# Original Research Article

# Outcome Analysis of Multi-Drug Resistant Tuberculosis Cases Treated by Individualized Regimens

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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. This study was conducted with objective to assess the clinical, radiological, conversion rate as well as the association with each other in Multi-Drug Resistant Tuberculosis (MDR-TB). This hospital based analytical type of observational study was conducted in the department of Respiratory Medicine, JLN Medical College Ajmer, on the 244 Multidrug Resistant Pulmonary Tuberculosis patients at PMDT site were included who were consecutively enrolled for category IV regimen during period, 1$^{st}$ January to 30$^{th}$ September 2012 . They (N=103) were followed up for 24 months clinically, and bacteriological by sputum smear, culture and Drug Susceptibility Testing (DST) at regular intervals. The data were analyzed by chi square test. Out of 244 patients, 74.6% patients were in the reproductive and economically productive age group of 16 - 45 years. According to radiological outcome, 66.9% evidence of radiological improvement, whereas 24 (23.3%) patients had radiological deterioration, while in 10 (9.7%) patients radiological picture was stationary. statistically highly significant association between clinical symptoms, radiological and conversion among follow up patients was observed(p value < 0.001). Sputum smear and culture conversion are very well associated with clinical and radiological improvement. Category IV regimen of DOTS-Plus under RNTCP program in MDR-TB patients produced significant improvement in body weight, bacteriological, and radiological examination.

**Keywords:** clinical symptoms, radiological, conversion, MDR patients.

## INTRODUCTION

Drug resistance is a threat to TB control programs worldwide. Patients infected with multiple-drug resistant strains are less likely to become cured [1], particularly if they are infected by HIV or suffer from another immune disease.

The prevalence of MDR-TB mirrors the functional state and efficacy of tuberculosis control programmes and realistic attitude of the community towards implementation of such programmes in the country [1].

Globally, only 48% of MDR-TB cases detected in 2011 were successfully treated. 16% died, 24% did not have their treatment documented or treatment interrupted and 12% were not cured despite proper treatment[2]. The prevalence of XDR among MDR-TB patients was estimated 3.2% [3]. MDR-TB is a great challenge to clinicians for both diagnosis and Management. It is among the most worrisome element of the Pandemics of antibiotic resistance because MDR-TB patients that fail treatment have a deadly outcome [4, 5].

Diagnosis of MDR-TB is purely laboratory based on culture and Drug sensitivity of the infecting

bacillary strains. Currently only a little numbers of the existing MDR-TB patients are being diagnosed due to severe laboratory constraints all over the world, especially in low income countries. RNTCP is now implementing the programmatic management of multidrug-resistant TB (MDR-TB - defined as resistance to at least isoniazid and rifampicin) cases in a phased manner and a standardized category-IV treatment regimen (STR) have been approved by the RNTCP National DOTS-Plus Committee [6].

We have planned to conduct this study, with objective to study effect of clinical parameters associate bacteriological outcome, culture conversion (Patients was considered sputum smear/ culture converted after having two consecutive negative results taken at least one month apart), at the end of IP with ultimate outcome of category IV regimen in MDR TB patients.

## METHODOLOGY

This hospital based analytical type of observational study was conducted in the department of Respiratory Medicine, JLN Medical College Ajmer, on the 244 Multidrug Resistant Pulmonary Tuberculosis patients at PMDT site patients with documented evidence of drug resistance to Rifampicin alone or along with Isoniazid from an Intermediate Reference Laboratory were included who were consecutively enrolled for category IV regimen during period, 1$^{st}$ January to 30$^{th}$ September 2012. These patients were followed for the present study at the completion of 24 months treatment of category IV. Informed consent of the patient was taken for the study. Approval from institutional ethical committee was obtained.

Following methods were used for Mycobacterial Culture & Sensitivity-
- Conventional solid egg-based Lowenstein-Jensen (LJ) media
- Molecular Line Probe Assay

In Ajmer, at State Tuberculosis Training and Demonstration Centre, Mycobacterial Culture and Drug sensitivity is done using Molecular Line Probe Assay. The negative samples from MDR suspect patients on LPA were subjected to culture on conventional solid egg-based Lowenstein-Jensen (LJ) media and DST was performed for Streptomycin (S), Isoniazid (H), Rifampicin (R), Ethambutol (E) and Pyrazinamide (Z).

Patients who were found to have MDR TB were hospitalized at PMDT site, department of respiratory medicine, J.L.N medical college Ajmer for pre treatment evaluation and initiation of category IV regimen, for a minimum duration of seven days Outcome of previously treated patients under RNTCP was also recorded as per treatment/regimen.

