ABSTRACT
Drug resistant tuberculosis, a phenomenon observed since the early days of introduction of anti-tubercular chemotherapy, is becoming an area of growing concern. It is posing threat to global efforts of tuberculosis control. A prompt recognition of mono-, poly- and multidrug-resistance is imperative for prognosis and formulating better management strategies. The prevalence of multi-drug resistant tuberculosis, mirrors the functional state and efficacy of tuberculosis control programme and realistic attitude of the community towards implementation of such programmes. The management of drug resistant tuberculosis is difficult, expensive, challenging and quite often leads to treatment failure. To avoid further transmission, a comprehensive approach for rapid detection, proper treatment and effective public health measures must be ensured. It must also be emphasized that even optimal treatment of MDR-TB 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 MDR-TB.

KEYWORDS: multi-drug resistant tuberculosis, mirrors the functional state and efficacy.

INTRODUCTION
Drug resistant tuberculosis is defined as a case of tuberculosis excreting bacilli resistant to one or more anti-tubercular drugs. Mono-resistance is defined as resistance to one anti-tuberculosis drug whereas poly-resistance is defined as resistance to more than one anti-tuberculosis drug, other than both isoniazid and rifampicin. Poly-resistance can be
Rifampicin resistance, multidrug resistant tuberculosis (MDR-TB) or extensive drug resistance (XDR-TB). Rifampicin resistance (RR) is defined as resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs and it includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance. Multidrug 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. Extensive drug resistance (XDR) refers to resistance to any fluoroquinolone, and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance. Identification of patterns of drug resistance is important as they carry different implications for treatment and management.

**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 Isoniazid (INH), streptomycin and ethambutol is $10^{6}$ and for ethionamide, cycloserine, capreomycin and thiacetazone $10^{3}$. The probability of resistance developing in a 2.5 cm cavity which harbors $10^{8}$–$10^{9}$ 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 multidrug resistant tuberculosis is a man-made problem.\(^{[1]}\)

**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.\(^{[2]}\) 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\(^{[3]}\), 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 no or a lesser risk of infection when contacts are exposed to tuberculosis bacilli resistant to high concentration of INH and SM. Ordway et al have observed that some MDR-TB strains that exhibit in vitro 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, rifampicin, 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 isoniazid, 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, isoniazid or both have a high rate of treatment failure\cite{10-12} and this forms a major threat to tuberculosis control programmes particularly for countries like India with poor resources.\cite{13} Four separate studies from New York conducted from 1995 to 1996 on response to therapy for patient with MDR-TB\cite{14-17} reported better outcome that can be demonstrated with early recognition of resistance and administration of effective drugs.

**Diagnosis Of Drug Resistant And Multidrug Resistant Tuberculosis**

It is needless to emphasize that early diagnosis and treatment of drug resistant and multidrug 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 multidrug 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.\cite{10} 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 combi-packs 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.\cite{18} 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’ phenomenon.\(^{20}\) 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 *M. tuberculosis* that are resistant *in-vitro* to at least isoniazid and rifampicin\(^{18}\) (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 set-up, 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 foolproof 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 retesting 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 from different laboratories for the same patient due to sampling of different populations of bacilli and different techniques employed. Standardization, coordination 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 are used. In BACTEC method, the released radiolabeled carbon dioxide is detected that indicates growth of \textit{M. tuberculosis} whereas in MGIT the oxygen sensitive fluorescent compound is used to detect growth of \textit{M. tuberculosis}. The rapid culture technique take much shorter time as compared to LJ media.\cite{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.\cite{28} In fact the rapid radiometric system offers a substantially more quantitative approach to the determination of susceptibility than other method,\cite{29} another major advantage of BACTEC system that it can also perform susceptibility test for pyrazinamide.

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 Mycobacterio-phages based assays like - FAST Plaque TB and Luciferase receptors phages (LRPs) have 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.\cite{30} Currently LiPA is not useful for detecting mutations responsible for drug resistance in second-line drugs. The Xpert MTB/ RIF assay enables simultaneous detection of Mycobacterium tuberculosis (MTB) and rifampicin resistance and it was endorsed by WHO in 2010.

