weeks of antituberculosis therapy⁹. It is advisable to monitor renal function and serum biochemistry regularly. Cutaneous reactions and hepatitis may occur rarely. Capreomycin is contraindicated in pregnancy and avoided in children⁹.

Ethionamide : Ethionamide (2-ethyl-pyridine-4-carboxylic acid thioamide) is a derivative of isonicotinic acid and exerts a bactericidal effect by inhibiting mycolic acid synthesis. However, isoniazid-resistant isolates of *M.tuberculosis* are susceptible to ethionamide suggesting different sites of action for these two drugs. Ethionamide is also structurally related to thioacetazone. Isolates resistant to thioacetazone are usually sensitive to ethionamide but ethionamide resistance is almost always associated with thioacetazone resistance. Prothionamide is the N-propyl derivative of ethionamide and has similar activity, clinical efficacy and adverse effects²⁰. Ethionamide is absorbed from the gastrointestinal tract and distributed widely throughout the body, including CSF. The drug is extensively metabolised in the liver with less than 1% appearing unchanged in urine. The usual daily dose is 15 to 20mg/kg. (500 to 1000mg.) in divided doses with a maximum daily dose of 1g. The main adverse effect of the ethionamide is gastrointestinal intolerance (nausea, metallic taste, epigastric discomfort, and diarrhoea). The drug should be introduced slowly in 250mg increments as tolerated, and can be given with milk or at bed time with a sedative to avoid nausea. Hepatitis with jaundice (4.3%) can occur up to 5 months after commencing therapy⁸. Withdrawal of therapy usually results in resolution. Hepatic enzymes should, therefore, be monitored monthly. Transient elevations in levels may be observed but they usually normalize despite continued administration of the drug. Hence, in absence of symptoms or jaundice, ethionamide administration should only be stopped, if there is a 5-fold elevation of AST or ALT. Other adverse effects include psychotic reactions, convulsions, headache, dizziness, peripheral neuritis, hypoglycaemia (important in patient with diabetes mellitus), hypothyroidism, gynecomastia, acne, menstrual abnormalities, impotence and alopecia and therefore, should be used carefully in patients with diabetes mellitus, liver disease and psychiatric conditions.

Quinolones : The newer broad spectrum compounds (sparfloxacin, levofloxacin,² moxifloxacin) exhibit greater in vitro activity against *M. tuberculosis* than the narrow spectrum fluoroquinolones (ciprofloxacin, ofloxacin). Ciprofloxacin has an early bactericidal action but neither ciprofloxacin nor ofloxacin have enhanced the sterilising ability of long term regimens containing isoniazid and rifampicin.

The quinolones exert a mycobactericidal effect by binding to the DNA-gyrase and inhibiting DNA-synthesis. There is no recognized cross resistance with other antitubercular drugs but there is complete cross-resistance within the fluoroquinolone group. This resistance develops readily and rapidly, and has been associated with mutations in DNA-gyrase. Fluoroquinolones must be used in combination with other effective drugs when treating MDR-TB. The usual daily dose is 600 to 800mg. (3-4 tablets) of ofloxacin or 1000 to 1500mg (4-6 tablets) of ciprofloxacin during the initial phase. If the dose of 600mg is poorly tolerated the daily dose can be reduced (400mg ofloxacin during the continuation phase. Either

can be given in a single daily dose or the daily dose can be divided in two doses^{16,17,18}.

They are well-absorbed orally with bioavailabilities ranging from 60% for ciprofloxacin to 95% for ofloxacin. Their distribution is ideal for treating TB with concentrations in the lung and in macrophages being several times higher than serum concentrations. These drugs also penetrate well into other tissues but not in CSF where levels can be variable. Quinolones are predominantly cleared by glomerular filtration so the dosage should be adjusted in renal failure. Adverse reactions are uncommon but gastrointestinal disturbances like anorexia, nausea, vomiting), neurological symptoms (dizziness, tremors, headaches, insomnia, mood changes, convulsions), hypersensitivity and crystalluria have been associated with quinolone therapy.

