**MANAGEMENT OF MULTI-DRUG RESISTANT TUBERCULOSIS:**
**PRACTITIONER’S VIEW POINT**

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**Summary:** Multi-Drug Resistant Tuberculosis (MDR-TB) is a growing hazard to human health worldwide and a threat to control of tuberculosis. Current estimates report the prevalence of primary and acquired MDR-TB in India as 3.4% and 25% respectively. MDR-TB is suspected if sputum is persistently positive for AFB along with clinical and radiological deterioration after multiple courses of irregular or regular treatment including 4 months of WHO retreatment regimens under direct observation. Diagnosis is confirmed by drug susceptibility testing from reliable and reputed laboratories under constant quality control. Reports of susceptibility should not be accepted uncritically. Treatment of MDR-TB should be at a specialized centre with standard microbiology laboratory facilities. Though treatment guidelines including standardized, empirical and individualized approaches have been laid down by the WHO but therapy should be tailored to the needs of the particular patient. Treatment of MDR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts to prevent morbidity, mortality and transmission of MDR-TB. Current proposal of DOTS Plus by WHO highlights the comprehensive management strategy to control MDR-TB. MDR-TB is a man-made problem and its emergence can be prevented by prompt diagnosis and effective treatment of all TB cases. Adoption of directly observed treatment short course (DOTS) to prevent the resistant/multi-drug resistant strains and careful introduction of second line drugs to treat patients with MDR-TB are the top priorities for the proper control of MDR-TB. **[Indian J Tuberc 2007; 54:3-11]**

**Key words:** Multi-Drug Resistant Tuberculosis, Diagnosis, Treatment

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**INTRODUCTION**

Drug resistant tuberculosis has been reported since the early days of introduction of anti-tubercular chemotherapy, but recently multi-drug resistant tuberculosis (MDR-TB), has been an area of growing concern, and is posing threat to global efforts of tuberculosis control. Prevalence of MDR-TB, in a community mirrors the functional state and efficacy of tuberculosis control programme and realistic attitude of the community towards implementation of such programmes. Management of MDR-TB is difficult, much expensive, challenging and quite often leads to treatment failure. The present write-up focuses on the management of MDR-TB.

**DEFINITION**

Multi-drug resistant tuberculosis is defined as disease due to *M tuberculosis* that is resistant to Isoniazid (H) and Rifampicin (R), with or without resistance to other drugs. Primary drug resistance is defined as drug resistance in a patient who has not received any anti-tubercular treatment in the past, while acquired drug resistance is defined as resistance that develops in a patient who has received prior chemotherapy. Recently the terms “resistance in new cases” and “resistance in previously treated cases,” have been proposed for use because of the difficulty to confirm the validity of the patients’ past history of treatment. When one is not sure whether the resistance is primary or acquired or unaware of patient’s previous treatment, drug resistance is known as initial drug resistance.

**MAGNITUDE OF PROBLEM**

**Global:** First information on global magnitude of MDR-TB came in 1997, when WHO - IUATLD reviewed 63 surveys, and reported that range of primary MDR-TB varied from 0-10.8% and acquired MDR-TB varied from 0-48% in various studies. In most regions of the world, the rate of MDR-TB was very low and varied considerably throughout the world, which was due to difference in degree of patients studied, the degree of misuse of drugs, the quality of enquiry regarding previous treatment and inadequate culture and drug susceptibility facilities...
in many parts of the world. Considering the limitations of previous studies, a WHO – IUATLD global project on anti-tubercular drug resistance surveillance spread over 35 countries in 5 continents was carried out during 1994-97, which reported the median prevalence of primary and acquired MDR-TB as 1.4% and 13% respectively. In this project, regions with prevalence of MDR-TB greater than 5% were labelled as MDR hotspots. Subsequent second report of this global project conducted from 1996-99, reported the median prevalence of primary and acquired MDR-TB as 1% and 9% respectively. Most of the previous hotspots were confirmed again, while new areas in Russia and China were added. The analysis trend has confirmed that MDR-TB is not a major problem in countries implementing tuberculosis control according to international guidelines for several years. Countries like Botswana, Chile, Cuba, Czech Republic and Uruguay have shown very low prevalence of MDR-TB, confirming that efficient tuberculosis control prevents the development and spread of MDR-TB. The third global surveillance of WHO – IUATLD, carried out in 1999-2002, reported median prevalence of primary and acquired MDR-TB as 1.1% (0-14%) and 7% (0-58.3%) respectively. After analysis, the cut-off value for hotspots was reset to 6.5% in this new report.