Xpert MTB/RIF was found to be highly sensitive (98%) and specific (98%) in detecting tuberculosis and rifampicin resistance (a reliable proxy for MDR) directly from sputum, in less than two hours. The assay is robust enough to be performed outside of conventional laboratories, at district and subdistrict level of health system but requires uninterrupted power.
supply. Widespread implementation of Xpert MTB/RIF would greatly enhance the diagnostic capacity for TB and MDR TB; its accuracy and ease of use represents a major milestone for TB and MDR TB care and control.[31] 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)[32] and restriction fragment length polymorphism (RFLP)[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 reinfection tuberculosis specifically in HIV infected patients[34] while luciferase reporter assay rapid system based on enzyme luciferase, involves the introduction of this enzyme into *M. 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 antimycobacterial activity.[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 complement to the standard methods.[36]

**Treatment Of Drug Resistant And Multidrug Resistant Tuberculosis**

The WHO recommends that treatment of drug resistant and multidrug 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 multidrug 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. Individualized 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 with their dosages used for treatment of multidrug resistant tuberculosis are given in Table 1. 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. A prospective study of 98 MDR-TB patients treated under modified DOTS-Plus showed that nausea and vomiting occurred in 24.5% of patients followed by hearing
disturbances (12.3%), dizziness/vertigo (10.2%) and arthralgia (9.2%). Other side effects observed were gastrointestinal intolerance, hypothyroidism and hepatitis. Agents responsible for these adverse effects were Kanamycin (ototoxicity), cycloserine (headache/psychosis), ethionamide (gastrointestinal intolerance/hypothyroidism) and pyrazinamide (arthralgia/hepatitis).[37] Author himself in one study of 39 patients of MDR-TB reported that 41% of patients experienced some side effects but only 21.1% of patients required stoppage or change of drug.[38] 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 thiacetazone (one way resistance — strains resistance to thiacetazone are susceptible to thioamides, the reverse is seldom the case), kanamycin/amikacin with streptomycin[39], rifampicin with rifapentine and rifabutin (> 70% strains)[40] and among various derivatives of fluoroquinolones.[41] 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 anti-mycobacterial 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[42], 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[43], amikacin and kanamycin[39], amikacin and capreomycin.[39] 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.

