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Multi drug and extensively drug-resistant TB (M/XDR-TB) management: Current issues

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ABSTRACT

Multi Drug and Extensive 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 retard the optimal management of such patients, and guidelines that have been developed largely on expert opinion are crowded with controversies. Lack of effective drugs, improper regimens prescribed by poorly trained doctors and unreliable Drug Susceptibility Test (DST) reports add to the magnanimity of the situation. 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 (SLDs) to reduce the morbidity and mortality and transmission of M/XDR-TB. M/XDR-TB is a man made problem and its emergence can be prevented by prompt diagnosis and effective use of first-line drugs in every new patient. The Programmatic Management of Drug Resistance Tuberculosis (PMDT-TB) proposed by the WHO has highlighted the comprehensive management strategy to control MDR-TB. Laboratory services for adequate and timely diagnosis of M/XDR-TB must be strengthened and programmatic management of M/XDR-TB must be scaled up as per target set by global plan. The proper use of second-line drugs must be ensured to cure existing MDR-TB, to reduce its transmission and to prevent XDR-TB. Sound infection control measures to avoid further transmission of M/XDR-TB and research towards the development of new diagnostics, drugs and vaccines should be promoted for proper control of M/XDR-TB. Copyright © 2013, INDIACLEN. Publishing Services by Reed Elsevier India Pvt Ltd. All rights reserved.

1. Introduction

Drug resistant tuberculosis has been reported since the early days of introduction of anti TB chemotherapy, but multi drug 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 to control TB. Though unfortunate, yet a reality is that MDR and XDR-TB is a man made problem. Poor clinical and control practices in new patients of TB generates MDR-TB. Mismanagement of MDR-TB with erratic use of second-line drugs may lead to development of XDR-TB.¹ More than 400,000 cases of

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MDR-TB and 25,000 cases of XDR-TB emerges globally every year as a result of poor management of drug sensitive as well as drug resistant TB.^{2–4} This write up reviews various issues related to management of M/XDR-TB.

2. Issues in diagnosis of M/XDR-TB

2.1. Importance of a proper treatment history

The main predictor of resistance to a particular drug is the demonstration of its prior use in monotherapy for more than one month. To obtain evidence of possible inadvertent or direct monotherapy, it is essential to be meticulous in obtaining the history of anti-tuberculosis treatment in all patients suspected of MDR-TB.^{5,6} There should be a detailed evaluation into 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 supervised or unsupervised and any drug intolerance that included partial or complete drug defaulting. If the treatment history is taken meticulously, any real or masked 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 in the retreatment plan.^{5,6} However, the limitation of this method lies in the patient's ability to remember the drugs taken in the past and/or access to patient prescriptions for previous anti TB treatment.

2.2. Importance of radiology

Though radiology is not a very reliable indicator for predicting drug resistance, 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 and increase in size of existing lesions and appearance of new lesions are signs of disease progression and activity. Serial X rays showing worsening as described above at the end of 3 months of regular and adequate treatment can make one suspicious of drug resistance. Such radiological worsening in addition to bacteriological (sputum smear +ve for 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 intercurrent pneumonia, pulmonary embolism and supervening carcinoma. Therefore, radiological worsening is a less reliable indicator of drug resistance.

2.3. Importance of drug susceptibility test (DST)

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 highly specific drug susceptibility test because the technique is complex, difficult to perform accurately even when skilled personnel are available and laboratory facilities are of high standard.⁷ Further one should realize

that laboratories vary in reliability; errors do occur in laboratories, different sensitivity pattern reports are obtained from the same patient from different laboratories. The clinical effectiveness or ineffectiveness of a drug cannot be predicted by DST with 100% certainty.^{4,7–9}

