MANAGEMENT OF DRUG RESISTANT AND MULTIDRUG RESISTANT TUBERCULOSIS

Rajendra Prasad, Etawah

INTRODUCTION

Drug resistant tuberculosis (DR-TB) has been reported since the early days of introduction of antitubercular 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 DR-TB and MDR-TB is difficult, much expensive, challenging and quite often leads to treatment failure. This chapter aims to illustrate the diagnosis and treatment of drug resistant and multidrug resistant tuberculosis.

DEFINITION

Drug resistant tuberculosis is defined as a case of tuberculosis excreting bacilli resistant to one or more anti-tubercular drugs. Multi-drug resistant tuberculosis (MDR-TB) is defined as disease due to M. tuberculosis that is resistant to Isoniazid and Rifampicin with or without resistance to other drugs (the culture and drug susceptibility test result being from an RNTCP accredited laboratory). Mono-resistance is defined as resistance to one antituberculosis drug while poly-resistance is defined as resistance to more than one antituberculosis drug, other than both Isoniazid and Rifampicin.

MECHANISM OF DRUG RESISTANCE

Drug resistance in tuberculosis occurs by random single step spontaneous mutation at a low but predictable frequency in large bacterial populations. There is no convincing evidence for the role of plasmids or transposons as in other bacterial pathogens. The probability of drug resistant mutants in the case of Rifampicin is $10^{-8}$, for INH, Streptomycin and Ethambutol is $10^{-6}$ and for Ethionamide, Cycloserine, Capreomycins and Thiacetazone $10^{-3}$. The probability of resistance developing in a 2.5 cm cavity which harbours $10^8$–$10^9$ bacilli is $10^6$ for INH and $10^8$ for Rifampicin and $10^{14}$ for INH and Rifampicin together. In reality therefore, only one of the bacilli in $10^{14}$ organisms will be resistant to both Isoniazid and Rifampicin. This illustrates a very fundamental principle that multi-drug resistant tuberculosis is a man made problem.

GENETIC BASIS OF DRUG RESISTANCE

Dramatic discoveries in the field of molecular biology in the last few years have greatly increased our understanding of the mechanism of drug resistance. The findings of such discoveries led to the conclusion that the primary mechanism of multiple drug resistance in tuberculosis is due to alterations in individual drug target genes. Isoniazid resistance has been found to be due to a defect in the kat G gene which codes for the catalase peroxidase enzyme. Mutation in Kat G, Inh A and ahp C (alkyl hydroperoxide reductase) genes are found in up to 90% of isoniazid resistance. Rifampicin resistance (>96%) has been associated with mutations in the rpo B gene. Pyrazinamide resistance (72-97%) to pncA mutations, Ethambutol (47-65%) to mutations in emb AB gene, Streptomycin resistance with rrs or rpsL mutations and Fluoroquinolone resistance (75-94%) with substitutions in gyr A gene. Apart from these 11 genes, additional genes and mechanisms may play a role particularly in association
with lower levels of resistance.

**VIRULENCE AND DRUG-RESISTANT STRAINS**

The traditionally received wisdom about drug resistant strains of tuberculosis that they are less virulent was based substantially on the observation by Cohn et al. that virulent strains of M. tuberculosis, when selectively bred in the laboratory for high level resistance to INH, became significantly less capable of producing progressive infection in animal models. This was associated with loss of catalase activity by bacilli. Snider et al. observed that there is a no lesser risk of infection when contacts are exposed to tubercular bacilli resistant to high concentration of INH and SM. Ordway et al. have observed that some MDR-TB strains that exhibit invivo growth rates and animal virulence characteristics comparable to the most virulent, wild type drug susceptible strains. Frieden et al. in their report of multi institutional spread of notorious ‘Strain W’ in New York City reported despite mutation in the Kat G locus, strain was catalase positive and grows rapidly in culture media and animals. Overall, evidences indicate that current drug-resistant strains have demonstrated the capacity to produce progressive disease in both normal and immunosuppressed contacts.

**IMPACT OF DRUG RESISTANCE ON THE OUTCOME OF CHEMOTHERAPY**

In early treatment era it was recognized that the resistance with Isoniazid (H) and streptomycin (S) was associated with increased risk of treatment failure but in current situation, the loss of single drug to resistance is potentially less significant because of availability and use of potent agents such as rifampicin, pyrazinamide, ethambutol (E). The most reliable data on treatment outcome were derived from British Medical Research Council (BMRC) short course chemotherapy trials performed in East Africa, Hong Kong, Singapore. Failure rate of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Streptomycin (S) containing regimen among such cases, was less than 5% in contrast to approximately 20% failure rate among cases assigned to less potent regimens. Thus it is possible to obtain good result with use of six months short course chemotherapy with Isoniazid, Rifampin, Pyrazinamide and streptomycin or Ethambutol when initial susceptibility test indicates resistance to Isoniazid and/or Streptomycin. It was also confirmed in Indian study that strains resistant to isonizid, streptomycin, or both neither pose a major problem nor affect the result of treatment in a big way provided proper regimens are used. On the contrary, patients infected with organisms resistant to rifampicin, isonizid or both have a high rate of treatment failure and this forms a major threat to tuberculosis control programmes particularly for countries like India with poor resources. Four separate studies from New York city between 1995-1996 on response to therapy for patient with MDR-TB reported better outcome can be demonstrated with early recognition of resistance and administration of effective drugs.