After a detailed clinical history each patient underwent a complete clinical workup including physical examination and a battery of tests as per proforma, comprising Skiagram chest Postero-anterior view, Complete blood count, Blood sugar Liver function tests (Transaminases, bilirubin) Renal Function Tests ( Serum Urea, Serum Creatinine)Thyroid profile (TSH)Serum electrolytes Serum uric a Complete urine examination HIV serology by ELISA.

Urine pregnancy test in female patients, other investigation as and when required e.g. CECT chest, Abdomen and Ultrasonography, Category IV regimen was started after pre-treatment evaluation for each patient, as per their weight bands according to RNTCP PMDT guidelines.

Health education and counseling was given to all, follow up to evaluate outcome was done as per following protocol:

Baseline datas were collected from records available at PMDT site.

According to protocol all patients should undergo a monthly follow up till 3 months, thereafter every 3 month till treatment completion for clinical examination and for any adverse drug reaction. All information to accomplish objective was collected by personal interview of study subjects at PMDT site using pre-designed proforma. Subjective perception of improvement and no improvement was criteria for clinical outcome in the form of improvement and no improvement (deterioration).

Follow up bacteriological evaluation was done as per RNTCP schedule.

Schedule for sputum smear microscopy, culture and sensitivity follow up examination

According to RNTCP guidelines [7] patients were considered Smear converted after having two consecutive negative smears, taken at least one month apart. Similarly patients were considered Culture Converted after having two consecutive negative cultures taken at least one month apart.

Time to culture conversion is calculated as the interval between the date of MDR-TB treatment initiation and the date of the first of these two negative consecutive cultures.

## Statistical Analysis

Microsoft word and Excel have been used to generate graphs, tables etc.To find out significance of difference in proportions in various groups Chi square test was applied and for the significance cut off P <0.05.

## RESULT

Out of 244 patients, 74.6% patients were in the reproductive and economically productive age group of 16 - 45 years. 78.7% from rural population, 79.92% of cases were males with male: female ratio of 4:1. Most of the patients (92.2%) were married(29.9%) patients were educated only up to primary school. 76.2% patients belong to upper lower class, (10.7%) patients belong to lower class, while patients belonging to

Lower middle and upper middle socio economic classes were 25 (10.2%) and 7 (2.9%) respectively. 145 (59.43%) patients had history of addiction to smoking, alcohol and others, whereas 99 (40.6%) patients had no history of addiction. Majority of the patients, 218 (89.3%) were underweight, while 26 (10.7%) patients had normal BMI. None of patient was overweight.

**Table-1: Demographic Characteristics of the Study population**

| Total No Of cases | No of cases=244 | Percentages (%) |
|---|---|---|
| **Age Group** | | |
| <15 | 3 | 1.23 |
| 16-25 | 49 | 20.08 |
| 26 -35 | 71 | 29.10 |
| 36 -45 | 62 | 25.41 |
| 46-55 | 36 | 14.75 |
| 56-65 | 20 | 8.20 |
| 66-75 | 3 | 1.23 |
| **Gender** | 244 | 100.00 |
| Male | 195 | 79.92 |
| Female | 49 | 20.08 |
| **Marital Status** | | 0.00 |
| Unmarried | 19 | 7.79 |
| Married | 225 | 92.21 |
| **Location** | | 0.00 |
| Rural | 192 | 78.69 |
| Urban | 52 | 21.31 |
| **SES** | | 0.00 |
| Lower | 26 | 10.66 |
| Upper lower | 186 | 76.23 |
| Lower Middle | 25 | 10.25 |
| Upper Middle | 7 | 2.87 |
| **Education** | | 0.00 |
| Illiterate | 138 | 56.56 |
| Primary | 73 | 29.92 |
| Middle | 15 | 6.15 |
| High | 7 | 2.87 |
| Graduate | 7 | 2.87 |
| Post Graduate | 4 | 1.64 |

According to criteria ,62 (25.4%) patients belong to MDR Suspect Criteria A, 176 (72.1%) patients belong to MDR Suspect Criteria B, and 6 (2.5%) patients belong to MDR Suspect Criteria C. Out of 241, 160 (65.6%) patients were HR resistant and 81 (33.2%) were Rifampicin mono resistant. DST results on Conventional LJ media were available only for 3 patients and showed HRE resistance in 1 patient and SHR resistance in 2 patients. . Out of 244 patients, 60 (24.6%) patients had documented h/o contact with TB patients, of which 53 (88.3%) patients had h/o contact with PTB patients, whereas 7 (11.7%) patients had h/o contact with MDR TB patients.(Table No1 )Treatment completion of follow up patients Out of 103 patients who came for follow up 88 (85.4%) patients had weight

gain, 13 (12.6%) patients had weight loss, and in 2 (1.9%) patients, weight remained stationary.