**General Principles For Designing Treatment Regimen For Mono And Poly Drug Resistant-Tb**

It has been observed in drug resistance surveys that the mono- and poly-resistant TB (17%) are more common than MDR-TB (3%).[44] If not properly managed amplification of resistance occurs leading to MDR. LPA gives resistance testing to both isoniazid and rifampicin within two days. With conventional DST, the diagnosis may be delayed for weeks or months resulting in amplification in the intervening period. Xpert MTB/RIF only tests for
rifampicin resistance and it cannot by itself distinguish between mono-resistant TB, poly-resistant TB and MDR-TB. Lack of such diagnostic facilities in resource-limited settings results in Mono-resistant and poly-resistant TB often being undiagnosed leading to false administration of standard first line drugs further increasing the risk of development of MDR-TB. The WHO eight month retreatment regimen which was previously thought to be adequate to treat lesser forms of resistance such as isoniazid mono- or poly-resistance, have shown poor results with failure of 18%–44% in those with isoniazid resistance.\cite{45,46} Such treatment practices were observed to lead to amplification (acquisition of additional resistance) to multidrug resistance.\cite{46-49} Only, very few randomized clinical trials have been performed to determine the best treatment for mono or poly-resistant TB.\cite{45} Most of these recommendations are based on limited data from observational cohort studies and the opinion of expert panels. Patients with isoniazid mono-resistance should be treated with six to nine months of rifampicin, ethambutol and pyrazinamide.\cite{45,50} DST to ethambutol and pyrazinamide are not reliable for routine regimen design and hence a DST from a reliable laboratory is warranted. DST showing resistance to ethambutol or pyrazinamide should be taken as resistant and the drugs should not be relied upon in a regimen designed to treat mono- or poly-resistant TB. Monitoring for possible rifampicin amplification should be done during treatment and MDR-TB regimen should be initiated if rifampicin resistance is detected. If there is uncertainty regarding the efficacy of ethambutol or pyrazinamide, the regimen for isoniazid poly-resistance with resistance pattern H, E, Z, (+/- S) could be used. Treatment with rifampicin–ethambutol–pyrazinamide plus a fluoroquinolone is also advisable. The data on management of patients with isoniazid poly-resistance are further scares. These patients have a higher risk of amplification to multidrug resistance if treatment fails and patients should be started on MDR-TB regimen if rifampicin resistance develops.\cite{45} All TB patients infected with strains resistant to rifampicin should be treated using a full MDR-TB regimen. Isoniazid should be continued until DST results to isoniazid are available. If DST of isoniazid shows susceptibility, isoniazid can be continued in the MDR-TB regimen. In case of RR-TB with non-availability of details regarding isoniazid resistance it is recommended to test for isoniazid using molecular testing such as line probe assays or conventional phenotypic methods. If isoniazid resistance cannot be ascertained, the addition of isoniazid to the regimen may be considered. Treatment regimens for the management of mono- and poly-resistant TB are shown in Table 2.
General Principles For Designing Treatment Regimens For Multidrug Resistant Tuberculosis

Early suspicion, diagnosis and appropriate treatment of MDR-TB is essential to prevent morbidity, mortality and transmission of MDR-TB. Treatment should ideally be initiated in a specialized centre with standard laboratory facilities. Single drug should not be added to a failing regimen. Intermittent therapy is not effective in multi-drug resistant tuberculosis and should be avoided. Standardized MDR-TB regimen makes it easier to estimate drug needs, manage, distribute drug stocks and in training of personnel in the treatment of MDR-TB patients. Individually designed regimens are based on the patient's history of past drug use, on drug susceptibility testing (DST) of isoniazid, rifampicin, the second-line injectable agents and a fluoroquinolone. Individualized regimens may achieve higher cure rates than standardized MDR regimens in few settings.[51] Even when standard regimens are used throughout treatment, patients experiencing severe adverse effects will need to have their MDR treatment individualized. 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 (see 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 four 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 anti-tuberculosis drug. When possible, all the drugs should be given once per day as the high peaks attained in once-a-day dosing may be more efficacious. PAS have traditionally been given in split doses during the day to reduce adverse effects. The drug dosage should be determined by body weight. The injectable agent should be continued for a minimum of 6 months and for at least 4 months after the patient first becomes and remains smear negative or culture-negative. The patient’s cultures, smears, X-rays and clinical status
may also aid in deciding whether or not to continue an injectable agent longer than the above recommendation, particularly in the case of patients for whom the susceptibility pattern is unknown, effectiveness of one or more agents is questionable, or extensive or bilateral pulmonary disease is present.\textsuperscript{[51]} Treatment of adverse drug effects should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious adverse effects. The minimum duration of treatment is 18 months after culture conversion. Preferably each dose is given as directly observed therapy (DOT) throughout the treatment. At least therapy should be under direct observation preferably for 3–4 months or till the sputum conversion. If directly observed treatment is not possible, adherence to treatment must be ensured by intense health education to patient and family member at start of treatment and during each follow-up visits and other adherence measures like checking empty blister packs. 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. DST of drugs with high reproducibility and reliability (and from a dependable laboratory) should be 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 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.\textsuperscript{[52-56]}