Although quinolones are used only for short periods to treat standard bacterial infections, they also appear to be well tolerated when used for 2 years or more in the long treatment of mycobacterial infections²². Animal studies have shown that the quinolones may adversely affect growing cartilage. Hence, these drugs should only be used during pregnancy or in children after balancing the potential benefits against this theoretical risk. Quinolones also increase serum theophylline concentrations and hence may increase the adverse effects of theophylline if given in combination. The absorption of quinolones may be reduced by concomitant administration of antacid preparations.

Cycloserine : (4-amino-3-iso-oxazolidinone) is a structural analogue of D-alanine that competitively blocks enzymes involved in the synthesis of the dipeptide, D-aryl-D-alanine. By inhibiting synthesis of this dipeptide, which is an essential component of the mycobacterial cell-wall, it limits cell growth and hence has a bacteriostatic effect. This mode of action is unique so cycloserine shares no cross-resistance with other antitubercular drugs¹⁰.

The drug is rapidly absorbed from the gastrointestinal tract and is widely distributed throughout the body, including the CSF. Clearance is mainly by glomerular filtration. The drug is introduced slowly over several days - starting 250mg daily for a few days, then 250mg twice daily for a few days and finally 750mg daily given as 500mg in morning and 250mg in the evening. Peak-serum concentrations (2 hours post dose) < 10mg/L may be less effective and concentrations > 30-35mg/L are associated with increased toxicity. These concentrations should be checked 1 to 2 weeks after commencing therapy and should be measured following the larger dose if the 500/250 mg regimen is used. Pyridoxine (50 to 100mg daily) has also been given with cycloserine in order to reduce the neurological adverse effects, particularly when given with isoniazid⁹.

Cycloserine administration is associated with significant neurological adverse effects - peripheral neuropathy, dizziness, tremor, headache, convulsions and behavioural complications - confusion, hyperactivity, depression, psychoses, suicidal ideation. Patients must, therefore be closely watched for mood and personality changes. These complications are more common in alcoholics, patients with epilepsy, and patients with renal involvement or previous psychiatric illness. Cycloserine also interferes with the elimination of phenytoin, further complicating its use in epilepsy.

Para-aminosalicylic Acid : PAS is a structural analogue of para amino benzoic acid (PABA) that has a bacteriostatic effect by competitively blocking the conversion of PABA into folic acid (an essential burine required for DNA-synthesis). It is readily absorbed from the gastrointestinal tract. It diffuses rapidly into caseous tuberculosis lesions but does not cross uninflamed meninges.²⁰ PAS is metabolised in the liver to acetyl-PAS and both compounds are excreted in the urine. Hence, PAS is generally avoided in renal failure.

PAS is introduced gradually over several days to a final dose of about 10 to 12 g/day in 3 or 4 divided doses. It is given with food or milk to minimise the gastrointestinal disorders. Few patients can tolerate the gastrointestinal adverse effects produced by combined administration of PAS and ethionamide. PAS may also inhibit the absorption of rifampicin. PAS is an expensive drug and is not readily available¹⁰.

Alternative treatment for MDR-TB : In spite of availability of "second-line" drugs for the treatment of MDR-TB, other alternative treatments may sometimes be required. Several established drugs may also be used for treatment of MDR-TB.