According to microbiological conversion, (60.2%) patients shows sputum conversion while (59.0%) patients shows culture conversion, 103 patients came for follow up, in which 81 (78.6%) patients reported clinical improvement, whereas 22 (21.4%) patients reported clinical deterioration.

According to radiological outcome, 66.9% evidence of radiological improvement, whereas 24 (23.3%) patients had radiological deterioration, while in 10 (9.7%) patients radiological picture was stationary. (Table 2)

Out of 244 patients, enrolled in our study, only 103 patients had reported for follow up and among them 101 (98.0%) patients reported one or more adverse drug reactions to these drugs.

In the economically productive age group of 16 - 45 years, Culture conversion was observed in 57.14% (n=104), whereas in follow up patients, 75.3% (n=61) clinical improvement and 62.9% (n=51) radiological regression was seen. In age group >45 years, 62.7 % culture conversion, 89.4 % clinical improvement, and 78.9 % radiological regression was seen.

In our study out of 103 patients, 81 (78.6%) patients reported clinical improvement and 68 (83.9%) patients of these also had radiological resolution, while 22 (21.3%) patients reported clinical deterioration out of which 20 (90.9%) patients had radiological progression. Thus, statistically highly significant (p value < 0.001) correlation between clinical symptoms and radiological response among follow up patients was observed.

Out of 103 patients, 80 (77.6%) patients were culture converted and 68 (85.0%) patients of this also showed radiological resolution, while 23 (28.7%) patients did not have culture conversion, out of which 19 (82.6%) patients also had shown radiological progression. Thus statistically highly significant (p value < 0.001) association between bacteriological and radiological response among follow up patients was observed.

Out of 103 patients, 81 (78.6%) patients had clinical improvement and 78 (96.3%) patients of these also were culture converted, while 22 (21.3%) patients reported clinical deterioration, out of which 20 (90.9%) patients had no culture conversion. Thus, statistically highly significant (p value < 0.001) association between clinical symptoms and culture conversion among follow up patients was observed. (Table 3)

**Table-2: Outcome analysis of the MDR Cases**

| .N=103 | No of patients | Percentage |
|---|---|---|
| weight gain | 88 | 85.44 |
| weight loss | 13 | 12.62 |
| Stationary | 2 | 1.94 |
| **Clinical outcome** | | |
| Improvement | 81 | 78.64 |
| Deterioration | 22 | 21.36 |
| **N=244** | | |
| **Sputum conversion** | 147 | 60.25 |
| **Cultural conversion** | 144 | 59.02 |
| **Adverse Drug Reactions** | | |
| **Present** | 101 | 41.39 |

**Table- 3: Association of Clinical Symptoms and Culture Conversion with Radiological Response**

| | Radi0logical response | | | |
|---|---|---|---|---|
| **Clinical Symptoms** | Progression | Resolution | Stationary | Total |
| Improvement | 4 | 68 | 9 | 81 |
| Deterioration | 20 | 1 | 1 | 22 |
| Total | 24 | 69 | 10 | 103 |
| Chi-square = 71.930 with 2 degrees of freedom; P < 0.001S | | | | |
| | | | | |
| **Culture Conversion** | | | | |
| converted | 5 | 68 | 7 | 80 |
| **not converted** | 19 | 1 | 3 | 23 |
| | 24 | 69 | 10 | 103 |
| Chi-square = 62.387 with 2 degrees of freedom; P < 0.001S | | | | |

**Table-4: Association of Clinical Symptoms with Culture Conversion**

| Clinical Symptoms | Culture Conversion | | Total |
|---|---|---|---|
| | converted | not converted | |
| Improvement | 78 | 3 | 81 |
| Deterioration | 2 | 20 | 22 |
| Total | 80 | 23 | 103 |
| Chi-square = 70.915 with 1 degree of freedom; P <0.001S | | | |

## DISCUSSION

In our study younger population with underweight patients are more affected in contrast to other studies [8, 9], while other demographic profile and clinical characteristics were similar to other studies, with male patients' predominance. Our study involved outcome analysis of MDR-TB patients managed with standardized a treatment regimen of 24 months under programmatic conditions of RNTCP.

