

## Multidrug resistant tuberculosis treatment in India

Rajendra Prasad<sup>1,\*</sup>, Nikhil Gupta<sup>2</sup>, Viswesvaran Balasubramanian<sup>1</sup>, Abhijeet Singh<sup>1</sup>

<sup>1</sup>Department of Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi, India.

<sup>2</sup>Department of Medicine, Era's Medical College, Lucknow, India.

**Summary** Multidrug-resistant tuberculosis (MDR-TB) is posing a major public health threat as well as a big challenge to global efforts of tuberculosis control. The management of MDR-TB patients 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:** Multidrug-resistant tuberculosis, second line drugs, treatment regimens, adjuvant therapies, treatment outcomes

### 1. Introduction

Multi-drug Resistant Tuberculosis (MDR-TB) is defined as disease due to *M. tuberculosis* that is resistant to isoniazid and rifampicin with or without resistance to other drugs (the culture and drug susceptibility test result being from an accredited laboratory). It has been an area of growing concern, and is posing a threat to global efforts of tuberculosis control (1). Treatment of MDR-TB is difficult, very expensive, challenging and quite often leads to treatment failure. This write up aims to review the treatment of MDR-TB in India.

### 2. Second line drugs and their dosage

The second line drugs (SLD's) with their dosages used for treatment of MDR-TB are shown below (Table 1). It is generally thought that, SLD's are frequently associated with very high rates of unacceptable adverse drug reactions (ADR's), 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 a modified strategy of Programmatic Management of Drug Resistant Tuberculosis (PMDT) formerly known as 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) (2). One study conducted among 39 patients with MDR-TB reported that 41% of patients experienced some side effects but only 21.1% of patients required stoppage or change of drug (3). Thus, it is practically possible to treat the MDR-TB patients with these drugs.

### 3. Cross-resistance

Cross-resistance has been reported between thioamides and thioacetazone (one way resistance –strains resistant to thioacetazone are susceptible to thioamides, the reverse is seldom the case), kanamycin/amikacin with streptomycin (4), rifampicin with rifapentine, and rifabutin (> 70% strains) (5) and among various derivatives of fluoroquinolones (6). 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 Minimum Inhibitory Concentration (MICs),

\*Address correspondence to:

Dr. Rajendra Prasad, Pulmonary Medicine, Vallabhbhai Patel Chest Institute, University of Delhi, Delhi 110007, India.  
E-mail: rprasadkgmc@gmail.com

**Table 1. Doses of anti-tuberculosis drugs used in MDR-TB**

Drugs	Average daily dosage	Daily dosage (mg)		Type of anti-mycobacterial activity	Ref.	
		Minimum	Maximum			
Group 1 First line oral agents						
Pyrazinamide (Z)	25 mg/kg	1200	1500	Bactericidal	(19)	
Ethambutol (E)	15 mg/kg	800	1200	Bacteriostatic		
Rifabutin (Rfb)	5–10mg/kg	150	600	Bactericidal		
Group 2 Injectable agents						
Kanamycin (Km)	15 mg/kg	750	1000	Bactericidal against actively multiplying organisms	(19)	
Amikacin (Am)	15 mg/kg	750	1000			
Streptomycin (S)	15 mg/kg	750	1000			
Capreomycin (Cm)	15 mg/kg	750	1000			
Group3 Fluoroquinolones						
Moxifloxacin (Mfx)	7.5–10mg/kg	400	400	Weakly bactericidal	(19)	
Ofloxacin (Ofx)	15–20 mg/kg	800	1000			
Levofloxacin (Lfx)	7.5–10mg/kg	500	1000			
Group 4 Oral Bacteriostatic second line drugs						
Ethionamide (Eto)	15–20 mg/kg	500–750	1000	Bacteriostatic	(19)	
Protionamide (Pto)	15–20 mg/kg	500–750	1000			
Para-aminosalicylic acid (PAS)	200–300mg/kg	10 g	12 g			
Cycloserine (Cs)	10–20 mg/kg	500–750	1000			
Terizidone (Trd)	10–20 mg/kg	500–750	1000			
Group 5 Agents with unclear role in treatment of Drug resistant TB						
Bedaquiline	400 mg once daily for 2 weeks, 200 mg thrice weekly for 22 weeks after food			Bactericidal	(19)	
Delamanid		100 twice daily		Bactericidal		
Clofazimine (Cfz)	4–5 mg/kg	100	300	Bacteriostatic		
Linezolid (Lzd)		600	1200			
Amoxicillin/clavulanate (Amx/Clv)		500/125	Twice a day	1000/250 Twice a day		Weakly bactericidal
Thioacetazone (T)	150 mg/day	-	-			
Imipenem /Cilastatin (Ipm/Cln) High dose	500–1000 mg/every 6 h	500 every 6 hourly	1000 every 6 hourly			
Isoniazid (High dose H)	16–20 mg/kg	600	900			
Clarithromycin (Clr)	10–15 mg/kg	500 twice a day	500 twice a day	Bactericidal (pH dependent)		