**DIAGNOSIS OF DRUG RESISTANT AND MULTI DRUG RESISTANT TUBERCULOSIS**

It is needless to emphasize that early diagnosis and treatment of drug resistant and multi drug resistant tuberculosis is of paramount importance not only from the patient’s perspective but also for the community at large, failing this there will be propagation of the deadly drug resistant bacilli, decreased chances of cure for the patient, increasing cost of therapy and unnecessary drug toxicity. The diagnosis of drug resistant and multi drug resistant tuberculosis is based on – Clinical, Radiological and Bacteriological evidences.

**CLINICAL EVIDENCE**

This comprises of the signs and symptoms and past history of anti-tubercular therapy. History of prior treatment with anti-tubercular drugs is most important. The other important aspects of the history include contact with a known case of resistant tuberculosis and patient’s place of residence which may have a high prevalence of drug resistance. The salient points in the past treatment history should include the drugs and regimens followed, dosage of drugs and duration of each course of treatment, regularity in taking the drugs, response to treatment in terms of relief of symptoms and bacteriological indices if available, and any adverse drug reactions suffered. The ICMR in its study has shown that longer duration of chemotherapy and single drug therapy in the past was associated with greater degrees of resistance. In the context of our country where illiteracy is the main culprit, several difficulties may be encountered in eliciting reliable information. Some of the common problems faced by the physician include unawareness or forgetfulness of the patient so that he is unable to give a proper history, poor record keeping of prescriptions, sputum examination reports and x-rays, drugs dispensed by private practitioners without a proper prescription and the practice of prescribing combipacks making it impossible for the patient to remember the names. MDR-TB Suspect is defined as a TB patient who fails an RNTCP Category I or III treatment regimen and any RNTCP Category II patient who is sputum smear positive at the end of the fourth month of treatment or later. It must be remembered that clinical evidences are the least reliable for the diagnosis of drug resistant and multi drug resistant tuberculosis. However, clinical deterioration in the presence of sputum smear positivity and/or radiological worsening can be considered due to resistance.

**RADIOLOGICAL EVIDENCE**

Though radiology is not a very reliable indicator for predicting drug resistance, yet it serves to complement the clinical and bacteriological evidence of the patient. The presence of...
multiple or giant cavities and destroyed lung increases the probability of drug resistance. Change in size of cavities, increase in size of existing lesions and appearance of new lesions are signs of disease progression and activity. Serial x-rays showing worsening in the forms as described above at the end of three months of regular and adequate chemotherapy can make one suspicious of drug resistance. These radiological findings at the end of three months in addition to positive sputum and/or clinical worsening can be diagnosed as resistant tuberculosis.19 However, one should also realize that radiological worsening may be due to pneumonia, pulmonary embolism and supervening carcinoma.

**BACTERIOLOGICAL EVIDENCE**

The bacteriological criteria serve as the gold standard in the detection of drug resistant tuberculosis. This is based on sputum smear microscopy and culture of *M. tuberculosis* and drug susceptibility testing (DST) to the various primary and second line anti-tubercular drugs. Sputum smear microscopy, after starting standard chemotherapy can show a positive, negative or suboptimal response. While positive response is characterized by sputum conversion at 2/3 months of chemotherapy, a negative response could mean persistent smear positivity at the end of 3 months of adequate chemotherapy and a suboptimal response by an initial fall in the sputum grade followed by a gradual rise - the so called ‘fall & rise’ phenomenon20 while the patient is on anti-tubercular therapy. The last two patterns increase the probability of drug resistant tuberculosis. The confirmation of the presence of drug resistance is obtained by culture of *M. tuberculosis* and drug susceptibility testing. Even the definition of drug resistance is one that is based on susceptibility test results i.e. Confirmed MDR-TB case is a MDR-TB suspect who is sputum culture positive and whose TB is due to *Mycobacterium tuberculosis* that are resistant *in-vitro* to at least isoniazid and rifampicin18 (the culture and DST result being from an accredited laboratory). Ideally DST should be done in all patients undergoing retreatment, but since this is not feasible in an Indian setup, it is better to do DST for MDR-TB suspects. It is, however, noteworthy that culture and sensitivity in spite of continuing to be the gold standard for diagnosis of tuberculosis and drug resistance, is not fool proof and one has to keep in mind the limitations of this highly specific test. This is because the technique is complex and it is difficult to perform sensitivity tests accurately even when skilled personnel are available and laboratory facilities are of a high standard. This is true even in highly industrialized nations such as the United Kingdom and the United States. In the United Kingdom re-testing of 234 strains of drug resistant bacilli by a reference laboratory showed discordant reports in 50-70% of the results reported by local laboratories.19 Additional limitations are the difficulty and unreliability of testing susceptibility to second line drugs.

