# RETROSPECTIVE AUDIT OF PATIENTS TREATED FOR MDR-TB IN RE-TREATMENT CATEGORY

**Waseem Saeed, Arshad Naseem, Jamal Ahmed**
**Department of Pulmonology, Military Hospital Rawalpindi, Rawalpindi, Pakistan**

**Objective:** To determine the efficacy of our modified anti-tuberculosis regimen in adult patients with multi-drug-resistant tuberculosis (MDR-TB) in the re-treatment category. **Methods:** Retrospective chart review of 176 patients in re-treatment category with diagnosis of MDR-TB from 1st Jan 1993 to 31st Dec 2002 managed at the Department of Pulmonology Military Hospital Rawalpindi, Pakistan. All the patients were given four standard first line anti-TB drugs along with any two second line drugs out of Ofloxacin/Ciprofloxacin/Levofloxacin, Amikacin, or Clarithromycin and treatment was modified after availability of drug susceptibility testing (DST). **Results:** Seventy-two percent of the patients were young men with mean age of 32.28±8.7 yrs, 53.4% had moderately advanced while nearly 30% had extensive disease. One-third cases had contact with a patient of pulmonary tuberculosis out of which one fifth had contact with a MDR-TB patient. Mean duration of diagnosis of tuberculosis before therapy was 41.11±14.32 months and 70% of the cases had received at least 2 prior anti-TB regimens. They had received a median of four anti-TB drugs in past and were infected with organisms that were resistant to a median of 3 first line anti-TB drugs. Resistance to Ethambutol and PZA was about 18% and 11% respectively. A median of six anti-TB drugs was used while mean duration of therapy was 22.17±2.17 months. Bacteriological cure was achieved in about 90% cases while radiological response was documented in nearly 78%. **Conclusion:** Modified initial management strategy followed by DST guided therapy has yielded excellent results and needs to be assessed in further trials for wider application.
**Keywords:** Modified regimen, Re-treatment TB, Multi-drug-resistant tuberculosis, MDR-TB, Tuberculosis

## INTRODUCTION

Worldwide, *Mycobacterium tuberculosis* remains the leading infective cause of mortality and morbidity.[1] It is estimated that nearly $9\times10^6$ new cases of active tuberculosis (TB) occur each year.[2] Presently, drug-resistant *Mycobacterium tuberculosis* is an important global threat, with a median of 9.9% of *M tuberculosis* strains now resistant to at least one drug in 35 countries or regions.[3] Multi-drug Resistant Tuberculosis (MDR-TB) indicates the presence of *M. tuberculosis* resistant to, at least, Isoniazid and Rifampicin[4], with or without resistance to other anti-TB drugs. MDR-TB is known to be a man-made disease and results from inappropriate anti-tuberculosis regimens, inadequate/ poor drug supplies, poor case handling and follow up; and poor patient compliance.[5]

Lot of controversy exists regarding the best policy to handle patients with resistant tuberculosis. In many countries, the widespread use of the standard short-course (SCC) regimen in all cases of TB has led to an increasing incidence of MDR-TB.[6,7] While in many studies, standard short courses as well as WHO recommended re-treatment regimens have been assessed to be inadequate treatment options in communities with high prevalence of drug resistant tuberculosis.[8,9] Incidence of MDR-TB is escalating in Pakistan and ranges 24–28% in different regions of Pakistan.[10,11] Recently, it is recommended that for patients who are at higher risk historically (prior therapy) or epidemiologically, and who have serious forms of tuberculosis, an empirically extended initial regimen may be appropriate.[12]

Keeping in mind the rising incidence of MDR-TB in Pakistan and delay in availability of AFB culture and drug sensitivity reports in our set up, we started a novel policy to start six anti-tuberculosis drugs at the time of initial diagnosis in all TB patients in re-treatment category. Then, we modified the regimen according to DST results in individual cases. We report our experience in treating patients with multi-drug-resistant tuberculosis in re-treatment category with our modified anti-TB regimen.

