Review Article

Multidrug and extensively drug-resistant tuberculosis management: Evidences and controversies

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ABSTRACT

Multi-drug and extensively drug resistant tuberculosis (M/XDR-TB) has been an area of growing concern among clinicians, epidemiologists, and public health workers worldwide. Lack of controlled trials in M/XDR-TB patients hinders the optimal management of such patients, and guidelines that have been developed based largely on expert opinion are controversial. Lack of new effective drugs, improper regimens prescribed by poorly trained doctors and unreliable drug susceptibility testing add to the magnitude of the problem. M/XDR-TB is mostly a man made problem and its emergence can be checked by prompt diagnosis and effective use of first-line drugs in every new patient. DOTS-Plus proposed by World Health Organization (WHO) has highlighted the comprehensive management strategy to control multi-drug resistant tuberculosis (MDR-TB). Laboratory services must be strengthened for adequate and timely diagnosis of M/extensively drug resistant tuberculosis (XDR-TB) and programmatic management of M/XDR-TB must be scaled up as per target set by global plan to stop TB 2011-2015. In MDR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes and should be considered when there is poor response to appropriate chemotherapy. Proper use of second-line drugs must be ensured to cure existing MDR-TB, to reduce its transmission and to prevent emergence of XDR-TB.

KEY WORDS: Diagnosis, extensively drug resistant tuberculosis (XDR-TB), multi-drug resistant tuberculosis (MDR-TB), treatment

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INTRODUCTION

Tuberculosis (TB) occurs worldwide and remains an important cause of morbidity and mortality in many countries. As per Global tuberculosis control: World Health Organisation (WHO) report 2010 of WHO, there were an estimated 9.4 million new cases of TB and 14.0 million prevalent cases causing death to 1.3 million people in 2009. In India there were an estimated 2.0 million (21% of the estimated worldwide burden) new cases and 0.28 million deaths due to TB during this year.[1] Drug-resistant TB has been reported since the early days of introduction of chemotherapy, but multidrug-resistant tuberculosis (MDR-TB) and more recently

extensively drug-resistant tuberculosis (XDR-TB) has been an area of growing concern and is posing a threat to global efforts of TB control. Though unfortunate, yet a reality is that M/XDR TB are manmade problems. Poor clinical practices and control strategies in new TB patients generates MDR-TB. Mismanagement of MDR-TB with erratic use of second-line drugs may lead to development of XDR-TB[2] More than 400,000 cases of MDR-TB and 50,000 cases of XDR-TB emerge globally every year as a result of poor management of drug-susceptible and drug-resistant TB.[3-5] Lack of proper laboratory services makes monitoring of treatment response difficult. This review discusses the evidence and controversies related to management of M/XDR TB.

Evidence and controversies in diagnosis of M/XDR-TB
Drug-resistant TB is a microbiological diagnosis and history of prior anti-tuberculosis treatment provides supportive evidence.

Importance of a proper treatment history
The main predictor of resistance to a particular drug is the demonstration of its prior use in, sometimes inadvertent,

monotherapy for more than one month. To obtain evidence of possible inadvertent monotherapy, it is essential to be meticulous in obtaining the history of antituberculosis treatment in all patients suspected of having MDR-TB.[6] There should be a detailed evaluation of the drugs used, the drug dosages if previous drug prescriptions are available, whether the drugs were fixed dose combinations or individual drugs, their reliability in terms of WHO approved bioavailability, whether the patients were compliant to these drugs, treatment was observed or unobserved and any drug intolerance leading to partial or complete drug defaulting. If the treatment history is taken meticulously, any real or inadvertent monotherapy previously received by the patient can be identified with reasonably good accuracy and one can accurately predict resistance to specific drugs and prevent their inclusion (or reliance on these drugs) in the retreatment plan. It can also identify the errors that caused many of the failures. A proper treatment history can also identify the drugs which had caused smear or culture conversion in the past and these drugs may be used in future regimens. However, the drawback lies in the inability of some patients to identify the drugs taken in the past and/or lack of access to prescriptions for previous antituberculosis treatment. For these reasons, the patient's treatment history should be taken by a person with experience in treating MDR-TB and previous treatment history may be taken as additional evidence for the diagnosis of drug-resistant tuberculosis.