In spite of all these odds, DST should be performed systematically against first-line drugs for all patients; it is adequate for isoniazid and rifampicin, but less so for streptomycin (SM) and ethambutol (EMB) for which the susceptibility results are more reliable than the resistance results, while for pyrazinamide (PZA) the BACTEC system is required.^{7–9} However, resistance to PZA is uncommon in the absence of resistance to other first-line drugs. If mono-resistance to PZA is observed, consideration must be given to the possibility that the etiologic agent is *M. bovis*, not *M. tuberculosis*.¹⁰ DST against second-line drugs is very variable and should not be carried out routinely on account of its difficulty, cost and poor reliability.^{7,11} In the present situation, if it is necessary, then DST to kanamycin (KM) and ofloxacin/levofloxacin, but not others, may be of great help, as long as they are carefully compared with the patient's treatment history.^{7,11} DST of drugs such as Ethionamide, Para-aminosalicylic acid, Cycloserine, Clofazimine, Linezolid, Amoxicillin/Clavulanate, Thioacetazone, Imipenem/Cilastatin and Clarithromycin does not have high reproducibility and reliability; guidelines strongly caution against basing individual regimens on DST of these drugs.¹² Even in well 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 mono-resistance to rifampicin is found in approximately 5% of strains, a high proportion of rifampicin resistance is associated with concurrent resistance to isoniazid (~95%). Thus the detection of resistance to rifampicin can be used as a marker for MDR-TB with a high level of accuracy.¹³ Resistance to rifampicin is associated in nearly all instances with cross-resistance to rifabutin and rifapentine.¹⁴ Rare strains with rifampicin 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 employed in cases with rifampicin resistance.¹⁵ Keeping above facts in mind, it is pertinent that drug susceptibility test should not be accepted uncritically. 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 efficacy of the drug in a new regimen.^{7–9,16,17}

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 like India. 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.¹⁸ Recently Xpert/Rifa test which is highly sensitive, specific, automated and real time molecular diagnostic test using DNA technologies for rapid and simultaneous detection of TB and Rif resistance has been endorsed by WHO in 2010 and it can diagnose TB and Rif resistance in 100 min¹⁹

3. Issues in treatment of M/XDR-TB

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

3.1. Individualised versus standardised regimen

Most of the guidelines for the management of Drug resistant TB are primarily for high income countries, where expert diagnostics and optimal care are available. Individualised regimens are based on individual DST and prior treatment history, require close follow-up by skilled professionals and incur high cost. For this reason, the WHO recommendations for the treatment of MDR-TB favoured the use of standardised treatment regimens in such circumstances.²⁰ The efficacy of this strategy has been confirmed by many reports.^{21,22} WHO has designed the DOTS-Plus which is an integral component of RNTCP to manage MDR-TB to be implemented through programme infrastructure in resource poor countries.²³ The RNTCP under DOTS-PLUS is using a standardised treatment regimen (STR) for MDR/XDR-TB.²⁴

3.2. Number of drugs in regimen for M/XDR-TB

One of the most controversial issues in the debate around MDR-TB is the number of drugs required to treat a patient with multi drug resistance. This has been mainly because of the absence of well designed controlled trials to compare different regimens.^{7,25–27} On reviewing various guidelines for the treatment of patients with drug resistance, e.g. that of ATS published in 1965,²⁷ 1966,²⁸ 1994²⁹ and 2003,³⁰ inconsistencies regarding the number of drugs to be included in the regimen and the validity of drug susceptibility testing were observed. Similar inconsistencies were also observed in BTS guidelines from 1990³¹ and 2000³² and WHO guidelines from 1996,³³ 2003,²⁰ 2006,³⁴ 2008 and the latest 2011 guidelines (Table 1).¹² The statement from the American Thoracic Society/Centres for Disease Control and Prevention/Infectious Diseases Society of America (ATS/CDC/IDSA) states that regimens employing four to six medications appear to be associated with better results.³⁰ They concluded that acceptable results have been obtained using more than four drugs, with favourable responses varying between 65%³⁵ and 85.5%.³⁶ Although the use of more drugs was not itself a favourable factor for cure, all the reports of MDR-TB treatment showed that limiting the number of active drugs that could be used in the presence of extensive patterns of drug resistance, had poor outcomes. WHO 2008 and 2011 guidelines for the programmatic management of drug resistant tuberculosis advocate the use of at least four drugs with either certain, or almost certain, effectiveness.¹² However, the problem with administration of four, six, or more drugs is the high probability of intolerance by the patient which will invariably cause default from treatment or refusal to take drugs when faced with the