## MATERIAL AND METHODS

A detailed retrospective chart review of 216 patients was carried out in re-treatment category with diagnosis of MDR-TB from 1st Jan 1993 to 31st Dec 2002, managed at the Department of Pulmonology Military Hospital (MH), Rawalpindi, Pakistan. Majority of TB cases are referred to MH from other in-city medical set-ups and from other parts of the country. Therefore, a large number of our TB cases belong to re-treatment group, disseminated tuberculosis, TB cases with failure of the standard short course chemotherapy, etc. Consequently, the chance of resistant tuberculosis in our cohort of patients was assessed to be quite high.

Only adults (age 15–54 yrs) with confirmed diagnosis of MDR-TB in re-treatment category, i.e., AFB culture positive cases with drug susceptibility test results consistent with resistance to Rifampicin and INH with or without resistance to other drugs were included

in the study. Re-treatment cases included those with relapse (treated with a complete course of anti-TB drugs in past and declared cured); treatment failures (new cases who remain or became sputum smear positive 5 moths or more after commencing standard 4 anti-TB treatment); and those who defaulted for 2 or more months (after at least receiving 3 first line anti-TB drugs for more than 4 weeks). Patients with incomplete follow up in records, resistant tuberculosis other than MDR-TB like monoresistance, MDR-TB cases with chronic renal failure requiring renal replacement therapy, decompensated chronic liver disease, insulin dependant diabetics, and advanced COPD requiring oxygen therapy were excluded from the study. MDR-TB among chronic cases (defined as smear positive at completion of a supervised full course of WHO re-treatment regimen) and patients with primary MDR-TB were also excluded from the study.

A total of 176 cases fulfilling the inclusion criteria have been included in this study. All patients in the re-treatment category were started on 6 best guess anti-tuberculosis drugs from the outset; it included the 4 standard first line anti-tuberculosis drugs and 2 second line drugs. In initial period of study (first 4–5 years), most cases had been given clarithromycin and ofloxacin as initial second line drugs, while in later part of the study (last 4–5 years), any 2 of injectable Amikacin, Ciprofloxacin, and Levofloxacin, have been used as preferential initial second line drugs. The treatment was later on modified keeping in mind prior treatment history, patient compliance and DST results. The average time period of initial best guess therapy was 10–12 weeks. Rifampicin and INH were stopped in all cases after the availability of DST results. All 176 patients were given at least 5 drugs after DST results in nine different individualized regimens as per resistance patterns. All the second line drugs not used in past or used for less than two months by the patient or for whom DST was not available had been considered as 'active'. An aminoglycoside, quinolone and macrolide had always been included in the regimen if possible, most preferably: Amikacin, Ofloxacin/Ciprofloxacin/ Levofloxacin or Clarithromycin. Review of regimen was subsequently done on three monthly basis or earlier due to side effects.

In majority of cases 5 drugs have been given for initial 3–6 months in post DST period and later on 3–4 drugs were continued for next 3–6 months. No less then 3 drugs were given throughout the course of regimen. All drugs were used simultaneously in normal adult doses on daily basis. Dosing intervals were adjusted according to individual tolerance and full doses were built up in 10–15 days in majority of our cases. All patients had been prescribed 50 mg of Pyridoxine daily. Treatment was given primarily on outpatient basis while most of the patients had one follow up visit in every 15 days for initial 3 months and then on monthly basis. The compliance of treatment was ensured by recruitment of 1st degree relatives into the management strategy.

The diagnosis was made on culture and sensitivity with Lowenstein Jenssen medium and in later part of study on standard BACTEC 460 radiometric culture method. The drugs sensitivities for all first line anti-TB drugs were checked while DST for second line anti TB was not checked. DST for PZA was started after availability of BACTEC. Sputum for AFB microscopy, AFB culture and sensitivity was done at base line, then after 3 and 5 months. AFB smear and culture was also repeated at 3 months after completion of anti-TB therapy. Mantoux test was done in all cases. Chest radiography, Blood complete picture, ESR, serum urea creatinine and electrolytes, serum uric acid levels, and hepatic functions were done at baseline. During treatment period renal as well as hepatic functions along with chest radiography were done regularly. The patients were classified as per radiological categories suggested by National Tuberculosis Association of USA (Table-1). A proforma was devised to record the data that included name, age, sex, weight, presenting complaints, relevant history especially duration of tuberculous disease (diagnosed), past anti-TB treatment detail like number of drugs used and their duration, radiological category of the patient, resistance pattern, treatment plan, side effects and end of treatment response.