In the United States 43 laboratories which were having above average laboratory standards tested the results of a reference laboratory. The results obtained were as follows – consistently good in 23, adequate in 9 and poor in 11. The WHO thus concluded that the wide scale on which unreliable sensitivity tests are reported, even in technically advanced countries, gives a cause for concern.21-23 However recently due to setting up of supranational reference laboratory network, there is improvement in quality susceptibility testing of national reference laboratories and surveys carried out within the WHO/IUATLD global project on drug resistance surveillance. These initiatives apply to surveillance and not to clinical practice.24 Susceptibility testing for isoniazid, rifampicin, the fluoroquinolones, and the injectable agents is fairly reliable. For other agents it is less reliable, and basing individualized treatments on DST for these agents should be avoided. The clinical effectiveness or ineffectiveness of a drug cannot be predicted by DST with 100% certainty.25

Laboratories performing culture/susceptibility testing are situated in only a few major cities in India. The WHO definition of resistance based on drug susceptibility reports therefore becomes only a theoretical exercise in our country in most occasions.20 The laboratories vary in reliability; errors occur in labs, different sensitivity reports are obtained of the same patient from different laboratories due to sampling of different populations of bacilli and different techniques employed. Standardization, co-ordination and cross checking facilities with reference laboratories do not exist in our country by and large, thus magnifying the problem. On this background, it is pertinent to reaffirm that drug susceptibility testing should not be accepted uncritically, they should be correlated with prior treatment history, smear result and x-ray and should be used as a guide for future therapies and not dictate treatment options. If sensitivity report does not fit with other available evidences, it should be discussed with a microbiologist and the test repeated.

**RAPID CULTURE TECHNIQUE**

In this technique culture time is reduced from an average 38.5 days to 18 days. Technique usually applied is BACTEC system and Mycobacterial Growth Indicator Tube (MGIT). In BACTEC, 7H12, and in MGIT, 7H9 middle Brooke media is used. In BACTEC method, the released radio labelled carbon dioxide is detected that indicates growth of *Mycobacterium tuberculosis* whereas in MGIT the oxygen sensitive fluorescent compound is used to detect growth of *M. tuberculosis*. The rapid culture technology takes much shorter time as compared to L.J. media.26,27 A higher degree of concordance has been documented between susceptibility data from the BACTEC system and those obtained by conventional solid media method.28 In fact the rapid radiometric system offers a substantially more quantitative approach to the determination of susceptibility than other method,29 another major advantage of BACTEC system that it can also perform susceptibility test
for pyrazinamide.\textsuperscript{30}

**MOLECULAR BIOLOGICAL TECHNIQUE**

For identification of resistance associated mutation molecular techniques like - DNA sequencing, Line Probe Assay (LiPA), DNA microarrays, molecular beacons, Single strand conformation polymorphism, fluorescent Resonance Energy Transfer probes, other PCR based techniques or Mycobacteriophages based assays like - FAST Plaque TB and Luciferase receptors phages (LRPs) has been used. WHO with the Stop TB Partnership, UNITAID and the Foundation for Innovative New Diagnostics (FIND) together unveiled a new Policy endorsing use of Line Probe Assays in low resource countries. There are two types, the Geno Type MTB-DR assay and INNOLiPA Rif.TB assay. Advantages include rapid screening of patients with MDR-TB risk and results within 2 days as compared to 2-3 months for conventional cultures. At present their use is limited to culture isolates and direct testing of sputum specimens. They are not recommended as a complete replacement to the conventional culture and DST.\textsuperscript{31} Currently LiPA is not useful for detecting mutations responsible for drug resistance in second line drugs. Molecular techniques involves detection of resistant genes or DNA sequencing of M. tuberculosis by amplification of nucleic acid and its identification. The Polymerase Chain Reaction single strand conformational polymorphism (PCR SSCP)\textsuperscript{32} and restriction fragment length polymorphism (RFLP)\textsuperscript{33,34} analysis are usually applied. The PCR when compared with culture results, the sensitivity, specificity, and positive predictive value were found 83.5\%, 99\% and 94.2\% respectively. RFLP gives fingerprint of strains which is specific for each strain of M. tuberculosis, so has more valuable place for molecular epidemiology in differentiating the strains. Overall, RFLP analysis has immense potential as a tool to study transmission patterns and the natural histories of primary and re-infection tuberculosis specifically in HIV infected patients\textsuperscript{34} while Luciferase Reporter Assay rapid system based on enzyme Luciferase, involves the introduction of this enzyme into Mycobacterium tuberculosis via a reporter phage system. Exposure of Luminous Mycobacterium to antimicrobial agents would block luminous activity in the sensitive bacilli but with no effect on resistant bacilli. This method requires substantial growth of mycobacterium population (about 10\(^6\)) yet, the potential of such methodology is intriguing, perhaps playing a role in industrial screening of large numbers of compounds for anti-mycobacterial activity.\textsuperscript{35} 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 compliment to the standard methods.\textsuperscript{36}