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 (7), more clinical and laboratory research is needed to understand the extent of fluoroquinolones cross-resistance and its clinical relevance. Cross-resistance has also been reported between ethionamide and INH (8), amikacin and kanamycin (4), amikacin and capreomycin (4). 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.

#### 4. General principles for designing treatment regimens for multi-drug 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 MDR-TB and should be avoided. A 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-TB regimens in few settings (9). Even when standard regimens are used throughout treatment, patients experiencing severe ADR's will need to have their 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.

**Table 2. Grouping of anti-tuberculosis drugs**

Group	Anti-tuberculosis Drugs	Ref.
Group 1 First-line oral agents	Pyrazinamide (Z); Ethambutol (E); Rifabutin (Rfb)	(19)
Group 2 Injectable agents	Streptomycin (S); Kanamycin (Km); Amikacin (Amk); Capreomycin (Cm)	(19)
Group 3 Fluoroquinolones	Levofloxacin (Lfx); Moxifloxacin (Mfx); Ofloxacin (Ofx)	(19)
Group 4 Oral bacteriostatic 2nd line agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Terizidone (Trd); Para-Aminosalicylic acid (PAS); Para-aminosalicylate sodium (PAS-Na)	(19)
Group 5 Drugs with unclear efficacy or unclear role in MDR-TB treatment, not recommended by WHO for routine use in MDR-TB patients	Bedaquiline (Bdq); Delamanid (Dlm); Linezolid (Lzd); Clofazimine (Cfz); Amoxicillin/Clavulanate (Amx/Clv); Imipenem/cilastatin (Ipm/Cln); Meropenem (Mpm); high-dose Isoniazid (high-dose H); Thioacetazone (T); Clarithromycin (Clr)	(19)

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 should not depend upon it 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 is shown below (Table 2).

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. Para-amino Salicylic acid (PAS) has traditionally been given in split doses during the day to reduce adverse reactions. 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 (10). Treatment of ADR's should be immediate and adequate in order to minimize the risk of treatment interruptions and prevent increased morbidity and mortality due to serious ADR's. 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 until sputum conversion. If directly observed treatment is not possible, adherence to treatment must be ensured by intense health education to patient and family members at start of treatment and during each follow-up visit 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 drug resistant tuberculosis (DR-TB) patients have chronically inflamed lungs, which theoretically produces the acidic environment in which pyrazinamide is active. Alternatively, in patients doing well, injectable pyrazinamide can be stopped 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 of its discomfort, because it is the last that stands between patient and death (11-17).

## 5. Programmatic management of drug resistant tuberculosis

Programmatic Management of Drug resistant Tuberculosis (PMDT) is an integral component of a tuberculosis control program to manage MDR-TB implemented through program infrastructure. The strategy is designed to manage MDR-TB using second-line anti-tuberculosis drugs within the Directly Observed

**Table 3. Suggested regimen for drug resistant/multidrug resistant tuberculosis before or without or unreliable DST reports**

