

## Treatment outcomes of multidrug resistance tuberculosis

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### Received:

16th June, 2018

### Accepted:

4th March, 2019

### Abstract

**Objective:** To identify the treatment outcomes among patients having confirmed diagnosis of multi drug resistant tuberculosis (MDR-TB).

**Study design:** Prospective cohort study

**Place and duration of study:** The study was conducted at programmatic management of drug resistant TB (PMDT) unit of Saidu Group of Teaching Hospital, Swat, a tertiary care hospital for a period of three years from May 24<sup>th</sup>, 2014 till May 23<sup>rd</sup>, 2017.

**Material and methods:** Fifty-one patients with confirmed diagnosis of MDR-TB were recruited in this study. Patients were provided with complete diagnostic facilities to include Sputum AFB, Gene X Pert and Sputum culture and sensitivity. Patients with MDR-TB were provided with five drugs during the intensive phase and four drugs during continuation phase of therapy. Demographic details, presence of pulmonary tuberculosis, human immunodeficiency virus infection; and previous TB treatment was recorded. Sensitivity to the second line anti-TB drugs and treatment outcomes (i.e. Cured, Treatment Failed, Mortality, Lost to Follow-up) were recorded based on World Health Organisation definition.

**Results:** All MDR-TB patients in this study had pulmonary tuberculosis, were HIV negative and had tuberculosis treatment in the past. Forty-three (84.3%) patients were not resistant to Second Line Drugs. Of the 51-patients, 36 (70.6%) were cured, 2 (3.9%) were not evaluated, 3 (5.9%) of patients were lost to follow-up; and treatment failed in one patient. Mortality recorded at follow-up was nine (17.6%) patients.

**Conclusion:** The programmatic management of the multi drug resistant tuberculosis patients has shown favourable outcomes with 70% cure rates.

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**Keywords:** multi drug resistant tuberculosis, first line drugs, second line drugs, prospective cohort, treatment outcome

### Introduction:

Multidrug resistance tuberculosis is caused by the strain of Mycobacterium Tuberculosis that is resistant to 2 most effective anti-Tuberculosis drugs (Isoniazid and Rifampicin).<sup>1-2</sup> This may and may not be accompanied with resistance to other first line drugs (FLDs) and second line drugs (SLDs).<sup>3</sup> MDR-TB may result from a primary infection or may occur with anti-TB treatment.<sup>4</sup> MDR-TB occurs due to human error that predisposes the mycobacteria to develop resistance; however certain genetic factors have also

been attributed to MDR-TB.<sup>5-8</sup> The most significant patient related reason that predisposes to MDR-TB is non-adherence and non-compliance to the tuberculosis treatment.<sup>9</sup>

Drug resistance Tuberculosis (TB) is a significant public health concern with number of reported cases on the rise, thereby placing extensive burden on the National Tuberculosis Programmes (NTPs).<sup>10-12</sup> It has been reported that globally, around 4.1% new cases and around 19% of previously treated TB cases developed

multi-drug resistant TB in the year 2016 and around 240,000 deaths were estimated due to MDR-TB.<sup>13</sup> Moreover, 30 high MDR-TB burden countries accounted for around 90% of the globally incident cases.<sup>13</sup> The statistics shows that MDR-TB had become a major obstacle for the successful control of TB globally and more importantly among developing countries.<sup>14</sup> Statistics from Pakistan have shown a rise in MDR-TB incidence from 1.5% in 2006 to 4.5% in 2009.<sup>15</sup> However, the recent small scale studies have reported the incidence of MDR-TB between 2% to 3%.<sup>16-17</sup> Furthermore, treatment of MDR-TB is more expensive with limited access to the properly equipped healthcare facilities, high treatment cost, involve longer duration and higher toxicity of treatment regimens and; less favorable treatment outcomes.<sup>18</sup> In addition, patients may fail treatment or could be lost to follow-up during prolonged treatment.<sup>19</sup>

The community-based treatment had shown improved clinical outcomes among MDR-TB cases in many countries globally. Therefore, the present prospective cohort study was conducted to identify the treatment outcomes among patients with confirmed diagnosis of MDR-TB enrolled at Programmatic Management of Drug Resistant TB (PMDT) Unit of Saidu Group of Teaching Hospital, Swat.

#### **Material and Methods:**

A prospective cohort study was conducted at PMDT Unit of Saidu Group of Teaching Hospital, Swat, the tertiary care hospital for a period of three years from May 24<sup>th</sup>, 2014 till May 23<sup>rd</sup>, 2017. Patients satisfying the inclusion and exclusion criteria from records available were included in this research. Patients having confirmed diagnosis of MDR-TB according to the drug sensitivity test and agreed not to change their place of residence during the treatment period were included in this research. Exclusion criteria included serious underlying medical and/or psychiatric illness, not willing to provide informed consent, known intolerance to a study drug, patients less than 18-years of age and; pregnant women.

