

Treatment outcomes of patients with drug resistant tuberculosis; Experience from a tertiary care hospital in Abbottabad

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The Authors declares that there is no conflict of interest.

ABSTRACT

Background: The emergence of Drug resistant tuberculosis (DR-TB) challenging all efforts against TB control and this disease now became a global health problem. It is a man-made problem and so this type of disease found more in retreatment cases.

Objective: This study was designed to study the outcome of management of drug-resistant tuberculosis in Abbottabad which is one of the PMDT sites managed by the National tuberculosis program Pakistan since 2013.

Methodology: This descriptive cross sectional study analyzes the data of DR-TB patients treated at the PMDT site Abbottabad from April 2013 to October 2018.

Results: A total of 227 patients with DR-TB have been treated at the PMDT site Abbottabad. The cure rate for DR-TB treatment regimens is 69.16%. Forty two (18.5%) patients died during the course of treatment, treatment failure was declared in 5 (2.2%) while 15 (6.61%) patients were lost to follow up. The frequency of primary MDR-TB was 15.42% during this course of treatment.

Conclusion: Despite a higher cure rates observed, there is a lot of room for improvement since primary MDR-TB appears to be on the rise. It is pertinent to adapt measures to increase patient compliance by keeping them motivated to adhere to treatment goals.

Keywords: MTB; DR-TB; MDR-TB; XDR-TB; Outcomes; Gene Xpert

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Introduction

Mycobacterium tuberculosis (MTB) has become the leading cause of mortality worldwide placing tuberculosis (TB), among the top 10 leading causes of death.¹ TB was responsible for an estimated mortality of 1.6 million in HIV-Negative people worldwide in 2017 and among HIV-positive people, tuberculosis caused an additional 0.3 million deaths.² In 2017, 500,000 new cases of tuberculosis were diagnosed in Pakistan.¹

Emergence of resistance to the anti-tuberculosis

drugs (ATT) has becoming a health problem worldwide.³ In 2017, for example 82% of the 558,000 people who developed rifampicin resistant tuberculosis had multi-drug resistant tuberculosis (MDR-TB).¹ MDR-TB is associated with increased costs of healthcare as well as increased risk of developing drug toxicities because of their use for prolonged periods of time.^{4,5}

The increasing number of people with MDR-TB and XDR-TB represents a threat to national TB control efforts [3], because the treatment of MDR-TB and XDR-TB takes longer than drug-susceptible TB, has

toxic side effects and treatment outcomes are often poor. Ongoing transmission, failure to diagnose drug resistant TB at initial presentation, and high mortality and treatment dropout rates are also challenges.

Pakistan is among the twenty two countries where the burden of tuberculosis is very high, in fact, the number of new tuberculosis cases in Pakistan constituted 5% of the total cases of tuberculosis worldwide in 2017.¹ Pakistan accounts for 61% of the burden of tuberculosis in the eastern mediterranean region with an annual incidence of 15,000 cases of drug resistant tuberculosis cases and approximately 510000 new tuberculosis cases.⁶ Pakistan ranks 4th in terms of highest prevalence of MDRTB.^{7,8}

The national tuberculosis control programme Pakistan is responsible for planning and implementation of strategies related to management of tuberculosis in Pakistan in line with the latest world health organization diagnostic and treatment guidelines with a financial support by the Global Fund.^{6,9}

The national TB program or NTP as it is commonly known have been involved in formal management of tuberculosis using a number of strategies known as DOTS, DOTS-PLUS and PMDT.¹⁰ Of the three, DOTS Plus strategy involved in management of drug-resistant tuberculosis using second line anti-tuberculosis drugs. PMDT or programmatic management of drug resistant tuberculosis replaced DOTS-plus and has been functioning in 30 hospitals across the country with the help of assistance from The Global Fund.¹⁰ According to the most recent estimates, the treatment success rate for MDR-TB/RR-TB cases who started treatment in 2015 is 64% in Pakistan.¹¹

This study was designed to study the outcome of management of drug-resistant tuberculosis in Abbottabad which is one of the PMDT sites managed by the National tuberculosis program Pakistan since 2013.