**TREATMENT OF DRUG RESISTANT AND MULTI DRUG RESISTANT TUBERCULOSIS**

The WHO recommends that treatment of drug resistant and multi-drug resistant tuberculosis should be ideally carried out in a hospital that has a specialized unit for dealing with such cases with trained doctors and laboratory personnel. There should be standard laboratory facilities for carrying out reliable drug susceptibility testing and uninterrupted supply of drugs. 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 guidelines in general have been laid down by the WHO, which have been found cost effective and feasible in resource limited countries but they may not be applicable to every patients where individualized treatment regimens depending on reliable sensitivity report may be used. Use of standardized or individualized treatment regimens is currently subject of operational studies to assess the feasibility and cost effectiveness. In some countries, a standardized regimen for certain groups of patients may be more appropriate than an individualized regimen, while in others the converse may be best. Most of the guidelines for the management of Drug resistant TB are primarily for high income nations, where expert diagnostics and optimal care are available. Low income nations will inevitably require different approaches than those of the more affluent, industrialized nations. Individualised regimens are based on individual DST and prior treatment history, require close follow up by skilled professionals and incur high cost. Management issues in second-line drugs are complex, especially when individualized treatment regimens are used. Drugs are frequently changed as a result of adverse effects, delayed DST results and poor response to treatment. Standardized regimens for middle to low income nations are based on DRS data from representative patient populations. Such regimens reduce the number of specialist physicians needed and cost of treatment by 5-10 times. WHO has designed the DOTS Plus regimen for managing MDR-TB in resource poor nations like India. Even in countries where reliable DST is available, standardized regimens may be chosen as a strategy over individualized regimens for the following reasons: Interpretation of DST to some of the first- and second-line drugs is difficult and could mislead regimen design. Standardized regimens can give guidance to clinicians and prevent basing decisions on DST that is not reliable, turnaround time for many culture-based DST methods is long, the laboratory may not perform DST of certain drugs, or may perform them at different times. Results from rapid methods (molecular) may be available within days, but only for certain first-line drugs such as isoniazid and rifampicin. Many laboratories perform second-line DST only after resistance to first-line drugs is confirmed. Accounting for the effectiveness of the 5 drug groups, it is a known fact that the first line drugs are more powerful, cheaper and effective. Given the circumstances it would be ideal to add one or more
first line drugs to any regimen based on the appropriate DST.

**SECOND LINE DRUGS AND THEIR DOSAGE**

The second line drugs used for treatment of drug resistant and multi drug resistant tuberculosis are given in Table 1 with their dosages in decreasing potency from top to bottom against mycobacterium tuberculosis. It is generally thought that, second-line drugs are frequently associated with very high rates of unacceptable adverse drug reactions, needing frequent interruption and change of regimen, but in clinical practice it is observed that these drugs are fairly tolerated. Author himself in one of study reported that 41% patients, experience some side effects but only 21.1% patients required stoppage or change of drug in their study of 39 patients of MDR-TB. Thus it is practically possible to treat the patients of MDR-TB with these drugs

**CROSS RESISTANCE**

Cross resistance has been reported between thioamides and thioacetazone (one way resistance – strains resistance to thioacetazoneare susceptible to thioamides the reverse is seldom the case), kanamycin/amikacin with streptomycin, rifampicin with rifapentine, and rifabutin (>70% strains) and among various derivatives of Fluoroquinolones. Cross-resistance between the fluoroquinolones is almost complete. Limited evidence suggests that the third-generation fluoroquinolones (notably moxifloxacin) do not have complete cross-resistance with the older generations and may have enhanced clinical benefit due to their low MICs, enhanced antimycobacterial activity, and improved biochemical structure providing metabolic stability and long half-life, theoretically reducing the selection of resistant mutants. While the clinical benefit of newer-generation fluoroquinolones has been validated in one small retrospective study, more clinical and laboratory research is needed to understand the extent of fluoroquinolone cross-resistance and its clinical relevance. Cross resistance has also been reported between ethionamide and INH, amikacin and kanamycin, amikacin and capreomycin. Strains resistant to streptomycin/kanamycin/amikacin are still sensitive to capreomycin. It is ineffective to use two drugs of the same group or to use a drug potentially ineffective because of cross-resistance.