a High dose isoniazid : In presence of confirmed MDR-TB isoniazid administration is not recommended^{3,10}. But, it has been observed that strains of *M. tuberculosis* identified in the laboratory as isoniazid resistant often contain mixtures of susceptible and resistant organisms. Sometimes isolates resistant to levels just above the critical concentrations for isoniazid (MICs of 0.2 to 5.0 mg/L) may be present. The high dose of isoniazid (16 to 20mg/kg (1 to 1.5 g/day), would eliminate susceptible organisms and those with low level resistance^{23,24}. Despite apparent in vitro resistance, isoniazid may retain appreciable residual activity against a particular strain of MDR-TB. No benefit is found in including isoniazid at a regular dosage in a regimen with cycloserine, ethionamide and/or pyrazinamide. However, sputum conversions were found in 69% in patients receiving high dose isoniazid as well as the retreatment regimen without any relapses in comparison to 21% of patients receiving retreatment regimen alone. High dose is associated with hepatotoxicity, peripheral neuropathy and convulsions (which may be prevented by giving higher dose of pyridoxine. Thus high dose isoniazid may be considered as an adjunctive drug in MDR-TB treatment, especially in developing countries unable to afford the expensive secondline drugs.

b Rifabutin : It is a derivative of rifampicin-S and may be more active than rifampicin against *M. tuberculosis*. It is rapidly absorbed from the gastrointestinal tract and has a serum half life of 16 hours (which is longer than rifampicin) and achieves higher concentration than rifampicin. The drug is eliminated by the kidney and the liver. Adverse effects include gastrointestinal disorders hypersensitivity, hepatotoxicity and hematological reactions^{24,25}. The critical concentration for rifabutin is 0.5 mg/L. The MICs of rifabutin for rifampicin sensitive and resistant strains of *M. tuberculosis* are <0.06 mg/L and 0.25 to 16.0 mg/L respectively. This wide-range of MICs suggest that few MDR-TB strains could be effectively treated with rifabutin²⁶. There is cross resistance between rifampicin and rifabutin. Though rifabutin

is equivalent to rifampicin in drug susceptible pulmonary-TB in HIV positive and negative patients, the sustained bacteriological response in MDR-TB was observed in 23 to 47% of patients. The outcome of therapy was independent of the concomitant medications and of resistance patterns, but it showed dose response effect with an 8% response for 150mg/day increasing to 50% response for the and 450 mg/day dosages²⁷. In spite of favourable pharmacokinetics and putatively superior activity of rifabutin, experience with this drug has suggested that it does not have a role in the treatment of MDR-TB.

c Clarithromycin : It is macrolide antibiotic and is well absorbed orally, attaining peak serum levels of 2 to 4mg/L and concentrates in the tissues. About 30 to 40% is excreted unchanged or as an active metabolite via the kidneys: biliary excretion accounts for the remainder. Adverse effects include nausea, diarrhoea, abdominal pain and bitter taste in mouth.

Though clarithromycin and azithromycin are useful in the treatment of many non-tuberculous mycobacterial infection, including MAC. But has demonstrated poor in vitro activity against *M. tuberculosis*. The MICs and MIC₅₀ were 16mg/L and 64 mg/L respectively^{28,29}. Its addition resulted in 4- to 32 fold reductions in the MICs of isoniazid, ethambutol and rifampin. The utility of clarithromycin as a "second-line" drug in the treatment of MDR-TB remains to be established.

d Clofazimine : It is a riminophenazine compound and effective against *Mycobacterium leprae* and MAC infections. After a single dose of 300mg, it attains a peak serum concentration of 1.0mg/L. A substantial portion of the unchanged drug is excreted in the faeces but metabolites are also detected in urine. Adverse effects include gastrointestinal disorders and skin discolouration. Though activity against *M. tuberculosis* has been demonstrated in-vitro and in-vivo, there are only anecdotal reports of successful treatment of MDR-TB³⁰.

e Amoxicillin-Clavulanic Acid : It is a B-lactam antibiotic and can penetrate the cell-wall of *M. tuberculosis* and bind with high affinity to four penicillin binding proteins (PBP). The resistance is due to presence of B-lactamases (in *M. tub.*) with penicillinase activity and can be inhibited by B-lactamase inhibitors (clavulanic acid, subclavam)^{31,32} or circumvented by the use of carbapenems (Imipenem) which are penicillinase resistant. It is bactericidal for *M. tuberculosis* isolates at an amoxicillin concentration of 4mg/L and a clavulanic acid concentration of 2mg/L or less. It is suggested to have an early bactericidal activity but this activity declines rapidly after the third day. This bactericidal activity needs further exploration in the treatment of MDR-TB.