Importance of radiology
Although radiology is not a reliable indicator for predicting drug resistance, it serves to complement bacteriological evidence of drug resistance. Change in size of cavities and increase in size of existing lesions and appearance of new lesions are signs of disease progression and activity. Serial radiographs showing worsening as described above at the end of three months of regular and adequate treatment can make one suspect drug resistance. Such radiological worsening in addition to bacteriological (sputum smear-positive for acid-fast bacilli (AFB)) and or clinical worsening can further increase the suspicion of drug resistance. However, one should also realise that radiological worsening may be due to inadequate drug regimens, non-adherence to therapy, intercurrent pneumonia, pulmonary embolism, or supervening carcinoma. Therefore, radiological worsening is a less reliable indicator of drug resistance.[7]

Importance of drug susceptibility testing
Diagnosis of M/XDR TB is confirmed by drug susceptibility testing (DST) from reliable and reputed laboratories under constant quality control. However, one has to keep in mind the limitation of DST because the technique is complex, difficult to perform accurately even when skilled personnel are available and laboratory facilities are of high standard. Further, one should realize that laboratories vary in reliability; errors do occur in labs and different susceptibility pattern reports may be obtained for the same patient from different labs. There is often lack

of standardization, coordination and cross checking by national and supranational reference laboratories in this country. The clinical effectiveness or ineffectiveness of a drug cannot be predicted by DST with 100% certainty.[5,8-10]

Inspite of all these odds, DST should be performed systematically against first-line drugs in all cases of suspected drug-resistant TB. DST is reliable for isoniazid (INH) and rifampicin (RMP), but less so for streptomycin (SM) and ethambutol (EMB) for which the susceptibility results are more reliable than the resistance results. For pyrazinamide (PZA) the BACTEC system is required.[8-10] However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs. If monoresistance to PZA is observed, the possibility is that *Mycobacterium bovis* rather than *M. tuberculosis* is the etiologic agent.[11] DST against second-line drugs is very variable and should not be carried out routinely on account of its difficulty, cost and poor reliability.[8,12] In the present situation of increasing prevalence of XDR-TB, DST to kanamycin (KM) and ofloxacin/levofloxacin may be of great help, as long as they are carefully compared with the patient's treatment history.[8,12] DST of drugs classified as Group 4 (ethionamide, prothionamide, para-aminosalicyclic acid, cycloserine, terizidone) and Group 5 (clofazimine, linezolid, amoxicillin/clavulanate, thioacetazone, imipenem/cilastatin, clarithromycin) by WHO does not have high reproducibility and reliability. Guidelines strongly caution against basing individual regimens on DST of these drugs.[13] Even in developed countries, where multiple methods are available for performing DST for second-line drugs, interpretation of the results requires cautious analysis by experienced staff since the concentrations used for each drug has not been standardised and the definitions of resistance vary widely, even between the best laboratories. Whilst it should be noted that monoresistance to RMP is found in approximately 5% of strains, a high proportion of RMP resistance is associated with concurrent resistance to INH (~95%).[14] Thus, the detection of resistance to RMP can be used as a marker for MDR-TB with a high level of accuracy.[15] Resistance to RMP is associated in nearly all instances with cross-resistance to rifabutin and rifapentine.[16] Rare strains with RMP resistance retain susceptibility to rifabutin; this is associated with uncommon mutations of the RNA polymerase locus in the bacillus. However, unless *in vitro* susceptibility to rifabutin is demonstrated, this agent should not be used in cases with RMP resistance.[16] Keeping above facts in mind it is pertinent that DST should not be accepted uncritically. As a general rule, if a patient has used a drug for more than a month with persistently positive smears or cultures, the strain should be considered as "probably resistant" to that drug, even if DST is reported as susceptible.[13] Accordingly, the diagnosis of MDR-TB should be based on the patient's treatment history and on the results of DST against INH and RMP, for which reliability approaches 100%. It should also be kept in mind that although drug resistance as detected by DST reflects the inefficacy of a drug in culture

media, it does not necessarily correspond to the inefficacy of the drug in a new regimen.[8-10,17,18]

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, such as India. Line probe assays are genotypic method for rapid detection of *M. tuberculosis* DNA and mutations associated with resistance to INH and RMP in clinical samples. Currently available commercial probes can detect mutations in *rpoB*, *katG*, *and inhA* genes. The advantages include rapid screening of patients with MDR-TB risk and results within 2 days as compared to 2-3 months for conventional cultures,[19] but line probe assay is not yet useful for diagnosis of XDR-TB.