Table 1 – Groups of second-line anti-tuberculosis agents.^a

Group name	Anti-tuberculosis agent
Second-line parenteral agent (injectable anti-tuberculosis drugs)	Kanamycin Amikacin Capreomycin
Fluoroquinolones	Levofloxacin Moxifloxacin Gatifloxacin Ofloxacin
Oral bacteriostatic second-line anti-tuberculosis drugs	Ethionamide Prothionamide Cycloserine Terizidone P-aminosalicylic acid
Group 5 drugs	Clofazimine Linezolid Amoxicillin/clavulanate Thioacetazone Clarithromycin Imipenem

^a Modified from reference 12.

appearance of severe side effects. It is not insignificant that 30–54% of patients experienced side effects that compelled them to discontinue one or two drugs.^{35,37} In spite of high rate of side effects, the observations made in a study in Peru show that, with good palliative measures and clinical experience in treating MDR-TB patients, drug regimens could be tolerated by patients.^{38,39}

3.3. Duration of injectables in M/XDR-TB

The next question arises in the duration of parenteral drug needed. Since no trials have been conducted to assess various regimens with different duration of injectables, it is not yet proved what the optimal duration of initial phase should be. The 1997 WHO guidelines advise a minimum of 3 months or until culture conversion in chronic patients,⁴⁰ whereas a minimum of 6 months is advised for chronic patients in the 2003 WHO guidelines.²⁰ The 2006, 2008 and 2011 WHO guidelines advise at least 6 months or at least 4 months after smear or culture conversion. 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.³⁵ 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.⁴¹

3.4. Total duration of treatment in M/XDR-TB

The recommended 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 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. Inadequate treatment duration will result in relapses and using an inadequate regimen may lead to treatment failure and additional acquired drug resistance, which would compromise future efforts at treatment.

3.5. Role of surgery in M/XDR-TB

After the discovery of effective drugs to fight TB, surgery was progressively abandoned until the 1970s, when it practically disappeared from case management. With the emergence of MDR and XDR-TB, the role of surgery has again surfaced due to an 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.^{16,27–30} 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.

Resection surgery should be timed to offer the patient the best possible chances of cure with the least morbidity, for example, when the disease is still localized to one lung or one lung lobe. In other words, surgery should not be considered as a last resort. WHO 2008 guidelines recommend at least 2 months of therapy prior to surgery. It has been shown that overall cure rate was substantially higher (81% vs 56%) when surgery was more frequently and aggressively applied.^{42–44}

3.6. Culture monitoring during treatment in M/XDR-TB

In DOTS-Plus program, 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. Sputum smears and cultures is 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. 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. So appropriate modifications in the culture schedule and outcome definitions is 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, ICMR, Govt. of India on 14–15 September 2007, at Chennai aimed at less follow-up culture at 4, 6, 12, 18 and 24 months (total 5 cultures).⁴⁵

4. Conclusion

The subject of M/XDR-TB has been an area of growing concern among clinicians, epidemiologists and public health workers worldwide. 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 SLDs to reduce morbidity and mortality and transmission of multi drug resistant tuberculosis. M/XDR-TB is a man made problem and its emergence can be prevented by prompt diagnosis and effective use of first-line drugs in every new patient. The proper use of second-line drugs must be ensured to cure existing MDR-TB, to reduce its transmission and to prevent 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.

Conflicts of interest

All authors have none to declare.