f Metronidazole : *M. tuberculosis* can adapt to low oxygen levels and it is the dormant organisms that undergo orderly metabolic changes to survive anaerobiosis and become susceptible to drugs like metronidazole (generally active against anaerobic organisms). Thus, this drug may have a role in eradicating persistent bacilli during the sterilization phase of treatment and in chemoprophylaxis³³. It might be useful in the management of drug-susceptible or MDR-TB. This potential role needs to be further studied.

Table 4 : Initial Phase

Initial Phase		Continuation Phase	
Drugs	Minimum duration months	Drugs	Duration in months
Aminoglycoside*	6	Ethionamide	12-18
Ethionamide	6	Fluoroquinolone	12-18
Fluoroquinolone	6	Pyrazinamide**	12-18
Pyrazinamide	6	Ethambutol +/-	12-18
Ethambutol +/-			

* Kanamycin, or amikacin, or capreomycin.

** Ciprofloxacin or Ofloxacin

Duration of Therapy (Table 4)

The optimal duration has not been clearly established. However, WHO recommend treatment with antitubercular drugs for a period of at least 18-24 months after sputum conversion or 12 months after sputum culture becomes negative to prevent relapse. The injectable drugs are preferably used for 6 months depending upon sputum conversion.

Monitoring Treatment

The most reliable marker is the bacteriological response⁸. Sputum examinations should be done, for semi quantitative smear and culture monthly, during the intensive phase of therapy^{24,3}. After sputum conversion smear examination and culture are obtained once in three months till the end of the therapy. Therapeutic response is judged in order of reliability, by bacteriology of sputum, radiology followed by clinical picture. Once sputum conversion has been obtained some experts recommend with drawing the weaker and more toxic drugs from the regimen². The patient then completes another 18 to 24 months' treatment with the remaining 2 to 3 well tolerated drugs³. Other experts would persist with the initial treatment hoping to improve the cure rate. A parenteral drug is given for 4 to 6 months until toxicity develops.

Outcome of Treatment

In a study - of 134 MDR-TB patients, 47(35%) had no response to therapy and 12 initial respondents relapsed, the overall response rate was 56% for a mean follow up period of 51 months (range 10 to 167)³⁴. MDR-TB resulted in a failure of 44% (and TB associated mortality rate of 22%). The median hospital, stay was more than 7 months; One had surgery; the median number of drugs administered per patient was 4 (32 patient had received six or ore drugs. However, in a later study of 25 evaluable patients, 24(96%) had clinical response, and all 17 for whom data on microbiological response were available had documented culture conversions⁴. The median follow up period was 91 weeks (range 41 to 225). However, the patients often had primary MDR-TB, and those with acquired disease had TB for a shorter period (median 2.5 years), had fewer drugs before treatment (median number of drugs, 3.5) and had access to quinolone treatment. In HIV positive patients with MDR-TB (table 5), the earlier reported median survival time for the MDR-TB patients was 2.1 months compared with 14.6 months for the controls. However, later studies reported median survival times reanging between 5.8 and 10 months^{35,36,37}. The survival time is prolonged in patients with CD4 + T lymphocyte counts above 200/mL, and in patients

receiving capreomycin and to a lesser extent, a fluoroquinolone and isoniazid^{38,39a,39b}.

Table 5 : The Influence of HIV status on Management of MDR-TB.