Evidence and controversies in treatment of M/XDR-TB
Treatment of M/XDR TB is difficult, costly, and challenging. Ideally treatment should be done with supervision by a doctor who is experienced in dealing with such cases, since this treatment represents the patients last chance of a cure. Unfortunately in many countries with inadequate resources, M/XDR-TB patients cannot receive individualised attention from specialist physicians, therefore case management needs to be simplified and standardised.

Individualised versus standardized regimen
Individualised regimens are based on individual DST and prior treatment history and require close follow up by skilled professionals. In standardized regimen, all patients with confirmed or highly probable M/XDR-TB receive the standard regimen based on drug resistance surveillance data from the representative population. Another approach is empirical treatment, where the regimen is designed considering previous antituberculosis treatment and drug resistance surveillance data from representative patient population. An empirical regimen is adjusted when DST results of the individual patient become available. Individualised approach is, however, an expensive approach that is difficult to implement in the majority of middle- and low-income countries, which bear the highest burden of MDR-TB. For this reason, the WHO recommendations for the treatment of M/XDR-TB favoured the use of standardised treatment regimens in such circumstances.[20] Such regimens reduce the number of specialist physicians needed and cost of treatment by 5-10 times.[13] The efficacy of this strategy has been confirmed by many reports.[21,22] WHO has designed the DOTS-Plus strategy for managing M/XDR-TB in resource poor countries. DOTS-Plus is an integral component of RNTCP (Revised National Tuberculosis Control Program) to manage M/XDR-TB to be implemented through programme infrastructure.[23] The RNTCP under DOTS-Plus 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, or ethionamide) or the 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. An injectable agent should be given for at least 6 months and the whole treatment duration is minimum 18 months beyond sputum conversion.[13] Fully standardized second-line treatment have shown to be feasible and cost effective in M/XDR-TB treatment.[24]

Number of drugs in regimen for M/XDR-TB
One of the most controversial issues regarding M/XDR-TB is the number of drugs required to treat patients. This is mainly because of the absence of good controlled trials to compare different regimens.[8,25-27] Changes in guidelines regarding the number of drugs to be included in the regimen for the treatment of M/XDR-TB can be seen in the various American Thoracic Society (ATS) recommendations published in 1965,[27] 1966,[28] 1994[29] and 2003[30] Similar changes are also observed in British Thoracic Society (BTS) recommendations[31,32] and WHO recommendations from 1996,[33] 2003,[20] 1997[7] and 2008.[13] These changes are probably due to the availability of data from more case series. Regimens employing four to six effective drugs appear to be associated with better results.[30] Acceptable results have been obtained using more than four drugs, with favourable responses varying between 65%[34] and 85.5%.[35] Although the use of more drugs was not reported as a favourable factor for cure, all the reports of MDR-TB treatment showed that limiting the number of effective drugs lead to poor outcomes. The WHO 2008 Guidelines for the programmatic management of drug-resistant tuberculosis advocate the use of at least four new drugs with either certain, or almost certain, effectiveness.[13] However, the problem with administration of four, six, or more drugs is the high probability of intolerance by the patient, which may cause default from treatment or refusal to take drugs when they face severe side effects. It is not insignificant that 30-54% of patients experienced side effects that compelled them to discontinue one or two drugs.[34-36] Given the significant global increase in MDR-TB in recent years, more solid evidence validating the various recommendations will certainly come to light in the near future. A study in Peru showed that, in spite of high rate of side effects, patients could tolerate drug regimens with good palliative measures.[24] A study done by author himself on the efficacy of a standardised second-line regimen, involving kanamycin, ethionamide, cycloserine and PAS in 39 patients showed that 16 patients, i.e., 41% developed side effects and out of these 8 patients (21.1%) developed significant side effects that required discontinuation/change of drugs. In spite of the regimen containing known offending agents like PAS and ethionamide, majority of the patients tolerated the regimen with a cure rate of 74.3% (29/39) at 2 years.[37]

Treatment of XDR-TB cases relies on drugs that are less potent and much more toxic than those used in the management MDR-TB. Treatment must contain at least 5 drugs to which isolates are susceptible. First-line agents with favourable susceptibility reports should be preferred over second-line drugs.