### Table 1: Doses of Antitubercular Drugs Used in Previously Treated Patients of TB

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Average daily dosage</th>
<th>Daily dosage (mg)</th>
<th>Type of anti mycobacterial activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Minimum</td>
<td>Maximum</td>
</tr>
<tr>
<td><strong>Group 1</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>First line oral agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide(Z)</td>
<td>25 mg/kg</td>
<td>1200</td>
<td>1500</td>
</tr>
<tr>
<td>Ethambutol(E)</td>
<td>15 mg/kg</td>
<td>800</td>
<td>1200</td>
</tr>
<tr>
<td>Rifabutin(Rfb)</td>
<td>5-10 mg/kg</td>
<td>150</td>
<td>600</td>
</tr>
<tr>
<td><strong>Group 2</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injectable agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kanamycin(Km)</td>
<td>15 mg/kg</td>
<td>750</td>
<td>1000</td>
</tr>
<tr>
<td>Amikacin(Am)</td>
<td>15 mg/kg</td>
<td>750</td>
<td>1000</td>
</tr>
<tr>
<td>Streptomycin(S)</td>
<td>15 mg/kg</td>
<td>750</td>
<td>1000</td>
</tr>
<tr>
<td>Capreomycin(Cm)</td>
<td>15 mg/kg</td>
<td>750</td>
<td>1000</td>
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<tr>
<td><strong>Group 3 Fluoroquinolone</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin(Mfx) Levofloxacin(Lfx)</td>
<td>7.5-10mg/kg</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Ofloxacin(Ofx)</td>
<td>15-20 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Group 4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral Bacteriostatic second line drugs</td>
<td>15-20 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Ethionamide(Eto)</td>
<td>15-20 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Prothionamide(Pto)</td>
<td>200-300 mg/kg</td>
<td>10 g</td>
<td>12 g</td>
</tr>
<tr>
<td>Para-aminosalicyclic acid(PAS)</td>
<td>10-20 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Cycloserine(Cs)</td>
<td>10-20 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td>Terizidone(Trd)</td>
<td>10-20 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Group 5</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Agents with unclear role in treatment of Drug resistant TB</td>
<td>1200mg/day</td>
<td>600</td>
<td>1200</td>
</tr>
<tr>
<td>Clofazidine(CFz)</td>
<td>2 gm/day</td>
<td>500/125</td>
<td>1000/250</td>
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<tr>
<td>Linezolid(Lzd)</td>
<td></td>
<td>Twice a day</td>
<td>Twice a day</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate (Amx/Clv)</td>
<td>150 mg/day</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Thioacetazone(Thz)</td>
<td>500-1000 mg/IV every 6 hrly</td>
<td>500 every 6 hrly</td>
<td>1000 every 6 hrly</td>
</tr>
<tr>
<td>Imipenem/Cilastatin (Ipm/Cln)</td>
<td>6 hrly</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>High dose Isoniazid(high-dose H)</td>
<td>16-20 mg/kg</td>
<td>600</td>
<td>500</td>
</tr>
<tr>
<td>Clarithromycin(Clr)</td>
<td>10-15 mg/kg</td>
<td>500</td>
<td>twice a day</td>
</tr>
</tbody>
</table>
Management of Drug Resistant and Multidrug Resistant Tuberculosis

DEFINITIVE randomized or control studies have not been performed to determine the best treatment for various patterns of drug resistance except for streptomycin resistance. The recommendation in these guidelines are based on evidences from the pre-rifampicin era, observational studies, general principles of microbiology and therapeutics in TB, extrapolations from established evidence and expert opinion. When a decision has been made to modify standard short course chemotherapy, the most effective regimen should be chosen from the start to maximize the likelihood of cure. Effective drugs should not be withheld for later use. The regimen should be based on previous treatment history, DST pattern and the possibility of strain of M. tuberculosis, having acquired new resistance while awaiting DST result. WHO has suggested regimen (Table 2) for mono and poly drug resistance when DST results are highly reliable and further acquired resistance while awaiting DST results is not a factor.43

GENERAL PRINCIPLES FOR DESIGNING TREATMENT REGIMENS FOR RESISTANT / MULTIDRUG RESISTANT TUBERCULOSIS44-50

Early suspicion, diagnosis and appropriate treatment of MDR-TB are essential to prevent morbidity, mortality and transmission of MDR-TB. Treatment should be initiated in a specialized centre with standard laboratory facilities. Single drug should not be added to failing regimen. Intermittent therapy is not effective in multi drug resistant tuberculosis and should be avoided. Past history of drugs taken by the patient and drugs commonly used in the country and prevalence of resistance to first line and second-line drugs should be taken into consideration when designing a standardized regimen. Regimens should consist of at least four drugs with either certain, or almost certain, effectiveness. If the evidence about the effectiveness of a certain drug is unclear, the drug can be part of the regimen but it should not be depended upon for success. Often, more than four drugs may be started if the susceptibility pattern is unknown, effectiveness is questionable for an agent(s) or if extensive, bilateral pulmonary disease is present. Design treatment regimens with a consistent approach based on the hierarchy of the five groups of anti tuberculosis drugs (Table 3).

Use any first line oral agent (Group-1) to which isolate is sensitive, use one injectable (Group-2), one fluoroquinolone (Group-3) and add as many second line bacteriostatic agents (Group-4) to makeup at least 4 effective drugs. Group-5 drugs are not recommended for routine use except where an adequate regimen is impossible with Group 1-4. Do not use ciprofloxacin as an antituberculosis drug. When possible, pyrazinamide, ethambutol and fluoroquinolones should be

<table>
<thead>
<tr>
<th>Table 2 : Suggested Regimen for Mono- and Poly-drug Resistance</th>
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</thead>
<tbody>
<tr>
<td>Pattern of drug resistance</td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>H (+ S) R, Z and E</td>
</tr>
<tr>
<td>H and Z R, E and fluoroquinolones</td>
</tr>
<tr>
<td>H and E R, Z and fluoroquinolones</td>
</tr>
<tr>
<td>R H, E, fluoroquinolones, plus at least 2 months of Z</td>
</tr>
<tr>
<td>R and E (+ S) H, Z, fluoroquinolones, plus an injectable agent for at least the first 2–3 months</td>
</tr>
<tr>
<td>R and Z (+ S) H, E, fluoroquinolones, plus an injectable agent for at least the first 2–3 months</td>
</tr>
<tr>
<td>H, E, Z (+ S) R, fluoroquinolones, plus an oral second-line agent, plus an injectable agent for the first 2–3 months</td>
</tr>
</tbody>
</table>