Methodology

This descriptive cross sectional study was conducted at the department of pulmonology and chest disease from April 2013 to October 2018. Data of all patients enrolled at the local PMDT site was acquired and analyzed for outcome. Rifampicin resistant tuberculosis or RR-TB was defined as resistance to rifampicin on Gene-Xpert analysis and / or sputum DST results. When resistance to both isoniazid and rifampicin was identified, the patient was identified as a case of MDR-TB. According to the NTP guidelines for

management of drug resistant tuberculosis, XDRTB or extremely drug resistant tuberculosis is defined as resistance to an injectable and a quinolone in a patient with MDRTB. Resistance to any first line drug except rifampicin was labelled as mono-drug resistant tuberculosis while resistance to any number of drugs, not involving rifampicin alone or in association with isoniazid was defined as poly drug resistant tuberculosis. Pulmonary tuberculosis was defined as tuberculosis affecting the lung parenchyma, while extra pulmonary tuberculosis was defined as tuberculosis involving every other organ of the body including the pleura.

The treatment outcome criteria for DRTB as laid down by the NTP were followed. As per definitions, patients were declared cured of DRTB when they completed a minimum of 20 months of treatment of which 18 months were past culture conversion without any evidence of treatment failure and at least three consecutive sputum cultures taken towards the end of treatment were negative for mycobacterium tuberculosis. Those who had completed the recommended duration of drug treatment without evidence of failure but didn't have cultures available at the end of treatment were declared treatment completed. Treatment failure was declared when the patients failed to show sputum conversion at the end of intensive phase, or showed bacteriological reversion during the continuation phase, or developed resistance to other drugs such as quinolones or developed adverse drug reactions severe enough to merit a discontinuation of treatment. Patients who died due to any reason during the course of treatment were categorized as died. Similarly, patients whose treatment got interrupted for at least 2 consecutive months were declared lost to follow up.

The data was analyzed in SPSS 20. Numerical data was described as mean \pm SD, while categorical data was described as frequencies and percentages. The outcome i.e., cure was stratified by age and gender to see effect modification. Post stratification chi-square test was applied and a p value ≤ 0.05 was taken as significant.

Results

There were a total of 227 patients enrolled at the PMDT site for management of drug resistant tuberculosis. The mean age of study cohort was 33.55 \pm 16.88 yrs. There were 104 (45.81%) males and 123 (54.19%) females. Most patients were diagnosed with MDRTB (66.52%), followed by RRTB (27.31%), XDRTB (3.08%), mono-drug resistant tuberculosis

(2.20%) and poly-resistant tuberculosis (0.88%). The cure rate was 69.16%. 42 (18.5%) patients died during the course of treatment, treatment failure was declared in 5 (2.2%) while 15 (6.61%) patients were lost to follow up. 8 (3.52%) were not evaluated because they had not completed their treatment duration. Interestingly, 35 (15.42%) of patients with MDRTB were those who had been diagnosed with any type of tuberculosis for the first time. The remainder (n=192; 84.58%) of cases were retreatment cases. These results are different from those reported earlier

in literature. Highest cure rate (100%) was seen in monoresistant tuberculosis followed by MDRTB (73.51%) and RRTB (59.68%)

Most (99.12%) of the patients had pulmonary tuberculosis, and all except one received long term standardized / individualized DRTB treatment regimen. When the outcome i.e., cure was stratified by age and gender no statistically significant association was observed ($p > 0.05$). Results are presented as tables below:

Table 1: Age of study participants

Variable	N	Mean	Std Dev	Minimum	Maximum
Age of patients	227	33.55	16.88	10.00	85.00

Table 2: Gender distribution of study cases

Sex of patients	Frequency	Percent
Male	104	45.81
Female	123	54.19
Total	227	100.0

Table 3: Distribution of study cases according to their Nationality

Nationality	Frequency	Percent
Pakistani	212	93.39
Afghani	15	6.61
Total	227	100.0

Table 4: Site of DR-TB

Site of DRTB	Frequency	Percent
Pulmonary	225	99.12
ExtraPulmonary	2	.88
Total	227	100.0

Table 5: Type of DR-TB among study cases

Value Label	Frequency	Percent
Multi Drug Resistant TB	151	66.52
Rifampicin Resistant TB	62	27.31
Extensive Drug Resistant TB	7	3.08
Polydrug Resistant TB	2	.88
Mono Drug Resistant TB	5	2.20
Total	227	100.0

Table 6: Treatment Strategy of study cases

Treatment Strategy	Frequency	Percent
Long-term (conventional Regimen)	225	99.12
Short-term Regimen	2	.88
Total	227	100.0

Table 7: Treatment Outcome of patients

Treatment Outcome	Frequency	Percent
Cured	157	69.16
Died	42	18.50
Failed	5	2.20
Lost to follow up	15	6.61
Not evaluated	8	3.52
Total	227	100.0

Table 8: Cross tabulation of treatment outcome with age of the patients.