**Table-1: Radiological classification of disease extent (National Tuberculosis Association of the USA)**

| **Minimal lesions** |
|---|
| Includes those that are of slight to moderate density but which do not contain demonstrable cavitation. They may involve small part of one or both lungs, but the total extent, regardless of distribution should not exceed the volume of lung on one side that occupies the space above the second chondrosternal junction and the spine of fourth or the body of the fifth thoracic vertebra. |
| **Moderately advanced lesions** |
| May be present in one or both lungs, but the total extent should not exceed the following limits: disseminated lesions of slight to moderate density that may extend throughout the volume of one lung or the equivalent in both lungs; dense and confluent lesions limited in extent to one-third the volume of lung; total diameter of cavitation if present must be less than 4 cm. |
| **Far advanced/Extensive lesions** |
| More extensive than moderately advanced. |

The outcome response was categorised as bacteriological cure, radiological response and failure of treatment. Patients were declared bacteriologically cured if they were sputum AFB negative at three months of individualized regimen after DST and remained so up to three months after completion of full therapy. Radiological response was defined as regression of active lesions/cavities

to minimal (>90% regression) without persistent soft opacities/nodules and/or significant (>1 cm) mediastinal or hilar lymphadenopathy/associated pleural effusion by 12 months of total treatment. Fibrotic bands, scarring and calcification were considered as evidence of healed tuberculosis and their presence was not considered as a failure of radiological response. Treatment was continued for 12–18 months after seroconversion depending upon clinical and radiological parameters. In our study, failure of treatment was defined as patients excreting tuberculous bacilli after 3 months of individualized re-treatment regimen (which was started after drug sensitivity results) as assessed by sputum smear positivity for AFB.

The rationale for our modified regimen is two-fold. First, as the major bulk of MDR-TB cases belong to re-treatment TB patient population, our strategy ensures the use of at least three active anti-TB drugs throughout the course of treatment. For example, use of WHO recommended re-treatment regimen, which includes 4 already used drugs from the previous regimen, may result in the administration of only 1–2 active drugs in a patient who is likely to harbour multi-drug-resistant strains. Secondly, an aggressive approach from the outset might prevent evolution of drug sensitive TB into drug resistant TB during the initial 2–3 months time till DST results are available. As in each patient with tuberculosis, there is a mixed population of organisms with naturally occurring resistance to various drugs. Resistant organisms will be selected if only 1–2 active drugs are used in the treatment, because approximately 1 in $10^6$–$10^8$ organisms exhibit intrinsic resistance to any given drug. The chance that an organism in a population is resistant to two drugs is roughly $10^{14}$, making resistance much less likely to emerge with combination therapy.

## RESULTS

Majority of our cases (127, 72.15%) were males while female were 27.85% (49). Most of our patients were young with a mean age of 31.23±4.3 years. As per radiological categorisation, 95 (53.97%) of our cases had moderately advanced disease, 56 (30.68%) had extensive disease and 27 (15.34%) patients had minimal disease. Fifty-six (31.81%) cases gave history of contact with a tuberculous patient out of which 33 (18.96%) cases had contact with MDR-TB patients (Table-1 and 2). Cough (170, 96.59%) and expectoration (162, 92.04%) were the most common symptoms while 69.88% (123) cases also had history of accompanying haemoptysis. Ninety-seven (45.11%) had history of fever and 58.52% (103) cases also complained of dyspnoea. Night sweats were documented in 87 (47.15%) patients. In treatment history, the mean duration of diagnosis of tuberculosis before our regimen was 41.11±14.32 months (range 12–60). About 70% (123) of our cases had received at least 2 prior anti-TB regimens and had received a median of 4 anti-TB drugs (range 3–5) and were infected with organisms that were resistant to a median of 3 anti-TB drugs (range 2–5).