Duration of injectable drug in M/XDR-TB

As no trials have been conducted to assess various regimens with different duration of injectable drugs in treatment of M/XDR-TB patients, the optimal duration of injectables is not known. A minimum of 3 months or until culture conversion was advised in chronic patients,[38] whereas recent WHO guidelines advise at least 6 months or at least 4 months after culture conversion.[7,13,20,39] In addition duration is also decided in correlation with other factors like other drugs in the regimen, bacteriological status and drug toxicity. Expert opinions on this subject are also contradictory since some experts tend to recommend 3–6 months,[8,18,40] while others suggest a minimum of 12 months after the cultures have become negative, or even throughout the treatment if the patient presents with extensive lung damage or a high degree of resistance.[41,42] In such cases the injectable agent can be continued throughout, if no significant side effects cause abruption of therapy. Intermittent therapy with the injectable agent (three times a week) can also be considered in patients in whom the injectable has been used for a prolonged period of time and when toxicity becomes a greater risk.[30] Simultaneous use of two injectable agents is not recommended due to the absence of proof of efficacy and potential amplification of drug toxicity.[33] The DOTS-Plus guidelines advocate use of the injectable drug kanamycin for a period of 6 months which can be extended up to 9 months.[43] In patients with renal impairment dose of injectable may have to be reduced according to creatinine clearance or it may have to be stopped if there is severe nephrotoxicity. Patients developing ototoxicity will need an expert opinion from otorhinolaryngologist regarding safety of continuation of the drug. WHO advices that injectable drugs in treatment of XDR-TB to be continued for extended duration of 12 months or possibly the whole treatment.[13]

Total duration of treatment in M/XDR-TB

The recommended total duration of treatment is guided by culture conversion. Despite emerging evidence that shorter regimens may be efficacious, WHO guidelines recommend continuing therapy for a minimum of 18 months after culture conversion. Extension of therapy to 24 months may be indicated in chronic cases with extensive pulmonary damage. The length of treatment for XDR tuberculosis has not been established and is often based on individual clinical presentations. Good outcome is seen with treatment of at least 18 months for oral agents and of at least 8 months after culture conversion for injectable drugs. In most cases the regimen does not contain 5 effective drugs, and clinician may have to adopt reinforcing strategies like extending the duration of treatment with the injectable agent or extending the duration of whole regimen with the addition of other drugs which have questionable activity against multidrug resistant tuberculosis.

Role of surgery in M/XDR-TB

After the discovery of effective drugs to fight TB, surgery was progressively abandoned and by the 1970s it practically disappeared from case management. With the emergence of M/XDR-TB, the role of surgery has again surfaced due to the inability to ensure complete cure with the available chemotherapy. Despite the absence of randomised trials assessing the role of surgery in the treatment of patients with MDR-TB, virtually all available guidelines and specific recommendations on the subject include a mention of surgery, although in a very secondary role.[18,27-29,42,44] In MDR-TB patients with localized disease, surgery, as an adjunct to chemotherapy, can improve outcomes provided skilled thoracic surgeons and excellent post-operative care are available. When unilateral resectable disease is present, surgery should be considered in patients when there is poor response to chemotherapy despite six to nine months of treatment with effective antituberculosis drugs, high risk of failure or relapse due to high degree of resistance, morbid complications of parenchymal disease, e.g., hemoptysis, bronchiectasis, bronchopleural fistula, or empyema, recurrence of positive culture status during course of treatment; and relapse after completion of antituberculosis treatment provided pre-operative lung function is adequate.