Group	Previous use of ATT	Drug regimen	Duration in months	Drugs given (Responders)	Duration in months	Drugs given (Non- Responders)	Ref.
I	Misused drugs like SHE and T	Rifampicin, Isoniazid, Ethambutol Pyrazinamide + Streptomycin	2-3*	Rifampicin Isoniazid Ethambutol + Pyrazinamide	9	Treat as Group II or Take help of DST result from accredited laboratory	(3)
II	Misused drugs like SHREZ & T	Streptomycin, Isoniazid, Rifampicin, Ethambutol Pyrazinamide	2-3*	Rifampicin Isoniazid Ethambutol + Pyrazinamide	9	Treat as Group III or Take help of DST result accredited laboratory	(3)
III	Failed after adequate 5 drugs (SHREZ)	Kanamycin, Ethionamide, Cycloserine, Pyrazinamide, Ethambutol	6-9	Ethionamide; Fluoroquinolone (Levofloxacin/ Ofloxacin) Cycloserine, Ethambutol	18	Treat as Group IV or Take help of DST result accredited laboratory and consider surgery	(3)
IV	Failed on group III treatment	Capreomycin, PAS, Moxifloxacin, High dose-INH, Clofazimine, Linezolid, Amoxicillin/ Clavulanate	6-12	PAS, Moxifloxacin, High dose-INH, Clofazimine, Linezolid, Amoxicillin/ Clavulanate	18	Consider surgery	(3)

\* depending on sputum conversion can be used for 3-6 months if toxicity does not intervene. R-rifampicin, H-isoniazid, E-ethambutol, Z-pyrazinamide, S-streptomycin, T-thiacetazone.

Treatment and Short course chemotherapy (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 known as Category IV regimen, comprised 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. 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 tuberculosis 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 a minimum of 18 months beyond sputum conversion. Fully standardized second line treatment has shown to be feasible and cost-effective in MDR-TB treatment (16,18).

In a 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 the author himself has used four groups of the regimen in treating resistant/multidrug resistant tuberculosis and found it to be effective (3). The suggested regimen by author is mentioned below (Table 3).

## 6. Duration of treatment

The optimal duration of therapy for MDR-TB has not been clearly established and duration remains questionable. World Health Organization (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 that bear the high burden of MDR-TB. The duration of injectable is also controversial. The 2006 and 2008 WHO guidelines advise at least 6 months or at least 4 months after smear or culture conversion. WHO guideline 2011 advises at least 8 months of injectable. In addition duration has to be decided in correlation with other factors also including other drugs in the regimen, bacteriological status and drug toxicity (11).

## 7. 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 until the end of therapy (11). If such a 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-rays should be done every 6 months whereas clinical monitoring preferably should be done every month (3).

## 8. 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.

## 9. Nutritional support

Drug-resistant tuberculosis treatment and care should contain integrated nutritional assessment counseling and support for the duration of the illness. Food support may improve treatment adherence in settings where food insecurity is an important access barrier (19). 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 (20).

## 10. 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 months prior to surgery and continued for 12-24 months after resection. It is indicated in patients who remain sputum positive, with resistance to a large number of drugs; and localized pulmonary disease (11).

## 11. Collapse therapy

It is a reversible surgical therapy that involves collapse of lung by artificial pneumo-peritoneum or pneumothorax used for cavity containing diseased lung with concept that compression of the cavity will change the local environment in a manner that will inhibit the mycobacteria. This therapy does not appear to be of general utility, although artificial pneumo-peritoneum and pneumothorax may be helpful in highly selected cases (21). However, controlled studies are lacking.

## 12. 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 cavity disease with heavy bacterial loads particularly when there is an increased chance of failure of medical treatment. It is thought to have a role in the rapid killing of bacteria, increases and improves penetration of anti-tubercular drugs in walled off lesions and helps in early closure of cavities and is of proven benefit in tracheal and bronchial stenosis due to endobronchial growth. It also reduces the trauma of surgery and post-operative complications.

## 13. 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 favorable results when given to drug resistant tuberculosis patients that had failed chemotherapy (22). Immunomodulation can be affected by enhancing pro inflammatory cytokines like IL-2, IL-12, IFN- $\gamma$ , TNF- $\alpha$ , 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, but have failed to confirm the utility of this therapy (23). Beneficial effect of parenterally used interferon gamma (IFN- $\gamma$ ) has been reported in disseminated disease attributable to mycobacteria other than tuberculosis that was refractory to chemotherapy (24). Favorable results were reported following one-month use of inhaled IFN- $\gamma$ , 500 micrograms thrice weekly. Interleukin-2 (IL-2) was used to restore antigen responsiveness, presumably *via* enhancing IFN- $\gamma$  production. Thalidomide has been shown to inhibit the *in vitro* release of TNF- $\alpha$  from peripheral blood monocytes. In patients with active tuberculosis it induces a significant gain in weight (25). However the