India: Clinical perception and several isolated reports indicated the development of drug resistance in India, since the beginning of chemotherapeutic era, but they failed to give an idea of national situation as a whole. Pioneering step in this direction was taken by Indian Council of Medical Research (ICMR) in 1965-67 when it conducted two surveys to estimate the prevalence of drug resistance. Several studies conducted subsequently in different parts of country, revealed that the total prevalence of primary / initial MDR-TB varies from 0-5%. The rates of acquired MDR-TB varies from 6 to 60%. The median prevalence of primary and acquired MDR-TB in India according to WHO-IUATLD report on global drug resistant surveillance, conducted between 1996-99 is 3.4% and 25% respectively. Despite the variable results of acquired MDR-TB, the message is very clear that it is not in isolated pockets, but in the country as a whole.

**RISK FACTORS OF DRUG RESISTANCE**

Three most important risk factors, identified in the causation of drug resistant tuberculosis are- inappropriate previous treatment with anti-tubercular drugs, high prevalence of drug resistant tuberculosis in the community and contact with patients known to have drug resistant tuberculosis. However standardized short course chemotherapy carries a little risk of emergence of MDR-TB. Other factors that may be responsible for increased risk of resistant tuberculosis are : Co-infection with HIV, socio-economically deprived groups in slums, prisons, correctional facilities, day care centres, intravenous drug abusers and other immuno-compromised states as in transplant recipients, anti-cancer chemotherapy recipients and patients with diabetes mellitus.

**SOURCES AND CAUSES OF DRUG RESISTANCE**

Multi Drug Resistant Tuberculosis is a man made problem. Blame for this goes to the government, the pharmaceutical industry, doctors, patients and their families, each of whom contributes in his/her own way to this problem. The government plays its share by providing poor infrastructure in the National Tuberculosis Control Programme, unnecessary administrative control on purchase with no proper mechanism on quality control and bioavailability tests. The pharmaceutical industry contributes by manufacturing drugs of uncertain bio-availability in fixed dose or inappropriate drug combinations, poor storage condition of drugs and substitution by inferior quality drugs by pharmacies. The doctor, by his lack of knowledge regarding doses, duration of treatment, side effects and standard regimens, frequent change of brand names and poor patient motivation, contributes the lion’s share to the problem. In one of the studies where prescriptions of 449 doctors were analyzed, 75% of the doctors were found to have made some prescription error. Added to this is the poor teaching and training facilities for them. Non-compliant patients due to monetary lack, lack of information, side-effects of drugs and social myths and misconceptions often do not adhere to treatment. Co-morbid conditions like diabetes, HIV, psychiatric conditions, the habits of smoking and alcoholism...
make the patient more vulnerable. To sum up, drug resistant tuberculosis usually results from inadequate drug therapy in multi-bacillary cases of tuberculosis, addition of single drug in cases of failure, difficulty in obtaining drugs by the poor due to lack of financial resources or social insurance, frequent shortage of second line anti-tuberculous drugs by poor management and/or financial constraints, use of drugs or combination of drugs (FDC) with unproven bioavailability, lack of motivation at the beginning of treatment and inadequate self-administration of drugs without direct observation in the intensive phase of therapy.

DIAGNOSIS OF MULTI-DRUG RESISTANT TUBERCULOSIS

It is needless to emphasize that early diagnosis and treatment of drug resistant tuberculosis is of paramount importance not only from the patient’s perspective but also for the community at large. The suspicion of MDR-TB occurs in following situations:

1. History of contact with known cases of Drug Resistant / MDR-TB patients.


3. Clinical deterioration is the least reliable evidence of treatment failure. If there is no accompanying bacteriological or radiological deterioration, clinical deterioration is unlikely to be due to tuberculosis.