REFERENCES

1. Prasad R, Garg R. XDR-TB: an emerging threat. *Chest India*. 2007;8:3–4.
2. WHO IUALTD Global Project on Anti-tuberculosis Drug Resistance Surveillance (2002–2007), Fourth Global Report; 2008.
3. Multidrug and Extensively Drug-resistant TB (M/XDR-TB): 2010 Global Report on Surveillance and Response. WHO/HTM/TB/2010.3.
4. Caminero JA. Treatment of multidrug-resistant tuberculosis: evidence and controversies. *Int J Tuberc Lung Dis*. 2006;10(8):829–837.
5. Mitchison DA. The segregation of streptomycin-resistant variants of *Mycobacterium tuberculosis* into groups with characteristic levels of resistance. *J Gen Microbiol*. 1951;5:596–604.
6. Prasad R, Nautiyal RG, Ahuja RC, et al. Treatment of new pulmonary tuberculosis patients: what do allopathic doctors do in India? *Int J Tuberc Lung Dis*. 2002;6:895–902.
7. Caminero JA. Management of multidrug-resistant tuberculosis and patients in retreatment. *Eur Respir J*. 2005;25:928–936.
8. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Eur Respir J*. 2005;25:564–569.
9. Canetti G. The J. Burns Amberson lecture. Present aspects of bacterial resistance in tuberculosis. *Am Rev Respir Dis*. 1965;92:687–703.
10. Moore M, Onorato IM, McCray E, Castro KG. Trends in drug-resistant tuberculosis in the United States, 1993–1996. *JAMA*. 1997;278:833–837.
11. Tuberculosis bacteriology—priorities and indications in high prevalence countries: position of the technical staff of the Tuberculosis Division of the International Union against Tuberculosis and Lung Disease. *Int J Tuberc Lung Dis*. 2005;9:355–361.
12. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis* – WHO 2008; 2011.
13. Tuberculosis: clinical diagnosis and management of tuberculosis, and measures for its prevention and control. Joint Tuberculosis Committee of the British Thoracic Society. BTS Guidelines: April 2006.
14. Moghazeh SL, Pan X, Arain T, Stover CK, Musser JM, Kreiswirth BN. Comparative antimicrobial activities of rifampin, rifapentine, and KRM-1648 against a collection of rifampin-resistant *Mycobacterium tuberculosis* isolates with