Influence	HIV Negative	HIV Positive
Treatment Failure	63 times	172 to 89% died
Relapse	2 times	within 4-19 week, 38 to 70% to TB
Resistance to	5.8 drugs	1 Median survival AIDS-1.5mths. 1 No AIDS 14.8 mths.
Each received	5.7 drugs	1 8%of contacts developed TB in 2 years
Duration Conversion	24 mths after conversion	Initial 65%
Long Term	56%	

Chemoprophylaxis For Contacts of MDR-TB

The CDC has recommended three levels of control :

- The use of *administrative measures* to reduce the risk of exposure (early recognition of potential TB patients, prompt laboratory diagnosis and immediate implementation of effective chemotherapy).
- The use of *engineering controls* to prevent the spread of TB bacilli (ventilated rooms, air-filtration and ultraviolet air disinfection) and
- The use of personal respiratory protective equipment such as high efficiency particulate air filter (HEPA)⁴⁰. However, these are expensive and cumbersome and therefore remain unproven.

Observation without preventive therapy has been recommended for most people exposed to MDR-TB. However, in those who are at high risk of progressing to active disease (HIV+ve), the potential regimens are pyrazinamide and ethambutol, or pyrazinamide and a quinolone and the proposed duration of therapy was 6 to 12 months. Patient's preference and any adverse effects become major factors as the benefit of MDR-TB prophylaxis is small. Treatment with pyrazinamide 1500 mg daily plus ciprofloxacin 750mg twice daily for 4 months do have some support from different experts^{41,42}.

BCG vaccination proved marginally "superior to screening and preventive treatment with post-infection prophylaxis with ciprofloxacin-pyrazinamide. Overall, BCG is only recommended for infants and children at continued risk of TB infection. However, BCG vaccination may now be considered for health care workers who remain exposed to MDR-TB despite the institution of comprehensive infection control programme⁴³.

Role of Surgery in Management of MDR-TB

Though medical therapy is the cornerstone of management of MDR-TB, but in best circumstances success rate is only in 40-50% of cases. However, combined with surgery the success rate may be 90-95%. The preoperative and postoperative medical therapy should be given for 24 months or 18 months after sputum conversion^{44,45}.

The aims of surgery in MDR-TB include :

- 1 Extensive drug resistance resulting in likely or proven failure of chemotherapy.
- 1 Presence of localized disease allowing successful debulking of abnormal lung without compromising lung functions.
- 1 Removal or closure of the cavity.
- 1 Bacteriological conversion
- 1 For the control of disease process, complications and sequelae.
- 1 Rehabilitation of the patient in his social & economic environment.

However majority of MDR- patients have too extensive a disease and/or too poor pulmonary functions to be considered suitable for surgery.

The indications for surgery in MDR-TB are :

- 1 Positive sputum with localised disease; negative sputum with significant pulmonary lesions and unstable lesion/cavity may also be considered for surgery.
- 1 Massive hemoptysis (600ml in 24 hours) or recurrent hemoptysis.
- 1 Chronic empyema
- 1 Bronchopleural fistula

The contraindications are :

- 1 Extensive diseases
- 1 Poor cardiopulmonary reserve
- 1 Active endobronchial disease

Success of Surgery :

- 1 It depends upon availability of medical therapy with susceptible/partially susceptible drugs; resulting in success rate of 90-95%. However, if the bacilli are resistant to all drugs, success rate drops to 50%.
- 1 It depends upon residual lung lesions; when there are no remaining lung lesions and susceptible drugs are available the success rate is nearly 90-95% but in presents remaining lung lesions because of bilateral involvement or poor lung function success drops to 60%.
- 1 It depends upon surgery being performed after three months of treatment with reserve/second line drugs since at this point of time, bacteria are still likely to be sensitive and the bacillary population is likely to be at its lowest.