possibility that thalidomide agents may ameliorate tissue injury in tuberculosis needs further study (26,27). The potential role of diverse agents such as transfer factor, indomethacin, and levamisole is yet to be established (28). 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 (29). *Mycobacterium w* (commercially available as Immuvac) has been extensively studied as an effective immunomodulator for treatment of leprosy. It enhances bacterial killing and lesion clearance when used as an adjuvant to multi-drug therapy for leprosy. *Mycobacterium w* shares antigens with *M. leprae* as well as *M. tuberculosis* suggesting its application in treatment of drug resistant tuberculosis. A 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 (30,31). Another advantage though not proven, may be that the Immuvac effect would be longer lasting and could take care of defaulters more meaningfully than chemotherapy alone, leading to a reduction in relapse rate and the emergence of MDR-TB. A meta-analysis to evaluate *Mycobacterium w* immunotherapy as an adjunct to chemotherapy in participants with pulmonary tuberculosis 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) (32). 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 ( $p = 0.04$ ) and liquid culture ( $p = 0.04$ ) 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 (33).

#### 14. 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 (34).

#### 15. 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 (11). Corticosteroids should never be given to patients with MDR-TB unless they are receiving adequate anti-tuberculosis therapy.

#### 16. Outcome of treatment

The outcome of treatment of MDR-TB is not very favorable and varied from 50-80% in different studies. In a retrospective analysis of 171 immunocompetent patients treated over a ten year period (1973-83) at the National Jewish Hospital in Denver, the overall favorable outcome was only a little over 50% (35). All patients were treated with individually tailored regimens in which they received at least 3 or 4 drugs that 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 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 (36). 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 (37). Khanna, *et al.* (38) 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.* (39) used kanamycin (6 months), ethionamide, sodium PAS and isoniazid for 18 months on a domiciliary basis and bacteriological conversion was achieved in 73% of the patients. In another study by Rupak Singla

*et al.* (40) bacteriological quiescence was achieved in 78% of the patients who completed the full therapy. Prasad, *et al.* (3,41) observed 75.5% sputum smear and culture conversion rate at the end of two years in 45 patients of MDR-TB patients by using kanamycin, ethionamide, PAS and cycloserine regimen. Out of 45 patients 34 (75.5%) patients were declared cured, these patients were followed for an 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 (42). 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% CI 64-73%) than other studies of treatment outcomes (58%, 95% CI 52-64%). In another prospective study by Prasad *et al.* of 98 MDR-TB patients treated as per DOTS PLUS protocol it was observed that the default and expiry rates were 7.1% and 10.2% respectively (43). It is observed that inadequate treatment duration will result in relapses, may lead to treatment failure and additional acquired drug resistance (44). In a study by Chan *et al.* on treatment and outcome analysis of 205 patients with MDR-TB, it was observed that surgical resection and fluoroquinolone therapy was associated with improved microbiological and clinical outcome (45). Fluoroquinolone resistance was associated with a higher proportion of treatment failures and deaths in MDR patients than non-fluoroquinolone-resistant cases. Addition of fluoroquinolones was associated with less chance of relapse and improved treatment outcomes (46-51). Kanamycin (52), capreomycin (53) and streptomycin resistance is associated with poor treatment outcomes. The outcome for patients with MDR-TB is not very favorable in non-immunocompetent patients; and the response in HIV positive patients is even bleaker. In the outbreaks of MDR-TB in and around New York City, 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 (54). 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 (55).

## 17. Conclusion

Multidrug resistant tuberculosis is a growing concern. Prompt identification in early stages and timely initiation of treatment is of utmost importance in curbing further spread of this deadly phenomenon. Despite growing evidence in treatment the outcome still remains unfavorable. It is prudent to formulate management strategies taking into consideration the limitations in diagnostic facilities in developing countries including India. And finally a proper understanding of these management principles is essential for better utilization of available resources, especially in those countries.