H = isoniazid; R = rifampicin; E = ethambutol; Z = pyrazinamide; S = streptomycin
pulmonary disease is present. Treatment of adverse drug one or more agents is questionable, or extensive or bilateral whom the susceptibility pattern is unknown, effectiveness of recommendation, particularly in the case of patients for or not to continue an injectable agent longer than the above X-rays and clinical status may also aid in deciding whether months after the patient first becomes and remains smear- or won permanently. DST of drugs with high reproducibility and reliability (and from a dependable laboratory) should be and cost effective in DR-TB treatment. The optimal duration of therapy for MDR-TB has not been clearly established and duration remains questionable. WHO guidelines recommend continuing therapy for a minimum of

<table>
<thead>
<tr>
<th>Group 1</th>
<th>First-line oral agents</th>
<th>Ethambutol (E); Pyrazinamide (Z); Rifabutin (Rfb)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 2</td>
<td>Injectable agents</td>
<td>kanamycin (Km); amikacin (Amk); capreomycin (Cm); streptomycin (S)</td>
</tr>
<tr>
<td>Group 3</td>
<td>Fluoroquinolones</td>
<td>moxifloxacin (Mfx); levofloxacin (Lfx); ofloxacin (Oflx)</td>
</tr>
<tr>
<td>Group 4</td>
<td>Oral bacteriostatic 2nd line agents</td>
<td>ethionamide (Eto); prothionamide (Pto); cycloserine (Cs); terizidone (Trd); p-aminosalicylic acid (PAS)</td>
</tr>
<tr>
<td>Group 5</td>
<td>(drugs with unclear efficacy or unclear role in MDR-TB treatment, not recommended by WHO for routine use in MDR-TB patients)</td>
<td>clofazimine (Cfr); linezolid (Lzd); amoxicillin/clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (IpCl); high-dose isoniazid (high-dose H); clarithromycin (Clr)</td>
</tr>
</tbody>
</table>

given once per day as the high peaks attained in once-a-day dosing may be more efficacious. Once-a-day dosing is permitted for other second-line drugs depending on patient tolerance; however ethionamide/ prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects. The drug dosage should be determined by body weight. Most drugs should be started at full dose, except cycloserine, ethionamide and PAS, in which case the dose of the drug can be increased over a two-week period (drug ramping)42,44 The injectable agent should be given at least for 6 months and the whole treatment duration is minimum of 18 month beyond sputum conversion. Fully appropriate measures appropriately, including surgery and nutritional and social support; all measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts as it is the last that stands between patient and death.34-50

DOTS PLUS

DOTS-Plus is an integral component of RNTCP to manage MDR-TB to be implemented through programme infrastructure. The strategy is designed to manage MDR-TB using second-line anti-TB drugs within the DOTS strategy in low- and middle-income countries like India. Therefore in every DOTS implementing unit of the country, DOTS would be prioritized above DOTS-Plus with the view that DOTS reduces the emergence of MDR-TB, and therefore the need for DOTS Plus over time. The RNTCP under DOTS PLUS will be using a standardized treatment regimen (STR) CATEGORY IV REGIMEN, comprising of 6 drugs (kanamycin, ofloxacin, ethionamide, cycloserine, pyrazinamide, and ethambutol) during 6-9 months of the Intensive Phase and 4 drugs (ofloxacin, ethionamide, cycloserine and ethambutol) during the 18 months of the Continuation Phase. p-aminosalicylic acid (PAS) is included in the regimen as a substitute drug if any bactericidal drug (Kanamycin, Ofloxacin, Pyrazinamide and Ethionamide) or any 2 bacteriostatic (Ethambutol and Cycloserine) drugs are not tolerated. This CAT IV regimen is highly suitable for high TB prevalent nations as well as low to middle income countries like India. Injectable agent should be given at least for 6 months and the whole treatment duration is minimum of 18 month beyond sputum conversion. Fully standardized second line treatment have shown to be feasible and cost effective in DR-TB treatment.18,49

In our Indian setup most of the time either DST results are not available or if available they are usually highly unreliable. Keeping this fact in mind, depending upon past history of anti-tuberculosis treatment author himself have used four groups of regimen in treating resistant / multidrug resistant tuberculosis and found to be effective.37 The suggested regimen by author is given in Table 4.