Preoperative assessment :

- 1 Whether unilateral/localised disease. The contralateral lung should be healthy but minimal healed lesion is, also, acceptable for resection.
- 2 Patient should be fit for major surgery or pneumonectomy.
- 3 Bronchoscopy should be done in all cases to rule out any endobronchial disease at the site of section of the bronchus.
- 4 Best results are seen when two or more susceptible drugs including one injectable drug is available.
- 5 Presence of uncontrolled diabetes-mellitus increases the chances of life threatening complications.
- 6 Pulmonary functions assessed clinically and by spirometry. The criteria for fitness require:-

- a FEV₁ of 1.5L or > in males & 1.3L or more in females or > 50% of predicted value.
- b The post operative FVC (by ventilation scan) should be > 800-1000ml.
- c The MV should be more than 50% of the predicted value. For thoracoplasty, FEV₁ upto 1 ltr. is enough.

Surgical Procedures for MDR-TB

- a Resection of lung: It is the surgery of choice as it takes away the disease bodily. Pneumonectomy, lobectomy, segmental resection or wedge resection may be as per the requirement of the case.
- b Thoracoplasty : If the resection is not feasible, due to extensive disease or poor lung function, thoracoplasty may be performed the specific indications are : (1) apical cavity, (2) apical cavity with disease in contralateral lung, (3) apical cavity with disease in the same lung.
Though good results are reported after thoracoplasty but the main drawback is unpredictability of results.
- c Cavemostomy : In a very few selected case, tube drainage of the a cavity with abundant bacilli, may be carried out.
- d Artificial pneumoperitoneum may be helpful in a highly selected case but usually not perform⁴⁶.

Morbidity or major complications after surgery

The complication rate in MDR-TB is 20-25%. The major ones being haemorrhage residual apical space, bronchopleural fistula or chronic empyema. The complications may be managed conservatively or if required surgically. The overall mortality from these procedure is 1.5 to 2%, but in "salvage" patients, this may be higher. Post surgically, sputum positivity is observed in 18-25% of patients, but with combined medical therapy or reoperation like "Completion pneumonectomy" Sputum - Status at the end (18-24months) of therapy is 3 to 5%. It is essential for the success of surgery and final cure that aggressive chemotherapy as in preoperative period is continued for 18 months after surgery. Over all cure rate after surgery is 90%. Overall complications like BPF is 10%; post operative empyema in 8% "The surgery in salvage" cases is not as optimistic because it is performed as a "last resort" Salvage cases have morbidity/mortality in 35% as against 7% in properly selected cases. This group includes patients with. (a) Destroyed lung with extensive pleural involvement; (b) Chronic empyema with disease in opposite lung; (c) Hemoptysis with bilateral disease; (d) Sputum positive or relapse in spite of best available drugs.

Tuberculosis with complications like diabetes, and uncontrolled extrapulmonary tuberculosis⁴⁶. In a study of 29 patients selected for surgery 23(79%) of the 29 patients remain sputum culture negative for 9 to 69 months (mean 39 months). However surgery was associated with some morbidity in this debilitated population: 2 post operative death; 1 relapsed and died; 1 patient developed pulmonary hypertension and another had respiratory insufficiency Appropriate drug therapy nutritional support and certain operative techniques may lead to cure rate over 90% in MDR-TB⁴⁷.

Adjuvant Therapies

In addition to the administration of antimicrobial drug therapy and surgery, various other modalities have been proposed but they remain experimental and of uncertain utility at present. They may provide some direction and hope for the development of novel antituberculous agents that are required for treating patients with MDR-TB. These include immunomodulation therapy, laser therapy

gene therapy and some novel chemo-therapeutics.

Immunotherapy or Immunomodulation

Immune modulation can be affected either by enhancing proinflammatory cytokines like IL-2, IL-12, IFN- γ , TNF-L or inhibiting the anti-inflammatory cytokines like IL-4, IL-5, IL-10, addition of serum to enhance humoral factors and diverting the harmful TH2 immune pathway to the beneficial Th1 response by vaccination utilizing *M. vaccae*. However, these are only experimental and controlled trails have failed to confirm utility of therapy.