**Programmatic Management Of Drug Resistant Tuberculosis**

Programmatic Management of Drug resistant Tuberculosis (PMDT) previously referred to as DOTS-Plus is an integral component of tuberculosis control programme to manage MDR-TB to be implemented through program 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. MDR TB patients under programmatic management of drug resistant tuberculosis will be using a standardized
treatment regimen (STR) Category IV regimen, comprising of 6 drugs (kanamycin, levofloxacin, ethionamide, cycloserine, pyrazinamide and ethambutol) during 6–9 months of the intensive phase and 4 drugs (levofloxacin, 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, levofloxacin, pyrazinamide and ethionamide) or any 2 bacteriostatic (ethambutol and cycloserine) drugs are not tolerated. This 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 months beyond sputum conversion. Fully standardized second line treatment have shown to be feasible and cost-effective in MDR-TB treatment.\textsuperscript{[57,58]} In setup where most of the time either DST results are not available or if available they may not be reliable. 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.\textsuperscript{[38]} The suggested regimen by author is given in Table 4.

**DURATION OF 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 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 injectable drugs is also controversial. The 2006 and 2008 WHO guidelines advise at least 6 months or at least 4 months after smear or culture conversion respectively.\textsuperscript{[53]} WHO guideline 2011 advice at least 8 months of injectable. In addition duration has to be decided in correlation with other factors also like other drugs in the regimen, bacteriological status and drug toxicity.\textsuperscript{[53]}

**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.\textsuperscript{1849} If such large number of smears and cultures for follow-up are not possible, then at least five smears and cultures must be done for follow-up (4, 6, 12, 18 and 24 months), X-ray should be done every 6 months whereas clinical monitoring preferably should be done every month.\textsuperscript{38}

**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 nutritional support, surgery, collapse therapy, laser therapy, immunomodulation therapy and gene therapy.

**NUTRITIONAL SUPPORT**

Drug-resistant TB treatment and care should contain integrated nutritional assessment counselling and support for the duration of the illness. Food support may improve treatment adherence in settings were food insecurity is an important access barriers.\textsuperscript{59} Vitamin B6 (pyridoxine) should be given to all MDR-TB patients receiving cycloserine or terizidone, and a high dosage of isoniazid or linezolid to prevent neurological side effects. Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have these deficiencies. If multivitamins and minerals (zinc, iron, calcium, etc.) are given, they should be dosed three to four hours apart from the fluoroquinolones, as these can interfere with the absorption of these drugs.\textsuperscript{20}

**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 for two month 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.\textsuperscript{54}

**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.\cite{61} However, controlled studies are lacking.

**LASER 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 multi-cavitary 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 endo-bronchial 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.\cite{62} 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.\cite{63} 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.\cite{64} Favourable results were reported following one month use of inhaled IFN- γ, 500 microgram thrice weekly. 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.\cite{65} However the possibility that thalidomide agents may ameliorate tissue injury in tuberculosis needs further study.\cite{66,67} The potential role of diverse agents such as transfer factor, indomethacin and levamisole is yet to be established.\cite{68} 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.\textsuperscript{[69]} *Mycobacterium w* (commercially available as Immuvac) has been extensively studied as an effective immune-modulator 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 randomized control study has demonstrated that this 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.\textsuperscript{[70,71]} Another advantage though not proven, may be that Immuvac effect would be longer lasting and could take care of defaulders more meaningfully than chemotherapy alone, leading to a reduction in relapse rate and the emergence of MDR-TB. A meta-analysis to evaluate *Mycobacterium w* (M w) immunotherapy as an adjunct to chemotherapy in participants with pulmonary TB (PTB) showed immunotherapy was effective at reducing time to sputum conversion at day 15 and day 30. After day 30, benefit was only demonstrated in the category II TB (re-treatment).\textsuperscript{[72]} In a double-blind, placebo-controlled trial, pulmonary multidrug-resistant tuberculosis subjects were randomly assigned to receive metronidazole (500 mg thrice daily) or placebo for 8 weeks in addition to an individualized background regimen. More subjects in the metronidazole arm converted their sputum smear \textasteriskcentered $P = 0.04$ and liquid culture \textasteriskcentered $P = 0.04$) to negative at 1 month, but these differences were lost by 2 months. Overall, 81% showed clinical success 6 months after stopping therapy, with no differences by arm. Newer nitroimidazoles with both aerobic and anaerobic activity, now in clinical trials, may increase the sterilizing potency of future treatment regimens.\textsuperscript{[73]}