## References

1. Multi-drug resistant tuberculosis. ICMR. 1999; 29:105-114.
2. Prasad R, Singh A, Srivastava R, Kushwaha R, Garg R, Hosmane G B, Jain A. Adverse drug reaction in treatment of multidrug resistant tuberculosis. *Chest*. 2013; 144:390A.
3. Prasad R, Verma S K, Sahai S, Kumar S, Jain A. Efficacy and safety of kanamycin, ethionamide, PAS, and cycloserine in multidrug resistant pulmonary tuberculosis patients. *Ind J Chest Dis Allied Sci*. 2006; 48:183-186.
4. Tsukamura M, Mizuno S. Cross-resistant relationships among the aminoglycoside antibiotics in *Mycobacterium tuberculosis*. *J Gen Microbiol*. 1975; 88:269-274.
5. Venkataraman P, Paramasivan CN, Prabhakar R. *In vitro* activity of rifampicin, rifapentine and rifabutin against south Indian isolates of *Mycobacterium tuberculosis*. *Ind J Tub*. 1993; 40:171-175.
6. Jain NK, Surpal BB, Khanna SP, Fatima T. *In vitro* activity of ofloxacin against clinical isolates of *Mycobacterium tuberculosis*. *Ind J Tub*. 1996; 43:183-186.
7. Yew WW, Chan CK, Leung CC, Chau CH, Tam CM, Wong PC, Lee J. Comparative roles of levofloxacin and ofloxacin in the treatment of multidrug-resistant tuberculosis: Preliminary results of a retrospective study from Hong-Kong. *Chest*. 2003; 124:1476-1481.
8. Canetti G, Kreis B, Thibur R, Gay P, Oe-Lirzin M. Donnees actualles su la resistance primare deus la tuberculose pulmonaire de "L" adulte in France, deuxieme enquete. In Centre d'Etudes sur la resistance Primaire (1) aunees 1865-66. *Rev Tuberc Pneumol*. 1967; 31:433-474.
9. Resch SC, Salomon JA, Murray M, Weinstein MC. Cost-Effectiveness of treating multi-drug resistant tuberculosis. *PLoS Med*. 2006; 3:e241.
10. World Health Organization. Treatment of tuberculosis: Guidelines (4th ed., WHO/HTM/TB/2009.420). Geneva, Switzerland, 2009. <http://www.who.int/tb/publications/2010/9789241547833/en/html> (accessed February 14, 2015).
11. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008 and 2011. WHO/HTM/TB/2008.402/2011/6. Geneva, Switzerland, 2008/2011. [http://whqlibdoc.who.int/publications/2008/9789241547581\\_eng.pdf](http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf) and [http://whqlibdoc.who.int/publications/2011/9789241501583\\_eng.pdf](http://whqlibdoc.who.int/publications/2011/9789241501583_eng.pdf) (accessed February 19, 2015).