Most common operative procedure in patients with M/XDR-TB is resection surgery and large case-series analysis has shown resection surgery to be effective and safe under appropriate surgical conditions. Resection surgery should be timed to offer the patient the best possible chances of cure with the least morbidity, when the disease is still localized to one lung or one lobe, and surgery should not be considered as a last resort. If surgical option is under consideration at least 6 to 9 months of chemotherapy is recommended prior to surgery in order to decrease the bacterial infection in the surrounding lung tissue.[45-47] WHO 2008 guidelines recommend at least 2 months of therapy prior to surgery. Post-operatively, therapy should be continued for 18 months (12-24 months) after culture conversion.[10,15,19,40] Specialized surgical facilities should include stringent infection control measures, since infectious substances and aerosols are generated in large quantities during surgery and during mechanical ventilation and postoperative pulmonary hygiene manoeuvres. Computerized tomography, pulmonary function testing, and quantitative lung perfusion/ventilation are recommended as part of the preoperative work-up. It has been shown that overall cure rate was substantially higher (81% vs. 56%) when surgery was more frequently and aggressively applied.[46,48]

Culture monitoring during treatment in M/XDR-TB

In the DOTS-Plus Program, sputum conversion is defined as two consecutive negative sputum 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. A Category IV patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment is declared cured. Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive The date of the first set of negative cultures and smears is used as the date of conversion. The recording and reporting system assesses the smear- and culture-status 6 months after the start of treatment as an interim outcome. Programmes often use the smear and culture conversion rate at 6 months to assess programme performance. The indices of cure, completed treatment, failures, duration of injectable agent, total therapy duration are decided on the basis of culture reports. As described above, injectable agent is used for a minimum of six months and at least four months past culture conversion and treatment is given for 18 months after culture conversion. Sputum smears and cultures are monitored monthly before smear and culture conversion and after conversion, the minimum period recommended for bacteriological monitoring is monthly for smears and quarterly for cultures. Programs with adequate culture capacity may choose to do cultures more frequently, every 1–2 months, after conversion. But in a resource poor country like India, performing frequent cultures (monthly in the intensive phase and three monthly in continuation phase) as prescribed in the guidelines is nearly impossible, considering the long wait period for the culture results, lack of skilled man power and poor quality control of labs both in the government and private sector. In India, only four National Reference laboratories and 11 existing accredited Intermediate Reference Laboratory (IRLs) currently are functioning to cater the need of approximately 99,000 MDR-TB patients. Appropriate modifications in the culture schedule and outcome definitions are the need of the hour. Taking note of this huge discrepancy Chennai consensus developed during the consultative meeting of national experts organized by the TB Research Centre, Indian Council of Medical Research (ICMR), Govt. of India on September 14-15, 2007, at Chennai aimed at reducing follow-up cultures to five at 4, 6, 12, 18, and 24 months of treatment.[49] Meanwhile, laboratory services must be strengthened for adequate and timely diagnosis of M/XDR-TB and programmatic management of M/XDR-TB must be scaled up as per target set by global plan to stop TB 2011-2015.[50]

Exclusion criteria in DOTS-Plus program
As described above, the DOTS-Plus initiative by the WHO and Govt. of India aims to appropriately manage MDR-TB patients, while treating primary cases on a priority basis. Exclusion criteria in the DOTS-Plus consider patients <15 years of age and patients who have taken more than one month of second line drugs.[43] A preliminary study done by the author among sixty MDR suspect patients showed that almost 65% of the patients had

received irregular prescription of second-line drugs with frequent changes being made in the second-line drugs. The most common prescribed second-line drugs were fluroquinolones and injectable aminoglycosides.[51] If these figures are to be followed the majority of MDR-TB patients would be excluded from receiving valuable treatment and in a country like India where second-line drugs are prescribed inconsistently for tuberculosis, even in primary cases, this clause requires considerable debate. DOTS-Plus programme in India has already discarded this exclusion criterion.

CONCLUSION

MDR and XDR-TB is hazardous to human health. Quality-assured culture and DST are indispensable for the diagnosis of M/XDR-TB. M/XDR-TB must be managed very effectively with careful use of second line drugs to reduce morbidity and mortality and transmission of multi-drug resistant tuberculosis and to prevent the development of XDR-TB. Sound infection control measures to avoid further transmission of M/XDR-TB and research towards development of new diagnostics, drugs and vaccines should be promoted to control M/XDR-TB.

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