DURATION OF TREATMENT

The optimal duration of therapy for MDR-TB has not been used to guide therapy. Do not depend on DST in regimen design for ethambutol, pyrazinamide, and Group 4 and 5 drugs. Pyrazinamide can be used for the entire treatment if it is judged to be effective. Many DR-TB patients have chronically inflamed lungs, which theoretically produce the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, pyrazinamide can be stopped with the injectable phase if the patient can continue with at least three certain, or almost certain, effective drugs. Use adjunctive measures appropriately, including surgery and nutritional and social support; all measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts as it is the last that stands between patient and death.34-50

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**Management of Drug Resistant and Multidrug Resistant Tuberculosis**

18 months after culture conversion until there is conclusive evidence to support a shorter duration of treatment. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage. This is, however, a highly expensive approach that is difficult to implement in the majority of middle- and low-income countries like India which bear the high burden of MDR-TB. The duration of injectables is also controversial. The 2006 and 2008 WHO guidelines advise at least 6 months or at least 4 months after smear or culture conversion. In addition duration has to be decided in correlation with other factors also like other drugs in the regimen, bacteriological status and drug toxicity.

**MONITORING OF TREATMENT**

Monitoring of treatment should be done with bacteriological, radiological and clinical methods. Sputum specimens should be obtained for semi-quantitative smear and culture every month from third month onwards during the intensive phase of therapy. Sputum conversion is defined as two sets of consecutive negative smears and cultures, from samples collected at least 30 days apart. Both bacteriological techniques (smear and culture) should be used to monitor patients throughout therapy. After sputum conversion smear examination and culture are done once in three months till the end of therapy. If such large number of smears and cultures for follow up is not possible, then at least five smears and cultures must be done for follow up (4, 6, 12, 18 and 24 months), X-Ray should be done every 6 months whereas clinical monitoring preferably should be done every month.

**ADJUVANT THERAPIES**

In addition to the administration of antimicrobial drug therapy various other treatment modalities may play a significant role in management of patients. These include surgery, collapse therapy, laser therapy, immunomodulation therapy and gene therapy.

**SURGERY**

The most common operative procedure is resection surgery. It is adjunct to chemotherapy and should not be considered as last resort. Chemotherapy should be given at least two months prior to surgery and continued for 12-24 months after resection. It is indicated in patients who remain sputum positive, with resistance to large number of drugs; and localized pulmonary disease.

**COLLAPSE THERAPY**

It is a reversible surgical therapy which involves collapse of lung by artificial pneumoperitonium or pneumothorax used for cavity containing diseased lung with concept that compression of the cavity will change the local environment in manner which will inhibit the mycobacteria. This therapy does not appear to be of general utility, although artificial pneumoperitonium and pneumothorax may be helpful in highly selected cases. However, controlled studies are lacking.

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### Table 4: Suggested Regimen for Drug Resistant / Multidrug Resistant Tuberculosis Before or Without or Unreliable DST Reports

<table>
<thead>
<tr>
<th>Drug regimen</th>
<th>Duration in months</th>
<th>Drugs given (Responders)</th>
<th>Duration in months</th>
<th>Drugs given (Non Responders)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Misused drugs like SHE and THZ</td>
<td>Rifampicin Isoniazid Ethambotol Pyrazinamide + Streptomycin</td>
<td>2-3*</td>
<td>Rifampicin Isoniazid Ethambotol + Pyrazinamide</td>
<td>9</td>
</tr>
<tr>
<td>II Misused drugs like SHREZ THZ</td>
<td>Streptomycin Isoniazid Rifampicin Ethambotol Pyrazinamide</td>
<td>2-3*</td>
<td>Rifampicin Isoniazid Ethambotol + Pyrazinamide</td>
<td>9</td>
</tr>
<tr>
<td>III Failed after adequate 5 drugs (SHREZ)</td>
<td>Kanamycin Fluoroquinolone Ethionamide Cyclosorine Pyrazinamide Ethambol</td>
<td>6</td>
<td>Ethionamide Fluoroquinolone (Levofloxacin/Ofloxacin) Cycloserine Ethambol +</td>
<td>18</td>
</tr>
<tr>
<td>IV Failed on group III treatment.</td>
<td>Capreomycin PAS Moxifloxacin High dose-INH Clofazamine Linezolid Amoxycillin/Clavulanate</td>
<td>6-12</td>
<td>PAS Moxifloxacin High dose-INH Clofazamine Linezolid Amoxycillin/Clavulanate</td>
<td>18</td>
</tr>
</tbody>
</table>

*Depending on sputum conversion can be used for 3-6 months if toxicity does not intervene; R-rifampicin, H-isoniazid, E-ethambol, Z-pyrazinamide, S-streptomycin, THZ-thioacetazone.
LA SER THERAPY

This has also been tried as an adjunct to chemotherapy in some countries such as Russia for the treatment of drug resistant TB. This is effective in multicavitary disease with heavy bacterial loads particularly when there is an increased chance of failure of medical treatment. It is thought to have a role in the rapid killing of bacteria, increases and improves penetration of anti-tubercular 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 complications.