4. Radiological deterioration in chest radiograph may be a sign of treatment failure. Increase in size of cavities, increase in existing lesion and appearance of new lesion are usually signs of disease progression. One should also realize that deterioration in chest radiograph, may be due to intercurrent pneumonia, pulmonary embolism or supervening carcinoma. Therefore, radiological evidences are less reliable. However, radiological worsening in addition to positive sputum and/or clinical worsening can indicate resistant tuberculosis.

5. Persistent positive sputum smear for AFB even after 4/5 month WHO retreatment regimens.

6. Fall and rise phenomenon in which sputum smear initially becomes negative (or even less positive), and then later becomes persistently positive. This indicates failure usually due to either the patients having ceased to take the drugs or to the development of resistance to all the drugs patient is receiving.

7. Report of sensitivity results indicating resistance to at least Isoniazid and Rifampicin is gold standard for the diagnosis of MDR-TB. However, one has to keep in mind the limitation of highly specific test because the technique is complex and difficult to perform accurately even when skilled personnel are available and laboratory facilities are of a high standard. Further one should also realize that laboratories vary in reliability, error occurs in labs, different sensitivity reports are obtained from the same patient from different laboratories. There is a lack of standardization, coordination and cross-checking with national and supranational reference laboratories in our country. Keeping above background in mind, it is pertinent that sensitivity test result should not be accepted uncritically, they should always be correlated with history, smear results and x-ray and should be used as a guide for future therapy and should not dictate treatment options. Therefore there is urgent need to develop standard laboratories under quality control of national and supranational reference laboratories in our country.

8. Newer molecular techniques like DNA sequencing, Line Probe Assay (LiPA), DNA microarrays, molecular beacons, Single strand confirmation polymorphism, fluorescent Resonance Energy Transfer probes, other PCR based techniques and Mycobacteriophages based assays like FAST Plaque TB and Luciferase receptors phages (LRPs) have been used for identification of resistance associated mutation. The expectation that molecular techniques would surpass conventional methods has yet not been realized because most of techniques still require detailed and systemic evaluation using standard techniques.
as references before their application in clinical setting. These techniques might be used as complement to the standard methods in situation of difficult diagnosis but should never be used solely for diagnosis of drug resistance²⁵.

TREATMENT OF MULTI-DRUG RESISTANT TUBERCULOSIS

The management of multi-drug resistant tuberculosis is an area that has been shrouded in a lot of myths and misconceptions, and therefore utterly chaotic. Though treatment guidelines, including standardized, empirical and individualized approaches have been laid down by the WHO, but therapy should be tailored to the needs of the particular patient.

Basic principles of chemotherapy in multi-drug resistant tuberculosis²⁶-³⁰

1. Treatment should be in a specialized centre with standard laboratory facilities.

2. Early diagnosis of MDR-TB and prompt initiation of treatment are important for successful outcome.

3. Designing an appropriate regimen needs experience and skill. Regimen should be based on previous history of anti-tuberculous drugs taken by the patients. Drugs susceptibility test when available from reliable laboratories should be used to guide therapy.

4. Regimens should contain at least four drugs that are highly likely to be susceptible based on drug susceptibility test and/or previous intake of anti-tuberculous drugs by the patient. Often more than four drugs may be started if the susceptibility pattern is unknown, if effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary tuberculosis is present.

5. Use any first line oral agent to which isolate is sensitive. Use one injectable, one fluoroquinolone and add as many second line bacteriostatic agents as needed to complete the regimens. Injectable agent should be continued for at least six months.

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

7. It is ineffective to combine two drugs of the same group or to combine in the prescribed chemotherapy regimen a drug potentially ineffective because of cross-resistance. Cross resistance has been reported between Thioamides and Thioacetazine, Kanamycin/Amikacin with Streptomycin²⁵,²⁶. Rifampicin with Rifapentine, Rifabutin (>70% strains) and among various derivatives of fluoroquinolones. Cross-resistance has also been reported between Ethionamide and Isoniazid, Viomycin and Kanamycin, Viomycin and Capreomycin. Strains resistant to Streptomycin/Kanamycin/Amikacin are still sensitive to Capreomycin.