Aerosolised, interferon- γ in conjunction with other second line drugs may be given to treat MDR-TB⁴⁸. The aim of this treatment was to activate pulmonary macrophages into effective phagocytic cells. It was well tolerated and resulted in temporary sputum smear (but not culture) conversions⁴⁹. *M. vaccae* has been used as immunotherapy in combination with ciprofloxacin, cycloserine and pyrazinamide, in the treatment of a patient with abdominal MDR-TB. The potential role of transfer factor, indomethasone, and Livamasole is still experimental. Ievamisole as an adjunct to drug treatment was reported to cause more rapid radiological clearing without affecting the clinical outcome.

Gene Therapy

The decoding of the human genome provides another fascinating aspect in the future therapeutic intervention of tuberculosis by identifying resistance genes, it will be possible to detect drug resistance before start of therapy and also to develop drugs that target these specific genes and thereby reducing the duration of therapy. A mutant *rpo B* gene has been produced that effectively mimics the mode of action of rifampicin and inhibits transcription⁵⁰. This mutant gene represents a potential suicide gene for MDR-TB if a delivery strategy can be developed.

Laser therapy :

This has been experimented in some countries like Russia and is effective in multicavitary disease with heavy bacterial loads, particularly, when there is an increased chance of failure of medical treatment. This, probably kills bacteria rapidly, increases and improves penetration of antitubercular drugs in walled off lesions and helps in early closure of cavities and is of proven benefit in tracheal and bronchial stenosis due to endobronchial growth. It also reduces the trauma of surgery and post operative complications⁵¹.

Novel Chemotherapeutics

A recently reported drug *ABT-255*, a 2-pyridone inhibits the bacterial DNA-gyrase and has MICs ranging between 0.016 to 0.031 mg/L for drug susceptible and drug resistant isolates of *M. tuberculosis*⁵². Similarly, branched-chain amino acid biosynthesis (*sulphoneturamethyl-a commercial herbicide*) had shown promising antitubercular activity⁵³. *OPU-100480* and *Linezolid* have been found to have activities similar to that of isoniazid and/or rifampicin. *PA-824 (introzimidazopyran)* has shown potent bactericidal activity against MDR-T and promising oral activity. The understanding of the cell-wall synthesis through the use of mycolic acid synthesis,

inhibitors such as thiolactamycin or the thiourea isoxyl may lead to the development of new specific antimicrobial agents. *Non-antibiotics* include chlorpromazine and thioridazine, which are antipsychotic the growth of *M. tuberculosis*⁵⁴. Hence, these phenothiazines and the related antihistaminics may need the attention of researchers.

What do we do Now?

- (a) Primary aim is to control the development of drug resistant tuberculosis which can be done by revision of "National Guidelines" based on levels of resistance, training of professionals in private sector, strengthening existing national tuberculosis control programme, restricting use of Rifampicin (for TB and Leprosy only)
- (b) Taking logistic measures to ensure regular supply of drugs at all levels of National tuberculosis control programmes and by ensuring measure like providing free/subsidized antitubercular drugs.
- (c) DOT is essential and therefore, supervised treatment with fixed drug combination and health education are integral to success. Strict drug quality control is also essential.
- (d) Providing widespread susceptibility testing with quality control laboratories.
- (e) WHO has proposed the work plan known as *DOTS-PLUS*⁵⁵ and established Green Light Committee⁵⁶ to implement it. Main focal point are to :- Ensure adherence to full course of treatment, cure MDR-TB with second line drug. Provide DOT-PLUS in areas where MDR-TB has emerged due to previous inadequate TB-control programmes; Provide DOT-PLUS in settings where the DOTS-strategy is fully in place to protect against the drug resistance; Implementation of DOTS-PLUS will minimize the risks of creating drug resistance to second line Anti TB Drugs; If possible, National Control Programme may apply "Molecular epidemiology detect virulent clones of MDR-TB; The support to drug discovery programme should be a priority.

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