**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.\textsuperscript{[74]}

**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. Prednisolone 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 to 2 weeks, starting at approximately 1 mg/kg and decreasing the dose by 5 to 10 mg per day. Injectable corticosteroids are often used initially when a more immediate response is needed.\textsuperscript{54} Corticosteroids should never be given to patients with MDR-TB unless they are receiving adequate anti-tuberculosis therapy.

OUTCOME OF TREATMENT

The outcome of treatment of multi drug resistant tuberculosis is not very favourable and varied from 50 to 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\%.\textsuperscript{75} 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.\textsuperscript{76} 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-TB responds relatively well to carefully selected regimens. However, the mean period of follow up was only 17 months.\textsuperscript{77} Khanna, et al\textsuperscript{78} used Kanamycin (6 months), Cycloserine, Ethionamide and Sodium PAS for 18 months in hospitalized patients and observed bacteriological conversion in 71\% of MDR-TB patients. Purohit, et al\textsuperscript{79} used Kanamycin (6 months), Ethionamide, Sodium PAS and Isoniazid for 18 months on domiciliary basis and bacteriological conversion was achieved in 73\% of the patients. In another study by Rupak Singla, et al\textsuperscript{80} bacteriological quiescence was achieved in 78\% of the patients who completed the full therapy. Prasad, et al\textsuperscript{38,81} observed 75.5\%
sputum smear and culture conversion rate at the end of two years in 45 patients of MDR pulmonary tuberculosis patients by using Kanamycin, Ethionamide, PAS and Cycloserine regimen. Out of 45 patients 34 (75.5%) patients were declared cured, these patients followed for average 17.4 months (3–60 months) two patients relapsed (5.7%) so long term outcome was around 70%. A systematic review and meta-analysis of the available therapeutic studies on the treatment of multidrug-resistant tuberculosis showed that the overall treatment success estimate was 62%, however the heterogeneity in study characteristics led to significant variation in reported treatment outcomes. Individualized treatment regimens had higher treatment success (64%, 95% CI 59-68%) than standardized regimens (54%, 95% CI 43–68%), although the difference was not significant. The proportion of patients treated successfully improved when treatment duration was at least 18 months and if patients received directly observed therapy throughout treatment. Studies that combined both factors had significantly higher pooled success proportions (69%, 95% CI64–73%) than other studies of treatment outcomes (58%, 95% CI 52–64%). In another prospective study by Prasad et al of 98 patients of MDR-TB treated as per DOTS Plus protocol it was observed that the default and expiry rates were 7.1% and 10.2% respectively. It is observed that inadequate treatment duration will result in relapses, may lead to treatment failure and additional acquired drug resistance. In a study by Chan et al on treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis, it was observed that surgical resection and fluoroquinolone therapy was associated with improved microbiological and clinical outcome. Fluoroquinolone resistance was associated with a higher proportion of treatment failures and deaths in MDR patients than non-FQ-resistant cases. Addition of fluoroquinolones were associated with lesser chances of relapse and improved treatment outcomes. Kanamycin, capreomycin and streptomycin resistance is associated with poor treatment outcomes. The outcome for patients with MDR-TB is not very favorable in immunocompetent patients, the response in HIV positive patients is even bleaker. In the outbreaks of MDR-TB in and around New York, between 1988 and 1992, predominantly in HIV infected individuals, mortality was in the order of 80% and the mean duration from diagnosis to death was 4 to 16 weeks. In patients having concomitant HIV and MDR-TB response rate appeared to be poor with high rates of treatment failure and mortality. In MDR-TB patients with localized disease, surgery, as an adjuvant to chemotherapy, can improve outcomes and should be considered when there is poor response to appropriate chemotherapy.
### Table 1: Doses of antitubercular drugs used in MDR-TB