8. All the drugs should be given in a single daily dose preferably, except PAS which is usually given in two divided doses in order to avoid problems of intolerance. Among Thioamides, Prothionamide is better tolerated than Ethionamide.

9. Intermittent therapy is usually not effective and should be avoided in multi-drug resistant tuberculosis.

10. No drug should be kept in reserve and the 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.

11. Therapy should be under direct observation preferably for 3-4 months or till the sputum conversion.

12. Surgical treatment should be considered as an adjunct to chemotherapy wherever applicable, as results of chemotherapy are very unpredictable.

13. All measures should be taken to persuade and encourage patients not to stop treatment despite
DRUGS USED IN MDR-TB AND THEIR TOXICITIES

The second line drugs used for treatment of multi-drug resistant tuberculosis are given in Table 1 with their dosages in decreasing potency from top to bottom against *mycobacterium tuberculosis*. Reserve drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and change of regimen. The author reported that 41% patients, experienced some side effects and only 21.1% patients required stoppage or change of drug in their study of 39 patients of MDR-TB\textsuperscript{31}. Second line reserve drugs, their toxicities and management are given in Table 2.

REGIMEN FOR MULTI-DRUG RESISTANT TUBERCULOSIS

World Health Organization recommended regimens\textsuperscript{26-30} without availability of sensitivity results are given in Table 3, while regimens with availability of sensitivity results are given in Table 4. In Indian...
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set-up, most of the time either sensitivity test results are not available or if available they are usually highly unreliable. Keeping this fact in mind, depending upon past history of anti-tuberculous treatment and resistance pattern, the author himself has used regimen containing Kanamycin, Ethionamide, PAS, Cycloserine, and Fluoroquinolone in treating multi-drug resistant tuberculosis and found to be effective in 3171% of patients.