**Table-2: Frequency of radiological findings (n=176)**

| X-Ray findings | No. | % |
|---|---|---|
| Nodulostriate lesions | 121 | 68.75 |
| Cavitation | 77 | 43.75 |
| Soft Opacity | 131 | 74.43 |

As regards the drug resistance patterns (Table-3), 31 (17.61%) of our cases were resistant to Ethambutol while 19 (10.79%) cases were resistant to Pyrazinamide. Twenty-six (14.77%) cases were resistant to Rifampicin, Isoniazid, and Ethambutol. Resistance to all 4 first line anti-TB drugs was seen in 3.97% (6) cases. PZA was used in 82.95% (146) cases and Ethambutol was given to 75.56% (133) cases. Eight second line drugs have been used in our study (Table-4). An aminoglycoside, quinolone and macrolide have always been included in the regimen if possible.

**Table-3: Drug resistance and frequency of use among most commonly used anti TB drugs**

| Drugs Used after DST | Incidence of resistance | Frequency of use |
|---|---|---|
| Pyrazinamide | 10.79 % (19) | 82.95 % (146) |
| Ethambutol | 17.61 % (31) | 75.56 % (133) |
| Amikacin | | 68.75 % (121) |
| Quinolones | | 96.02 % (169) |
| Clarithromycin | | 83.52 % (147) |
| Streptomycin | | 18.18% (32). |

**Table-4: Drugs used for MDR-TB patients**

| Conventional anti-tuberculosis drugs used | Second Line drugs used |
|---|---|
| Rifampicin | Amikacin |
| Isoniazid | Ofloxacin/Ciprofloxacin/Levofloxacin |
| Pyrazinamide | Clarithromycin |
| Ethambutol | Ethionamide |
| Streptomycin | Cycloserine |

Amikacin was given to 121 (68.75%) patients and streptomycin to 32 (18.18%). Ofloxacin was given to 85 (48.29%) cases, Levofloxacin to 52 (29.54%) while Ciprofloxacin to 39 (22.15%) patients. A total of 9 different post DST regimens had been used. The 4 most common combinations have been: Amikacin, Ofloxacin, Clarithromycin, PZA and Ethambutol, a regimen given to 51 (28.97%) patients. A combination of Amikacin, Levofloxacin, Ethambutol, PZA and Clarithromycin was used in 39 (22.15%) cases. Amikacin, Ciprofloxacin, Clarithromycin, PZA and Ethambutol was given to 31 (17.61%) patients; and Streptomycin, Ofloxacin, Ethionamide, Clarithromycin,

and PZA was used in 23 (13.06%) cases. Eleven (6.25%) cases underwent surgical resection. A median of 6 anti-TB drugs were used while mean duration of therapy was 22.17±2.17 months.

Most of our patients tolerated the anti-TB drugs well. Only 2.84% (5) developed features of ototoxicity, hyperuricemia was seen in 6.25% (11) cases and 9.65% (17) cases had arthralgia (requiring analgesics). Thirty-one (17.61%) patients developed drug induced hepatitis, but only 11 (6.25%) cases required modified drug regimens, and 157 (90.22%) patients had bacteriological cure while radiological response was achieved in about 78% (137) cases.

## DISCUSSION

As major burden of MDR-TB stems from re-treatment TB cases, existence of diverse management entities like relapse, failure, treatment default denies the evolution of an effective standardized chemotherapeutic regimen. The results of our novel strategy to institute 6 drugs from the outset in re-treatment of TB patients and later modifying the regimen based upon DST have been very encouraging with an overall success rate of more than 90%. The success rate in MDR-TB cases in past have been low. A retrospective analysis of 171 MDR-TB patients (from 1973–1983) at Denever in 1993[13] reported an overall response rate of only 56%, while a decade later, the same institute has documented an overall initial success rate of 75% in 205 similar cases over next 14 yrs[14]. A recent community based study of MDR-TB cases in Lima has reported a cure rate of 83%[15], while successful outcomes in middle-income countries have ranged from 50% in Taiwan[16] to more than 80% in Korea[17] and Turkey[18].