Treatment completion of follow up patients Out of 103 patients who came for follow up 88 (85.4%) patients had weight gain, 13 (12.6%) patients had weight loss, and in 2 (1.9%) patients, weight remained stationary. Kalpeshjain [10] following drug treatment, a significant increase in mean body weight was observed at every 3 months till the end of study. A significant increase in body weight ($P$ <0.0001) was observed at the end of the 24 months of drug treatment.

Out of 244 patients, enrolled in our study, only 103 patients had reported for follow up and among them 101 (98.0%) patients reported one or more adverse drug reactions to these drugs. Kalpeshjain (2014) [10], thirty five (26%) patients developed ADRs that required withdrawal of causal drug.

Sputum culture conversion is the first indicator of the response to treatment and early conversion is definitely desirable.

In this study 144 (59.02%) patients were converted to negative culture during follow up. In most of the patients (n=138, 56.55%) culture conversion started at the end of 3 month. However among 103 follow up patients culture conversion was seen in 80 (77.6%) patients. The sputum culture conversion rate varies from 74% to 92% in different studies reported across globally [11, 12]. Singla *et al.* [13] (2002-06), culture conversion rate was 82.0% within 3 months. Joseph *et al.* [14] (2006-07) in which 84.0% patients achieved culture conversion at 3 months, Kalpeshjain [10] bacteriological improvement 89 (68%) achieved sputum culture conversion within 9 months. Out of these 89 patients, 73 (82%) became culture-negative within 3 months of treatment, and 84 (94%) within 6 months. Thus it was observed that time of culture and smear conversion in most of the patients was 3 months, which indicates that effective management of MDR TB with an adequate regimen with high end dosing, can make the patient non infectious rapidly and probably gives better outcome results in long term. In his study Yew *et al.* [15] found that negative sputum culture at 3 months was predictive of eventual cure in all MDR TB patients.

Thus monitoring monthly sputum culture in the initial 6 months, helps greatly in predicting outcomes and is recommended by WHO. Thus sputum culture conversion during or at the end of intensive phase is a useful interim indicator of treatment outcome for patients with multidrug resistant TB and that sputum culture conversion is an appropriate first goal of therapy. This is not surprising, because sputum culture conversion occurs far rapidly than final treatment outcome which occurs late, and is a function of the pathogenesis of the disease.

Out of these patients, only 103 patients came for follow up after treatment completion and radiological regression was noticed in 69 (67.0%) patients while radiological progression was seen in 24 (23.3%) patients, whereas 10 (9.7%) patients had shown stationary radiological picture. In study conducted by Dhingra *et al.* [16] radiological regression was noticed in 67.0% patients, and they concluded that radiological regression was associated with favorable treatment outcome.

In our study 68 out of 81 patients showed positive radiological and bacteriological response whereas 1 among 22 patients with radiological resolution showed poor treatment response. The relation between bacteriological and radiological response was found to be highly significant (p value<0.001) in the study. Patients who showed improvement in symptoms also showed radiological response which was highly significant (p value<0.001). Radiological response to treatment, in the form of clearance of shadows, decrease in size/thinning of cavity wall and resolution of cavities were good predictor of favorable outcome with a strong correlation. 32% - 78% radiological responses were noted in by Waseemsaeed *et al.* [17] (78%), Dhingra *et al.* [16] (67%) and H S Subhash *et al.* [18] (32.5%). Overall 98.5% culture conversion occurred in patients with radiological regression, while in patients with radiological progression of disease only 20.8% patients had shown culture conversion.

In our study out of 103 follow up patients, clinical improvement was seen in 81 (78.6%), whereas 22 (21.4%) patients had clinical deterioration. However we were unable to find any study which directly correlates clinical subjective criteria and treatment outcomes or impact on culture conversion rates. However in our study 78 (96.3%) patients who experienced clinical improvement had culture conversion while in only 2 (9.1%) patients culture conversion occurred who had no clinical improvement, and this correlation was statistically highly significant (p value<0.001). The interpersonal variability of perception of improvement or deterioration of symptoms may vary considerably between individual subjects, thus more studies are required for further interpretation of results. Moreover, the symptoms associated with co-morbidities and ADRs may also be responsible for subjective clinical outcome.

**CONCLUSION**

Despite high rate of drug resistance in studied population, an overall fair proportion of patients achieved culture conversion at 3 months and radiological regression. This may help in better care of individual patients by identifying them early and treating them vigorously.

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