- known rpoB mutations. *Antimicrob Agents Chemother*;40:2655–2657.
15. Bodmer T, Zürcher G, Imboden I, Telenti A. Mutation position and type of substitution in the beta-subunit of the RNA polymerase influence in-vitro activity of rifamycins in rifampicin-resistant *Mycobacterium tuberculosis*. *J Antimicrob Chemother*. 1995;35:345–348.
 16. Caminero JA. *A Tuberculosis Guide for Specialist Physicians*. Paris, France: International Union Against Tuberculosis and Lung Disease; 2005.
 17. Iseman MD, Wood AJJ. Treatment of multidrug-resistant tuberculosis. *N Engl J Med*. 1993;329:784–791.
 18. Who Press Release *New Rapid Test for Dr-Tb for Developing Countries* Geneva; June 30 2008.
 19. Small DM, Pai M. *New Eng J Med*. 2010;363:1070–1071.
 20. World Health Organization. *Treatment of Tuberculosis: Guidelines for National Programmes*. WHO/CDS/TB/2003.313. 3rd ed. Geneva, Switzerland: WHO; 2003.
 21. International Organization for Migration Tuberculosis Working Group. Outcome of second-line tuberculosis treatment in migrants from Vietnam. *Trop Med Intern Health*. 1998;3:975–980.
 22. Van Deun A, Hamid Salim MA, Kumar Das AP, Bastian I, Portals F. Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh. *Int J Tuberc Lung Dis*; 8: 560–567.
 23. DOTS PLUS Guidelines, Revised National Tuberculosis Control Programme, Central TB Division Directorate General Health Services, Ministry of Health & Family Welfare. New Delhi: Nirman Bhawan; Sep 2008.
 24. Suárez PG, Floyd K, Portocarrero J, et al. Feasibility and cost effectiveness of standardised second line drug treatment for chronic tuberculosis patients; a national cohort study in Peru. *Lancet*. 2002;359:1980–1989.
 25. Caminero JA. Number of drugs to treat multidrug-resistant tuberculosis. From the authors. *Am J Respir Crit Care Med*. 2004;169:1337.
 26. Iseman MD. Statements of ATS, CDC, and IDSA on treatment of tuberculosis. From the authors. *Am J Respir Crit Care Med*. 2004;169:317.
 27. American Thoracic Society. Chemotherapy of pulmonary tuberculosis in adults: the choice of drugs in relation to drug susceptibility. A statement of the Committee on Therapy. *Am Rev Respir Dis*. 1965;92:508–512.
 28. American Thoracic Society. Treatment of drug-resistant tuberculosis. A statement by the Committee on Therapy. *Am Rev Respir Dis*. 1966;94:125–127.
 29. American Thoracic Society, Centers for Disease Control and Prevention, American Academy of Pediatrics. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med*. 1994;149:1359–1374.
 30. American Thoracic Society, Centers for Disease Control and Prevention, Infectious Disease Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167:603–662.
 31. Citron KM, Darbyshire JH, Ormerod LP, Smith ML. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations of the joint tuberculosis committee of the British Thoracic Society. *Thorax*. 1990;45:403–408.
 32. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*. 1998;53:536–548.
 33. Crofton J, Chaulet P, Maher D, et al. *Guidelines for the management of drug-resistant tuberculosis*. WHO/TB/96.210. Geneva, Switzerland: WHO; 1997.
 34. World Health Organization. *Guidelines for the Programmatic Management of Drug-resistant Tuberculosis*. WHO/HTM/TB/2006.361. Geneva, Switzerland: WHO; 2006.
 35. Goble M, Iseman MD, Madsen LA, Waite D, Ackerson L, Horsburgh R. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *N Engl J Med*. 1993;328:527–532.
 36. Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *Int J Tuberc Lung Dis*. 1998;2:877–884.
 37. Geerligs WA, Altena R, de Lange WCM, van Soolingen D, van der Werf TS. Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. *Int J Tuberc Lung Dis*. 2000;4:758–764.
 38. Furin JJ, Mitnick CD, Shin SS, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis*. 2001;5:648–655.
 39. Prasad R, Verma SK, Sahai S, Kumar S, Jain A. Efficacy and safety of kanamycin, ethionamide, PAS, and cycloserine in multidrug resistant pulmonary tuberculosis patients. *Indian J Chest Dis Allied Sci*. 2006;48:183–186.
 40. World Health Organization. *Treatment of Tuberculosis: Guidelines for National Programmes*. WHO/TB/97.220. 2nd ed. Geneva: Switzerland; 1997. WHO.
 41. Central TB Division, Directorate General of Health Services, Ministry of Health & Family Welfare. *Revised National Tuberculosis Control Programme DOTS-Plus Guidelines*; November 2009.
 42. Freixinet J, Rivas JJ, Rodríguez de Castro F, et al. Role of surgery in pulmonary tuberculosis. *Med Sci Monit*. 2002;8:CR782–CR786.
 43. Pomerantz M, Madsen LA, Goble M, Iseman MD. Surgical management of resistant mycobacterial pulmonary infection. *Ann Thorac Surg*. 1991;52:1108–1112.
 44. Chan ED, Laurel V, Strand MJ, et al. Treatment and outcome analysis of 205 patients with multi-drug resistant tuberculosis. *Am J Respir Crit Care Med*. 2004;169:1103–1109.
 45. Proceedings of consultative meeting of national experts organized by the TB Research Centre, ICMR, Govt. of India 14–15 September 2007, at Chennai.