12. Prasad R. Management of multidrug resistance tuberculosis: Practitioner's viewpoint. *Indian J Tub.* 2007; 54:3-11.
13. World Health Organization. Treatment of tuberculosis: Guidelines for national programmes (WHO/CDS/TB/2003.313). Geneva, Switzerland, 2003. [http://whqlibdoc.who.int/hq/2003/who\\_cds\\_tb\\_2003.313\\_eng.pdf](http://whqlibdoc.who.int/hq/2003/who_cds_tb_2003.313_eng.pdf) (accessed January 29, 2015).
14. Crofton J, Chaulet P, Maher D. World Health Organization. Guidelines for the management of drug resistant tuberculosis. WHO/TB/96: 210. Geneva, Switzerland, 1997.
15. Mukherjee JS, Rich ML, Socci AR, Joseph JK, Virú FA, Shin SS, Furin JJ, Becerra MC, Barry DJ, Kim JY, Bayona J, Farmer P, SmithFawzi MC, Seung KJ. Programmes and principles in treatment of multi-drug resistant tuberculosis. *Lancet.* 2004; 363:474-481.
16. Suarez PG, Floyd K, Portocarrero J, Alarcon E, Rapiti E, Ramos G, Bonilla C, Sabogal I, Aranda I, Dye C, Raviglione, Espinal MA. Feasibility and cost-effectiveness of standardized second-line drug treatment for chronic tuberculosis patients; a national cohort study in Peru. *Lancet.* 2002; 359:1980-1989.
17. Rich ML, Mukherjee J, Socci A, *et al.* The PIH guide to management of multidrug-resistant tuberculosis. International edition, Partners in Health, Boston, MA, USA, 2003; pp. 1-165.
18. Ministry of Health and Family Welfare, Central TB Division, DGHS. Revised National Tuberculosis Control Programme Guidelines for the programmatic management of drug-resistant tuberculosis (PMDT) in India. MOHFW India, 2012. <http://www.tbcindia.nic.in/.../Guidelines%20for%20PMDT%20in%20India%2013> (accessed February 2, 2015).
19. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.23. Geneva, Switzerland, 2014. [http://www.who.int/tb/challenges/mdr/programmatic\\_guidelines\\_for.../en/](http://www.who.int/tb/challenges/mdr/programmatic_guidelines_for.../en/) (accessed February 27, 2015).
20. Sinclair D, Abba K, Grobler L, Sudarsanam TD. Nutritional supplements for people being treated for active tuberculosis. *Cochrane Database Syst Rev.* 2011; 11:1-139.
21. Nitta AT, Iseman MD, Newell JD, Madsen LA, Goble M. Ten-year experience with artificial pneumo-peritoneum for end-stage, drug-resistant pulmonary tuberculosis. *Clin Infect Dis.* 1993; 16:219-222.
22. Etemadi A, Farid R, Stanford JL. Immunotherapy for drug-resistant tuberculosis. *Lancet.* 1992; 340:1360-1361.
23. Stanford JL. *Frontiers in mycobacteriology. Symposium sponsored by National Jewish Center for Immunology and Respiratory Medicine, Vail, Colorado, October, 1997.*
24. Holland SM, Eisenstein EM, Kuhns DB, Turner ML, Fleisher TA, Strober W, Gallin JI. Treatment of refractory disseminated nontuberculosis mycobacterial infection with interferon gamma. *N Engl J Med.* 1994; 330:1348-1355.
25. Moller DR, Wysocka M, Greenlee BM, Ma X, Wahl L, Flockhart DA, Trinchieri G, Karp CL. Inhibition of IL-12 production by thalidomide. *J Immunol.* 1997; 159:5157-5161.
26. Tramontana JM, Utaipat U, Molloy A, Akarasewi P, Burroughs M, Makonkawkeyoon S, Johnson B, Klausner JD, Rom W, Kaplan G. Thalidomide treatment reduces tumor necrosis factor-alpha production and enhances weight gain in patients with pulmonary tuberculosis. *Mol Med.* 1995; 1:384-397.
27. Klausner JD, Makonkawkeyoon S, Akarasewi P, Nakata K, Kasinrek W, Corral L, Dewar RL, Lane HC, Freedman VH, Kaplan G. The effect of thalidomide on the pathogenesis of human immunodeficiency virus type 1 and *Mycobacterium tuberculosis* infection. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996; 11:247-257.
28. Edwards D, Kirkpatrick CH. The immunology of mycobacterial diseases. *Am Rev Respir Dis.* 1986; 134:1062-1071.
29. Singh MM, Kumar P, Malaviya AN, Kumar R. Levamisole as an adjunct in the treatment of pulmonary tuberculosis. *Am Rev Respir Dis.* 1981; 123:277-279.
30. Patel N, Deshpande MM, Shah M. Effect of an immunomodulator containing *Mycobacterium w* on sputum conversion in pulmonary tuberculosis. *J Indian Med Assoc.* 2002; 100:191-193.
31. Patel N, Tripathi SB. Improved cure rates in pulmonary tuberculosis category II (re-treatment) with *mycobacterium w*. *J Indian Med Assoc.* 2003; 101:680-682.
32. Pandie S, Engel ME, Kerbelker ZS, Mayosi BM. *Mycobacterium w* immunotherapy for treating pulmonary tuberculosis – a systematic review. *Curr Pharm Des.* 2014; 20:6207-6214.
33. Carroll MW, Jeon D, Mountz JM, *et al.* Efficacy and safety of metronidazole for pulmonary multi-drug resistant tuberculosis. *Antimicrob Agents Chemother.* 2013; 57:3903-3909.
34. Smith I. Stop TB: Is dots the answer? *Ind J Tub.* 1999; 46:81-89.
35. Goble M, Iseman MD, Madsen LA, Waite I, Ackerson L, Horsburgh CR. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and streptomycin. *N Engl J Med.* 1993; 328:527-532.
36. Schaaf HS, Botha P, Beyers N, Gie RP, Vermeulen HA, Groenewald P, Coetzee GJ, Donald PR. The 5-year outcome of multi drug resistant tuberculosis patients in the Cape Province of South Africa. *Trop Med Int Health.* 1996; 1:718-722.
37. Park SK, Kim CT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary tuberculosis resistant to isoniazid and rifampicin. *Int J Tuber Lung Dis.* 1998; 2:877-884.
38. Khanna BK. Treatment of long-term tuberculosis treatment failures. *Ind J Tub.* 1985; 32:171-175.
39. Purohit SD, Gupta M, Agnihotri SP, Madan A, Gupta PR. Management of chemotherapy failures. *Ind J Tub.* 1991; 37:383.
40. Singla R, Myneedu VP, Jaiswal A, Puri MM, Jain RC. Ethionamide, cycloserine, isoniazid, sodium PAS and kanamycin in re-treatment of drug failure pulmonary tuberculosis patients. *Ind J Tub.* 1995; 42:23-26.
41. Prasad R. Long term treatment outcome in multi-drug resistant tuberculosis (MDR-TB). *Chest.* 2004; 126:836A.
42. Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, Gandhi NR, Galvaniet AP. Treatment outcomes among patients with multidrug-resistant tuberculosis: Systematic review and meta-analysis. *Lancet Infect Dis.* 2009; 9:153-161.
43. Prasad R, Singh A, Srivastava R, Kushwaha RS, Garg