IMMUNOTHERAPY OR IMMUNOMODULATION

Therapeutic modulation of the immune system to enhance the host’s immunity to control tuberculosis and to shorten the durations of chemotherapy required to ‘cure’ patients with drug susceptible disease has been tried with some success. Mycobacterium vaccae have shown transiently favourable results when given to drug resistant tuberculosis who had failed chemotherapy.52 Immune modulation can be affected by enhancing pro inflammatory cytokines like IL-2, IL-12, IFN-γ, TNF-α, inhibiting the anti inflammatory cytokines like IL-4, IL-5, IL-10, addition of serum to enhance humoral factors or diverting the harmful Th2 immune pathway to the beneficial Th1 response by vaccination utilizing M. vaccae. However these therapies are adjuncts and have proved useful in selected cases of drug resistant tuberculosis and randomized control trials, have failed to confirm the utility of this therapy.53 Beneficial effect of parenterally used interferon gamma (IFN-γ) have been reported in disseminated disease attributable to mycobacteria other than tuberculosis that was refractory to chemotherapy.54 Favourable results were reported following one month use of inhaled IFN-γ, 500 microgram thrice weekly. Cytokine therapy has been shown to have clinical utility in modifying the inflammatory manifestation of the lepromatous type of disease.55 Interleukin-2 (IL-2) was used to restore antigen responsiveness, presumably via enhancing IFN-γ production. Thalidomide has been shown to inhibit the in-vitro release of TNF-α from peripheral blood monocytes. In patients with active tuberculosis it induces a significant gain in weight.56 However the possibility that thalidomide agents may ameliorate tissue injury in tuberculosis needs further study.57,58 The potential role of diverse agents such as transfer factor, indomethacin, and levamisole is yet to be established.59 Levamisole as adjunct to drug treatment has been reported to cause more rapid radiological clearing in the treated group. However it did not significantly affect the clinical outcome.60 Mycobacterium w (commercially available as Immuvac) has been extensively studied as an effective immunomodulator for treatment of leprosy. It enhances bacterial killing and lesion clearance when used as an adjuvant to multi-drug therapy for leprosy. Mycobacterium w shares antigens with M leprae as well as M. tuberculosis suggesting its application in treatment of drug resistant tuberculosis. A randomised control study has demonstrated that this drug may be responsible for overall reduction of duration of therapy, with no change in sputum conversion rate compared with the traditional short course chemotherapy in new as well as re-treatment cases of tuberculosis.61,62 Another advantage though not proven, may be that Immuvac effect would be longer lasting and could take care of defaulters more meaningfully than chemotherapy alone, leading to a reduction in relapse rate and the emergence of MDR TB. Recently, a randomised control trial has been initiated in 2007 and is under progress in order to establish its efficacy and safety as an adjunct therapy in New Pulmonary Tuberculosis (Category 1) Patients.

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, enabling us to considerably reduce the duration of therapy.63

ROLE OF STEROIDS

The adjuvant use of corticosteroids in DR-TB patients has been shown not to increase mortality and can be beneficial in conditions such as severe respiratory insufficiency, severe drug induced rashes and central nervous system or pericardial involvement. Prednisone is commonly used, starting at approximately 1 mg/kg and gradually decreasing the dose to 10 mg per week when a long course is indicated. Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease or when patient is in a very low general condition. In these cases, prednisone may be given in a short course, tapering over 1–2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5–10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.44

OUTCOME OF TREATMENT

The outcome of treatment of multi drug resistant tuberculosis is not very favourable and varied from 50-80% in different studies. In a retrospective analysis of 171 immunocompetent patients treated over a ten year period (1973-83) at the National Jewish Hospital in Denver, the overall favourable outcome was only a little over 50%.64 All patients were treated with individually tailored regimens in which they received at least 3 or 4 drugs which they had not received previously, or to which they were known to be susceptible. Of the 134 patients evaluated for efficacy, 65% became culture negative and 35% failed to respond. Of those who became culture negative, 14% eventually relapsed giving an overall favorable outcome in 56% of patients. Of the patients who failed, 46% died of tuberculosis. In the Cape Province South Africa the 5 year
outcome of 240 MDR-TB patients was death in 48%, cure in 33%, 15% were respiratory disabled and 13% were still bacteriologically positive. However, not all the reports are so grim. In a retrospective analysis reported from South Korea, of 107 patients with MDR-TB treated with at least four drugs to which they had not been exposed to before, or to which they were known to be susceptible, in 63 patients with sufficient follow up data, 52 (82.5%) responded to chemotherapy. There was no subsequent relapse among the patients who responded, and there were no tuberculosis related deaths. The author concluded that, MDR Tuberculosis responds relatively well and there were no tuberculosis related deaths. The author was no subsequent relapse among the patients who responded, follow up data, 52 (82.5%) responded to chemotherapy. There were known to be susceptible, in 63 patients with sufficient

6. Ordway DJ, Sonnenberg MG, Donahue SA, Belisle JT, Orme IM

CONCLUSION

The subject of drug resistant and multi drug resistant tuberculosis is a vast one and an area of growing concern among clinicians, epidemiologists, public health workers worldwide. New researches in the areas involving molecular biology and application of these in the field of epidemiology could help in better understanding of the mechanisms of drug resistance and development of newer diagnostic tools and effective drugs to control Multidrug resistant tuberculosis. Till such time multi-drug resistant tuberculosis must be managed very effectively to reduce morbidity and mortality and transmission of multi-drug resistance tuberculosis. It must also be emphasized that even optimal treatment of multi-drug resistance tuberculosis will not alone curb the epidemic. Efforts must be focused on the effective use of first line drugs in every new case so as to prevent the ultimate emergence of multi-drug resistant tuberculosis.

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