Our study has many limitations as regards the analysis of better outcomes. First, as most of our patients were not well educated and well versed with anti-TB drugs, their sub-categorization into re-treatment groups was not possible which may had led to a large proportion of relapse and partial default cases in our study. As these sub-groups of re-treatment category are known to respond better; this may have translated into good outcomes in our study. Secondly, the exclusion of 40 patients who did not have complete follow up; may had not tolerated the regimen or have not responded to our regimen yielded an overall better outcome in our study. Thirdly, an underestimation of failure rates and overestimation of cure rates is possible, as smear microscopic positivity has been used as the standard criterion to assess the outcome. Ideally, assessment of treatment outcomes should be based on sputum culture to increase the sensitivity. Fourthly, some baseline demographic and clinical characteristics of our patients favoured better outcomes. Like, majority of our cases were relatively young with few co morbid conditions (as extreme old age, CRF, COPD, and insulin dependant diabetics were excluded) and Chronic TB cases with MDR were also not studied. The time period of diagnosed disease before our modified regimen was started was 41 months, which although comparable to 48 months in a study of MDR-TB cases[15], it was reported to be about 6 years in another study[18]. Similarly, prior use of a median of 5 anti-TB drugs and a median of 4 drugs to which isolates were found to be resistant translates into a possibility of a better outcome then prior use of a median of 7 anti-TB drugs and mycobacterium strains that were resistant to a median of 6 drugs in other studies.[15] Fifthly, use of Amikacin and Levofloxacin in the later part of the study from the outset, has probably resulted in use of at least 3 bactericidal drugs, to which isolate is likely to be sensitive, and has thus translated into an overall better outcomes. Finally, we have used 5–6 drugs for 6–9 months in initial period and then have given a minimum of at least 3 drugs till completion of regimen, so more number of drugs had been used in our study. Overall more number of drugs has been used with rationale to utilise drugs effective against different phases of mycobacterium. Other studies have also linked better outcomes with high number of drugs used.[13,17]

About 11% and 18% of our isolates were resistant to PZA and Ethambutol, which is quite low as compared to noted resistance rates of about 60% and 70% respectively[14]; however, other local studies have noted similar resistance rates[10]. DST to first line drugs was performed for all patients as per standard protocols, while DST for second line drugs was not done as DST for second line drugs is not very widely recommended.[19] Even for first line drugs, DST has variable reliability: adequate for Rifampicin and INH but much less so for Streptomycin and Ethambutol.[20] As all patients in our study had history of prior anti-tuberculosis treatment or treatment failure; the incidence of MDR-TB is estimated to be quite high in such cases .[21] Although use of 6 drugs from outset is not widely practiced, has its advocates of empirical treatments with up to 7 drugs until DST results are available, with further adaptation of the regimen subsequent to these results.[22] In initial period we have mostly used a quinolone and macrolide combination, primarily due to ease of their use. The further rationale for use of Clarithromycin was its reported ability to restore the anti-mycobacterial activity of Isoniazid, Rifampicin and Ethambutol against MDR strains.[23] Frequency of adverse effects was remarkably low as compared to other studies, which may be due to demographic characteristics of our patients or 40 patients who were unable to follow up may have done so due to adverse effects.

## CONCLUSION

Management of multi-drug-resistant tuberculosis especially in re-treatment group is a multifaceted

dilemma. It not only represents the patient's last hope of cure but also challenges the expertise of treating health professional. We have devised a standardized treatment protocol for initial management period (before DST) in re-treatment group of tuberculosis patients with excellent results. This regimen is required to be assessed in randomized controlled trial for wider application.

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## Address for Correspondence:

**Major Dr. Arshad Naseem**, Consultant Physician and Registrar in Pulmonology, Military Hospital, Rawalpindi, Pakistan.