- R, Verma S K, Hosmane GB, Jain A, Ranganath TG. Treatment outcomes of multi-drug resistant tuberculosis patients in modified DOTS-PLUS: A new strategy. *Eur Respir J*. 2012; 40:3321A.
44. Prasad R, Srivastava DK. Multi-drug and extensively drug-resistant TB (M/XDR-TB) management: Current issues. *Clinical Epidemiology and Global Health*. 2013; 1:124-128.
  45. Chan ED, Laurel V, Strand MJ, Chan JF, Huynh ML, Goble M, Iseman MD. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med*. 2004; 169:1103-1109.
  46. Jiang RH, Xu HB, Li L. Comparative roles of moxifloxacin and levofloxacin in the treatment of pulmonary multidrug-resistant tuberculosis: A retrospective study. *Int J Antimicrob Agents*. 2013; 42:36-41.
  47. Chiang CY, Enarson DA, Yu MC, Bai KJ, Huang RM, Hsu CJ, Suo J, Lin TP. Outcome of pulmonary multidrug-resistant tuberculosis: A 6-yr follow-up study. *Eur Respir J*. 2006; 28:980-985.
  48. Migliori GB, Lange C, Girardi E, Centis R, Besozzi G, Kliiman K, Codecasa LR, Spanevello A, Cirillo DM; SMIRA/TBNET Study Group. Fluoroquinolones: Are they essential to treat multidrug-resistant tuberculosis? *Eur Respir J*. 2008; 31:904-905.
  49. Ahuja SD, Ashkin D, Avendano M, *et al*. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: An individual patient data meta-analysis of 9,153 patients. *PLoS Med*. 2012; 9:e1001300.
  50. Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, Lee J. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest*. 2000; 117:744-751.
  51. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH, Holm Delgado MG, Keshavjee S, DeRiemer K, Centis R, D'Ambrosio L, Lange C, Bauer M, Menzies D. Resistance to fluoroquinolones and second-line injectable drugs: Impact on multidrug-resistant TB outcomes. *Eur Respir J*. 2013; 42:156-168.
  52. Jeon CY, Hwang SH, Min JH, *et al*. Extensively drug-resistant tuberculosis in South Korea: Risk factors and treatment outcomes among patients at a tertiary referral hospital. *Clin Infect Dis*. 2008; 46:42-49.
  53. Migliori GB, Lange C, Centis R, Sotgiu G, Mütterlein R, Hoffmann H, Kliiman K, De Iaco G, Lauria FN, Richardson MD, Spanevello A, Cirillo DM; TBNET Study Group. Resistance to second-line injectables and treatment outcomes in multidrug-resistant and extensively drug-resistant tuberculosis cases. *Eur Respir J*. 2008; 31:1155-1159.
  54. Fischl MA, Daikos GL, Uttamchandani RB, Poblete RB, Moreno JN, Reyes RR, Boota AM, Thompson LM, Cleary TJ, Oldham SA, Saldana MJ, Lai S. Clinical presentation and outcome of patients with HIV infection and tuberculosis caused by multi-drug resistant bacilli. *Ann Intern Med*. 1992; 117:184-190.
  55. Prasad R. Multidrug and extensively drug-resistant tuberculosis management: Evidences and controversies. *Lung India*. 2012; 29:154-159.

(Received March 12, 2015; Revised April 1, 2015; Re-revised May 23, 2015; Accepted June 25, 2015)