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Average daily dosage</th>
<th>Daily dosage (mg)</th>
<th>Type of antimycobacterial activity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group 1 First line oral agents</strong></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 Injectable agents</strong></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>
</tr>
<tr>
<td><strong>Group 3 Fluoroquinolones</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin (Mfx)</td>
<td>7.5–10 mg/kg</td>
<td>400</td>
<td>400</td>
</tr>
<tr>
<td>Ofloxacin (Ofx)</td>
<td>15–20 mg/kg</td>
<td>800</td>
<td>1000</td>
</tr>
<tr>
<td>Levofloxacin (Lfx)</td>
<td>7.5–10 mg/kg</td>
<td>500</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Group 4 Oral bacteriostatic second line drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide (Eto)</td>
<td>15–20 mg/kg</td>
<td>500–750</td>
<td>1000</td>
</tr>
<tr>
<td>Prothionamide (Pto)</td>
<td>15–20 mg/kg</td>
<td>500–750</td>
<td>1000</td>
</tr>
<tr>
<td>Para-aminosalicyclic acid (PAS)</td>
<td>200–300 mg/kg</td>
<td>10 g</td>
<td>12 g</td>
</tr>
<tr>
<td>Cycloserine (Cs)</td>
<td>10–20 mg/kg</td>
<td>500–750</td>
<td>1000</td>
</tr>
<tr>
<td>Terizidone (Trd)</td>
<td>10–20 mg/kg</td>
<td>500–750</td>
<td>1000</td>
</tr>
<tr>
<td><strong>Group 5 Agents with unclear role in treatment of Drug resistant TB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bedaquiline</td>
<td>400 mg once daily for 2 weeks, 200 mg, 3 times a week for 22 weeks after food</td>
<td></td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Delaminad</td>
<td>100 twice daily</td>
<td></td>
<td>Bactericidal</td>
</tr>
<tr>
<td>Drug</td>
<td>Dose</td>
<td>1st Dose</td>
<td>2nd Dose</td>
</tr>
<tr>
<td>-----------------</td>
<td>------</td>
<td>----------</td>
<td>----------</td>
</tr>
<tr>
<td>Clofazimine (Cfz)</td>
<td>4–5 mg/kg</td>
<td>100</td>
<td>300</td>
</tr>
<tr>
<td>Linezolid (Lzd)</td>
<td>600</td>
<td>1200</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/clavulanate (Amx/Clv)</td>
<td>500/125</td>
<td>1000/250</td>
<td></td>
</tr>
<tr>
<td>Thioacetazone (T)</td>
<td>150 mg/day</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Imipenem/Cilastatin</td>
<td>500–1000</td>
<td>500 every</td>
<td>1000</td>
</tr>
<tr>
<td>Linezolid (Lzd)</td>
<td>mg/every 6 h</td>
<td>6 hourly</td>
<td>every 6 hourly</td>
</tr>
<tr>
<td>Isoniazid (highdose H)</td>
<td>16–20 mg/kg</td>
<td>600</td>
<td>900</td>
</tr>
<tr>
<td>Clarithromycin (Clr)</td>
<td>10–15 mg/kg</td>
<td>500 twice a day</td>
<td>500 twice a day</td>
</tr>
</tbody>
</table>
TABLE 2: Treatment regimens for the management of mono- and poly-resistant TB.