Treatment Outcome			
age of patients	Cured	Others	Total
upto 33	105.00	38.00	143.00
More than 33	52.00	32.00	84.00
Total	157.00	70.00	227.00

Chi-square tests.

Statistic	Value	D f	Asymp. Sig. (2 -tailed)	Exact Sig. (2-tailed)	Exact Sig. (1-tailed)
Pearson Chi - Square	3.29	1	.070		
Likelihood Ratio	3.25	1	.071		
Fisher's Exact Test				.076	.049
Continuity Correction	2.78	1	.096		
Linear - by-Linear Association	3.28	1	.070		
N of Valid Cases	227				

Table 9: Cross tab of Sex of patients and Treatment Outcome

Treatment Outcome			
Sex of patients	Cured	Others	Total
Male	72.00	32.00	104.00
Female	85.00	38.00	123.00
Total	157.00	70.00	227.00

Chi-square tests.

Statistic	Value	Df	Asymp. Sig. (2 -tailed)	Exact Sig. (2-tailed)	Exact Sig. (1-tailed)
Pearson Chi - Square	.00	1	.984		
Likelihood Ratio	.00	1	.984		
Fisher's Exact Test				1.000	.550
Continuity Correction	.00	1	1.000		
Linear - by-Linear Association	.00	1	.984		
N of Valid Cases	227				

Discussion

The cure rate of MDRTB treatment was 69.16% at our center. A recent study from china reported a cure rate of 44.6% in their study cohort.¹² In their study, a diagnosis of drug resistant tuberculosis was made on the basis of phenotypic DST, while we utilized the Gene-Xpert/Rif-Res test to diagnose drug resistant tuberculosis. Being male and increased age were associated with a less favorable outcome in that study.¹² On the other hand, we did not find any significant association of age and gender of patients with the cure from DRTB.

A study from Taiwan reported a treatment success of 82.4% for a cohort of DRTB patients treated over a period of five years. The death rate in that study was 12.1%, treatment failure was recognized in 2.6% and 2.9% patients were lost to follow up.¹³ The differences between ours and their study could be explained on the basis of differences in sample size.

In a meta-analysis published recently, which analyzed patient data from twenty five countries in fifty studies, a success rate of 61% was noted.¹⁴ The authors further reported worse outcomes with kanamycin and capreomycin. In contrast, ours was a descriptive cross sectional study and the data are from a single center only. A recently published study from India reported that cure was observed in 52% (n=415) patients treated for MDRTB. Interestingly, 24% of their study participants were lost to followup while 16% died during treatment.¹⁵ The cure rates among patients with MDRTB remained high (73.55%) and similar results have been reported from South Africa where 72.9% patients with MDRTB had a post-treatment favorable outcome.¹⁶ A study from Nawabshah, Pakistan reported that a favorable outcome in terms of treatment success was observed in 38.44% of patients.¹⁷ however, the sample size of that study was only 36 patients while the patients were followed for a period of 4 years. The frequency of primary MDR-TB cases in our study was 15.42%. This is quite high from that reported earlier for Pakistan,^{18,19,8} however, the earlier data were probably collected from many centers and therefore could represent a collective estimate as compared to the results from our study. However, such increased frequency is not unusual elsewhere in the world. For example, according to the WHO, in 2013, 19% of newly diagnosed tuberculosis cases were primary MDRTB cases.²⁰ A study from Peru, exploring the risk factors for MDRTB reported that the frequency of MDRTB in patients with risk factors was as high as 13.6%.²¹ Similarly, a study from India reported that the frequency of primary MDRTB in MDRTB cases was 11.63%. The increased number of

primary MDRTB in our study is a worrying sign. Further research is indicated to determine if the primary MDRTB is really increasing in the general population or whether it was a one-off anomaly.

It is evident that the treatment success rate for drug resistant tuberculosis varies across the globe. A number of factors have been ascribed to this fact,^{14,22} although we did not attempt to find such factors.

Conclusion

Although the success rate of drug resistant tuberculosis treatment regimens is variable across the globe and cure rates are improving the incidence of primary MDRTB is apparently increasing. Keeping in view the longer duration of treatment and increased number of drugs to be taken, it is pertinent to adapt measures to increase patient compliance by keeping them motivated to adhere to treatment goals

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