All eligible patients recruited in this research were provided with complete diagnostic facilities that included; Sputum AFB, Gene X Pert and Sputum culture and sensitivity. Sputum AFB and Gene X Pert were performed at the PMDT site, while sputum culture and sensitivities were done at the provincial reference laboratory of Peshawar. To ensure consistency, all specimens were sent to single laboratory, standard procedures and protocols were followed.

All patients with MDR-TB were provided with free of cost drugs under the PMDT program. These drugs were given during an insensitive phase, consisted of five drugs that also included an injectible drug, while during continuation phase four drugs were given. Monitoring for adverse effects, managing adverse effects and treatment monitoring were done at PMDT during each visit. Any necessary investigations for adverse effects were carried out at the hospital site. Moreover, sputum AFB, sputum culture and sensitivity during the treatment were carried out according to the recommendation of NTP.

A structured questionnaire was used to record the data. The demographic details (i.e. age, gender and region of residence) were recorded. Moreover, presence or absence of pulmonary tuberculosis, human immuno-deficiency virus infection, and having previous TB treatment in the past was also recorded. Moreover, the drug sensitivity and resistance to the second line drugs were recorded. Importantly, the treatment outcomes (i.e. cured, treatment failed, mortality, lost to follow-up) were recorded and defined as per the World Health Organisation definition.<sup>20</sup> The patients was defined as Cured if treatment completed (minimum of 18 months past culture conversion) without evidence of failure with three or more consecutive culture taken at 30 days apart and found negative after an intensive phase. Treatment failed was defined as treatment terminated or permanent change of atleast two anti-TB drugs. Mortality was defined as death during treatment for any reason. Loss to follow-up was defined as a patient whose treatment was interrupted for the period of two consecutive months or more.

Table-1: Characteristics of the Study Participants (N = 51)

Characteristics	n (%)
<b>Age in years</b>	
18 – 24 years	20 (39.3)
25 – 34 years	17 (33.3)
35 – 44 years	9 (17.6)
45 – 54 years	4 (7.8)
55 – 64 years	1 (2)
<b>Gender</b>	
Male	21 (41.2)
Female	30 (58.8)
<b>Region (locality of residence)</b>	
Swat	31 (60.8)
Shangla	6 (11.8)
Lower Dir	4 (7.8)
Kohistan	2 (3.9)
Bajawar Agency	2 (3.9)
Bunir	3 (5.9)
Upper Dir/ Chitral and Malakand Agency	1 (2)
<b>Pulmonary Tuberculosis</b>	
Yes	51 (100)
No	0 (0)
<b>HIV negative</b>	
Yes	51 (100)
No	0 (0)
<b>Tuberculosis treatment in past</b>	
Yes	51 (100)
No	0 (0)

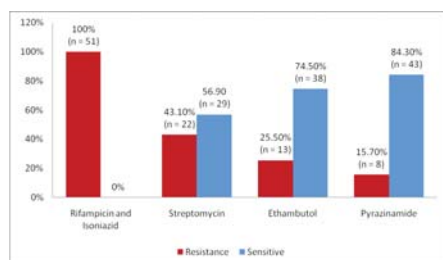


Figure 1: Resistance Pattern among Multidrug Resistance Tuberculosis patients with First Line Drugs (FLD)

The present study was conducted according to ethical guidelines of Helsinki declaration and Pakistan Medical and Research Council (PMRC). The study was initiated after the approval from Ethical Review Committee (ERC) of Saidu Group of Teaching Hospital, Swat. Written informed consent was obtained from all the participants prior to enrollment in this prospective cohort study, where they were comprehensively explained about the study objectives,

research processes involved, risks and benefits associated with the research. Importantly, the study participant's confidentiality and anonymity were maintained throughout the research process. All treatment was provided free of charge.

Study data collected analysed using SPSS version 21 (IOBM). The data recorded on the pre-designed structured performa was entered in the SPSS software and validated twice for any incorrect entries. Descriptive statistics were performed where categorical variables were reported as frequency/ percentage.

### Results:

Table-1 gives details of the characteristics of the study participants. The mean age of the study cohort was \_\_ years and over half of the patients (59%) were females. Over one-third aged (25-34) years and under one-third aged 35 years and above. The region or locality of the study participants were as follows; Swat (60.8%), Shangla (11.8%), Lower Dir (7.8%), Bunir (5.9%), Bajawar Agency (3.9%), Kohistan (3.9%) and Upper Dir/ Chitral and Malakand Agency as (2%). All patients recruited in this study had pulmonary TB, had received TB treatment in the past and were HIV negative.

The figure-1 shows resistance pattern among MDR-TB patients in our study cohort to First Line Drugs (FLD). With 43.1% resistant to Streptomycin; 25.5% resistant to Ethambutol and 15.7% were resistant to pyrazinamide.