<table>
<thead>
<tr>
<th>Pattern of drug resistance</th>
<th>Suggested Regimen</th>
<th>Minimum Duration of Treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (± S)</td>
<td>R, Z and E (+/-FQ)</td>
<td>6–9</td>
<td>Use Xpert MTB/RIF at month 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment. Some experts add a FQ to the regimen.</td>
</tr>
<tr>
<td>H and E (+/-S)</td>
<td>R, E and FQ</td>
<td>9–12</td>
<td>Use Xpert MTB/RIF at month 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to first and second-line anti-TB drugs. Some experts recommend using a second-line injectable agent for first three months</td>
</tr>
<tr>
<td>H,E,Z (+/-S)</td>
<td>R, FQ, plus ethionamide, plus a second line injectable agent for the first 2-3 months.(+/-Z)</td>
<td>18</td>
<td>A longer course (6 months) of the second-line injectables may strengthen the regimen for patients with extensive disease. Z should be added if resistance is uncertain. Use Xpert MTB/RIF at month 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to second-line anti-TB drugs.</td>
</tr>
<tr>
<td>R mono or poly drug resistance</td>
<td>Full MDR-TB regimen plus H</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

The use of Xpert MTB/RIF at month 0, 2 and 3 is not intended for monitoring response to therapy as the test may be positive for *Mycobacterium tuberculosis* for patients with a positive response and even after cure. Rather, it is intended only to detect rifampicin amplification during therapy.

H=isoniazid; S=streptomycin; R=rifampicin; Z=pyrazinamide; E=ethambutol; FQ=fluoroquinolone.

Table 3: Grouping of anti-tuberculosis drugs.

| Group 1 First-line oral agents | Pyrazinamide (Z); Ethambutol (E); Rifabutin (Rfb) |
| Group 2 Injectable agents      | Streptomycin (S); Kanamycin (Km); Amikacin (Amk); Capreomycin (Cm) |
| Group 3 Fluoroquinolones       | Levofloxacin (Lfx); Moxifloxacin (Mfx); Ofloxacin (Ofx) |
| Group 4 Oral bacteriostatic 2nd line agents | Ethionamide (Eto); Protonamide (Pto); Cycloserine (Cs); Terizidone (Tmd); Para-Aminosalicylic acid (PAS); Para-aminosalicylate sodium (PAS-Na) |
| Group 5 (drugs with unclear efficacy or unclear) | Bedaquiline (Bdq); Delamanid (Dlm); Linezolid |
Table 4:- Suggested regimen for drug resistant/multidrug resistant tuberculosis before or without or unreliable DST reports.

<table>
<thead>
<tr>
<th>Group</th>
<th>Previous use of ATT</th>
<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</td>
<td>Misused drugs like SHE and T</td>
<td>Rifampicin Isoniazid Ethambutol Pyrazinamide + Streptomycin</td>
<td>2–3*</td>
<td>Rifampicin Isoniazid Ethambutol + Pyrazinamide</td>
<td>9</td>
<td>Treat as Group II or Take help of DST result from accredited laboratory</td>
</tr>
<tr>
<td>ii</td>
<td>Misused drugs like SHREZ T</td>
<td>Streptomycin Isoniazid Rifampicin Ethambutol Pyrazinamide</td>
<td>2–3*</td>
<td>Rifampicin Isoniazid Ethambutol + Pyrazinamide</td>
<td>9</td>
<td>Treat as Group III or Take help of DST result accredited laboratory</td>
</tr>
<tr>
<td>iii</td>
<td>Failed after adequate 5 drugs (SHREZ)</td>
<td>Kanamycin Ethionamide Cycloserine Pyrazinamide Ethambutol</td>
<td>6–9</td>
<td>Ethionamide Fluoroquinolone (Levofloxacin/Ofloxacin) Cycloserine Ethambutol</td>
<td>18</td>
<td>Treat as Group IV or Take help of DST result accredited laboratory and consider surgery</td>
</tr>
<tr>
<td>iv</td>
<td>Failed on group III treatment</td>
<td>Capreomycin PAS Moxifloxacin Hig dose-INH Clofazimine Linezolid Amoxycillin,Clavulanate</td>
<td>6–12</td>
<td>PAS Moxifloxacin High dose-INH Clofazimine Linezolid Amoxycillin/Clavulanate</td>
<td>18</td>
<td>Consider surgery</td>
</tr>
</tbody>
</table>

*depending on sputum conversion can be used for 3–6 months if toxicity does not intervene


REFERENCES