### Table 2: Toxicities and their management.

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Suspected Agent(s)</th>
<th>Suggested Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>Cycloserine</td>
<td>Suspend suspected agent pending resolution of seizures</td>
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<tr>
<td></td>
<td>Isoniazid</td>
<td>Start anticonvulsant therapy.</td>
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<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>Increase Pyridoxine to 200-mg/ day.</td>
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<td></td>
<td></td>
<td>Restart suspected agent in lower dose if essential to the regimens.</td>
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<tr>
<td></td>
<td></td>
<td>Discontinue suspected agent if it can be done without compromising regimen.</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>Kanamycin</td>
<td>Document hearing loss.</td>
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<tr>
<td></td>
<td>Streptomycin</td>
<td>Change to Capreomycin.</td>
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<tr>
<td></td>
<td>Amikacin</td>
<td>Increase frequency and/or lower the dose of suspected agent.</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>Discontinue drug if it can be done without compromising regimen. The risk of further hearing loss must be weighed against the risk of stopping the drugs.</td>
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<tr>
<td></td>
<td>Clathromycin</td>
<td></td>
</tr>
<tr>
<td>Psychotic symptoms</td>
<td>Cycloserine</td>
<td>Hold suspected agent for short period (1-4 weeks).</td>
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<tr>
<td></td>
<td>Isoniazide</td>
<td>Initiate anti-psychotic drugs.</td>
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<tr>
<td></td>
<td>Fluoroquinolone</td>
<td>Lower the dose of drug.</td>
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<tr>
<td></td>
<td>Ethionamide</td>
<td>Discontinue drug if it can be done without compromising regimen.</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Ethionamide, PAS</td>
<td>Assess for dehydration, rehydrate if needed.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Initiate anti-emetic therapy.</td>
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<tr>
<td></td>
<td></td>
<td>Lower the dose of drug.</td>
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<tr>
<td></td>
<td></td>
<td>Discontinue drug if it can be done without compromising regimen.</td>
</tr>
<tr>
<td>Gastritis</td>
<td>Ethionamide, PAS</td>
<td>H2 -blocks, proton pump inhibitors, Antacids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hold suspected agent for short period (1-7 days)</td>
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<tr>
<td></td>
<td></td>
<td>Lower the dose of drug.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Discontinue drug if it can be done without compromising regimen.</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>Pyrazinamide</td>
<td>Stop all therapy</td>
</tr>
<tr>
<td></td>
<td>Ethionamide</td>
<td>Rule out other potential causes of Hepatitis.</td>
</tr>
<tr>
<td></td>
<td>PAS</td>
<td>Re-introduce drug serially while monitoring liver function with most likely agent introduced last.</td>
</tr>
<tr>
<td>Renal Toxicity</td>
<td>Kanamycin</td>
<td>Discontinue suspected agent.</td>
</tr>
<tr>
<td></td>
<td>Capreomycin</td>
<td>Consider using Capreomycin if an amino-glycoside had been prior injectable in regimen.</td>
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<tr>
<td></td>
<td>Amikacin</td>
<td>Consider dosing 2-3 times a week if drug is essential and patients can tolerate.</td>
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<tr>
<td></td>
<td></td>
<td>Adjust dose according to creatinine clearance.</td>
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<tr>
<td>Hypothyroidism</td>
<td>PAS</td>
<td>Initiate thyroxine therapy.</td>
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<tr>
<td></td>
<td>Ethionamide</td>
<td>Completely reversible on discontinuation of drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The combination of Ethionamide with PAS is more associated with hypothyroidism.</td>
</tr>
<tr>
<td>Hypokalaemia and Hypomagnesaemia</td>
<td>Capreomycin</td>
<td>Check serum potassium levels.</td>
</tr>
<tr>
<td></td>
<td>Kanamycin</td>
<td>If potassium is low check magnesium and calcium.</td>
</tr>
<tr>
<td></td>
<td>Amikacin</td>
<td>Replace electrolytes as needed.</td>
</tr>
</tbody>
</table>

### DURATION OF TREATMENT

The optimal duration of therapy for MDR-TB has not been clearly established and duration remains questionable. However, several authorities including the WHO recommend treatment with anti-tubercular drugs for a period of at least 18-24 months after sputum conversion or 12 months after sputum culture becomes negative to prevent relapse. Injectable drugs are preferably used for at least six months.
and at least four months after the patients first become and remain sputum smear or culture negative.

**MONITORING OF TREATMENT**

Sputum specimens should be obtained for smear and culture monthly during intensive phase of therapy. After sputum conversion, smear examination and culture are done once in three months till the end of therapy. Markers of response in order of reliability are bacteriology of sputum, radiology followed by the clinical picture.

**Surgery**

Surgery should be considered in patient with persistent culture positive MDR-TB despite effective medical treatment. If the patient has localized disease,
reasonable lung function and only two or three (weak) drugs available, surgery should be seriously considered. Resectional surgery is done as an adjunct to medical treatment. It has been shown that overall cure rate was substantially higher (81% vs 56%) when surgery was more frequently and aggressively applied. Feasibility and success of surgery appear to be substantially enhanced by nutritional support. In one of the recent studies use of resection surgery and fluoroquinolone therapy was associated with improved microbiological and clinical outcome.

CONCLUSION

MDR–TB is a growing hazard to human health world wide. MDR-TB is suspected if sputum is persistently positive for AFB with clinical and radiological deterioration after multiple courses of irregular/regular treatment. Drugs susceptibility test for Mycobacterium tuberculosis from reliable and reputed laboratory under constant quality control is gold standard for the diagnosis of MDR-TB. Do not accept sensitivity report uncritically if it is not from a reliable lab. Treatment should be in a specialized centre with standard microbiology laboratory. MDR–TB is a man made problem and its emergence can be prevented by prompt diagnosis and effective treatment of all TB cases. Adoption of Directly Observed Treatment - short course (DOTS) to prevent multi-drug resistant strains and careful introduction of second line drugs to treat patients with MDR-TB are the top priorities for the proper control of MDR-TB.

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