Table-2 gives details of the resistance pattern in our patients to second line drugs with 43 (84.3%) not showing resistance to SLDs. Four (8%) patients were resistance to; Fluoroquinolone and one each to Amikacin and one patient to three SLDs (Amikacin/ Fluoroquinolone/ Capreomycin) Fluoroquinolone/ Capreomycin and one patient to three SLDs (Amikacin/ Fluoroquinolone/ Capreomycin

Figure-2 gives details of the treatment outcomes with (71%) patients were cured 4% were not evaluated, were lost to follow-up, 2% failed

Table-2: Resistance pattern among Multidrug Resistance Tuberculosis patients with Second Line Drugs (SLD)

Second Line Drugs (SLDs)	Resistant n (%)
Floroquinolone	4 (7.8)
Amikacin	1 (2)
Capreomycin	1 (2)
Floroquinolone - Capreomycin	1 (2)
Amikacin - Floroquinolone - Capreomycin	1 (2)
Not Resistant to SLDs	43 (84.3)

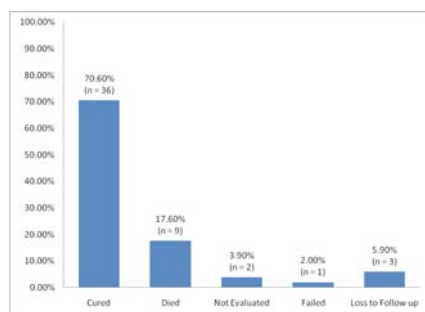


Figure 2: Treatment outcomes of Multidrug Resistance Tuberculosis

treatment and overall mortality was 18%.

### Discussion:

The results of the present prospective cohort study highlighted the treatment outcomes of the Multi-drug Resistance Tuberculosis patients. Among 51-patients, majority 36(70.6%) patients were cured, the treatment was failed in only 1-patient while the mortality was recorded at follow-up among 9(17.6%) patients.

Pakistan is a country that ranked 5<sup>th</sup> in TB and 4<sup>th</sup> among MDR-TB high burden countries globally.<sup>21</sup> Moreover, the case detection of MDR-TB has been comparatively low as 63%, thereby majority of patients remained undiagnosed and untreated.<sup>22</sup> A study reported that MDR-TB among newly notified cases were 4.3%, while among retreatment cases was slightly less than 20%.<sup>23</sup> A study from the province of Khyber Pakhtunkhwa (KPK) has reported that MDR-TB being diagnosed among newly notified cases was 3%, and more than one quarter (26%) among previously treated patients.<sup>24</sup> A study reported that around 17% of the MDR-TB patients were relatives with MDR-TB, reflected that close contacts predisposes the infection.<sup>25</sup> Moreover, the study from Punjab, Pakistan reported that MDR-TB being diagnosed among newly notified cases was 4%, and 19.4% among

patients previously treated.<sup>26</sup>

The results of the present prospective cohort study reported that among 51-patients with MDR-TB, majority 36(70.6%) patients were cured. Treatment success rate was better than those observed in other studies: (40-70%) in 25 countries,<sup>27</sup> 54% in Shanghai<sup>28</sup> and 48% in South Korea,<sup>29</sup> but lower than Germany (80%).<sup>30</sup> The possible reasons accounted for improved treatment outcomes are trained treatment supporters and use of individualized regimens at the highest recommended doses. However, it has been reported in the previously published studies that directly observed treatment and individualized regimens are predictors of successful treatment outcome.<sup>31</sup> High treatment success rate can be accounted due to a low default rate; and patients are provided free treatment, at times transport allowances, counselling by psychologists, and providing treatment facilities at the nearest PMDT centre.

In Pakistan studies have been done locally and success rate was found to be 41.37% which is quiet low as compared to the success rate described elsewhere in the world.<sup>32</sup> In one local study Inayat et al have shown success rate of 38.44% which is quite low as compared to our study and it's because of the cost of medicine the patients had to purchase themselves.<sup>33</sup> The current study reported the cure rate as 70.6% being same as reported internationally. The difference in the local studies is due to this new system i.e. PMDT due to which many of the hindrances have been removed and led to better compliance of the patients and hence improved outcomes. In one local study by Khan et al showed 74.3% cured outcome which is close to our results.<sup>34</sup>

The present study conducted had number of limitations. Firstly, the study was conducted at only hospital setting, PMDT Unit of Saidu Group of Teaching Hospital, Swat. Secondly, study participants (MDR-TB) patients were enrolled through non-probability consecutive sampling technique, which would have induced the selection bias. Moreover, limited only fifty one participants were enrolled in this study and



were followed. Thus, consecutive sampling technique, limited number of study participants and recruitment from only study site had limited the generalisability of the study findings as treatment outcomes among MDR-TB patients.

### Conclusion:

The conclusion could be drawn that the programmatic management of the MDR-TB patients had shown improved treatment outcomes and therefore in Pakistan where the prevalence Tuberculosis is high and MDR-TB has shown continuous rise, there is an immediate need to expand the program in the country in order to achieve the WHO goals in future.

**Conflict of interest:** None

**Funding source:** None

### Role and contribution of authors:

Dr Abdul Jabbar, conceived idea and research objective, designed, did data collection, data analysis & writing of manuscript

Dr Akhter Ali Khan, did literature search, data collection, review and final editing of Manuscript

Dr Wasil Khan, did literature review, data analysis and final editing of manuscript

Dr Muhammad Abdul Samad, did data analysis and final review of manuscript

Dr Hafeez Abdul Jabbar collected the data and references

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