

Long Term Follow up of Multi Drug Resistance Tuberculosis Patients After 3-4 Years of Starting Second Line Anti Tubercular Drugs

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Abstract

Objective: To determine the rates of mortality, default, relapse and treatment success in MDR TB patients during the last few years and to observe other risk factors associated with this disease.

Methods: This cohort study was conducted during April 2014 to November 2015. Confirmed MDR TB patients who started their antitubercular treatment during years 2008 to 2010 were included in this study. Addresses and contact numbers of all the patients were noted from the files. Patients who died during or after treatment due to any reason, an International standard verbal autopsy questionnaire was filled on.

Results: Data of 131 patients who started their antitubercular treatment during year 2008 to 2010 was collected retrospectively and 31 (23.6%) were excluded from the study. Of the remaining 100 patients 71 were male and 29 were females. Thirty five out of 100 patients died during or after completion of anti-tubercular treatment while 65% were alive. Records shown that 62% of the patients have family history of TB, furthermore 71% of the total patients had previous history of anti-tubercular treatment. Of 35 death cases 65% had previous history of antitubercular treatment. About 55.4% of the alive patients had good compliance while 59.0% of the death cases had bad or no compliance.

Conclusions: High mortality rate of patients after long time from initiation of MDR TB treatment was observed in present study revealed associated risk of death during or after completion of treatment.

Key Words: *Follow-up, MDR-TB, Second line drugs, pulmonary TB.*

Introduction

Tuberculosis (TB) has been a great health issue worldwide. Millions of people perceive the infection every year and disease posed as second most

major cause of death around the globe, after the human immune-deficiency virus (HIV). Over 95% deaths are related to TB in under developed and developing countries and it is also one of the three top most reasons of women in age range of 15 to 44¹. Prevention and control of TB is one of the major problems regarding public health in Pakistan. World Health Organization (WHO) has estimated 420,000 patients acquire TB infection annually with an incidence of 231/100,000 population. Multidrug resistant (MDR) TB incidence has been reported up to 4.3% in new TB cases while 19% in re-treatment TB patients². World Health organization has endorsed directly observed short treatment (DOTS) and has been implemented among health entities of

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whole countries since 2005³. However the emerging problem of MDR TB is anti-tubercular treatment contributing to compromise the TB controls programs⁴. It is true that MDR TB is creating big problems for National TB control program however effective treatment can result in cure⁴. Under the circumstances follow-up of such cases is important to understand the long-term efficacy of treatment and impact of the disease on the patient's physical and socioeconomic well being⁴.

Multidrug resistant TB is the disease caused by the strain of *Mycobacterium tuberculosis* complex, resistant to isoniazid and rifampicin together either resistant to other anti-tubercular agents from first line drugs or not. Reasons behind global impact of MDR TB include partial or inadequate treatment, incorrect drugs regimen, low quality drugs and improper time frame of medication⁴. Therefore, existence of such patients in public may result in direct spread of resistant among healthy people. In 2008, WHO estimated a total number of 440,000 patients of MDR TB around the world and 85% of this burden is hidden in only twenty seven high-burden countries⁵. In 2009 the National Health Laboratory Services (NHLS) in South Africa diagnosed 9,070 MDR-TB and 594 extensively drug resistant TB cases while 7,386 MDR-TB cases and 741 extensively drug resistant TB cases were detected during 2010 which shows that There is an urgent need for dramatic scale-up of access to effective MDR-TB and extensively drug resistant TB management⁶. According to current literature from South Africa, treatment of MDR TB patients is not effective which contributes to surge the progress of extensively drug resistant TB⁷. A recent study undertaken in KwaZulu-Natal elaborated the poverty profile and showed that 75% of families having MDR or extensively drug resistant TB cases are headed by women⁸, therefore they cannot be admitted to hospital for a long period due to responsibilities such as caring for young children. According to center for global development reported that one third of patients died having MDR TB in 2008⁹. A person infected from MDR strain of TB can

infect up to 20 people in his life¹⁰. Prevalence of MDR TB is not known exactly in Pakistan however some studies have shown as high prevalence of MDR TB as 30.7% and 28% in Rawalpindi¹¹. Aga Khan University has reported 47% MDR TB in Karachi¹². An increasing trend of primary MDR from 11.9% to 12.8% and acquired MDR from 23% to 27% has been observed in Lahore from 2003 to 2006¹³. These high rates of MDR TB stimulated us to conduct a follow up study in this kind of patients. It is an established fact that TB is a communicable disease and Pakistan ranks 6th among the list of high tuberculosis burden countries. The growing threat of MDR TB is an additive burden on the poor socioeconomic resources of the community. If MDR TB patients remain untreated or non-compliances can easily spread the resistant strains to others. In this scenario the work is much important according to the public health point of view. This study will be extremely helpful to set a base line to see the rates of mortality, default, and relapse and treatment success in MDR TB patients during the last few years and shall be compared with the success rates of DOTS, which has recently established its MDR TB treatment.

Methods

This is a cohort study and was done by Pakistan Health Research Council TB Research Centre in association with Department of Pulmonology, King Edward Medical University, Mayo Hospital Lahore from April 2014 to November 2015. A total of 100 patients who were registered during years 2008 and 2010 in department of Chest Medicine Mayo Hospital Lahore and subjected to MDR TB treatment was our study population.

Patients admitted in TB ward that were bacteriologically and clinically diagnosed as MDR TB and started MDR TB treatment regimen were included in this study. Retrospective analysis of all such patients diagnosed and initiated their MDR TB treatment during January 2008 to December 2010 was our target population. Clinical history, *Mycobacterium* TB culture reports and drug sensitivity

testing reports of all the patients were re-checked from the files and matched with the Laboratory register. A verbal informed consent was taken from the respondents as anti-tubercular treatment. Patients who were died during or after treatment due to any reason a International standard verbal autopsy questionnaire was filled¹⁴. Addresses and contact numbers of all the patients were noted from the files. Initially patients were contacted telephonically and were offered fare charges to visit PMRC TB research Center. The patients who could not be contacted telephonically were visited to take interview. The patients were grouped according to their districts and district wise visits were arranged.

A semi-structured questionnaire was used to collect demographic information and tenure of treatment, relapses and reasons if the patient is defaulted. Relapse were considered as the patients who completed their second line anti-tubercular treatment for 24 months and after sometime again started anti-tubercular treatment due to reoccurrence of TB symptoms. One spot specimen of sputum was also being collected for AFB smear microscopy and Mycobacterium TB culture to ensure the cure rate. Data was analyzed by using the SPSS version 20.0. Qualitative variables like gender, marital status, and family history of TB etc. were presented in frequency and percentages. Quantitative variable like age is presented in mean $\pm$ SD. Range of quantitative variables was also presented. MedCalc online software was used to apply chi-square test to calculate the P values of different variables taking 95% confidence level. P value ≤ 0.05 is considered as significant.

Results

Data of 131 patients who started their anti-tubercular treatment during year 2008 to 2010 was evaluated. Addresses/ phone numbers of 16 (12.2%) patients could not be verified while 15 (11.4%) patients refused to provide any information and were excluded from the study. Off the remaining 100 patients 71(50.7%) were male and 29(20.7%) were female with female to male ratio of 1:2.44.

Thirty five out of remaining 100 subjects were died during or after completion of anti-tubercular treatment and 65 were yet alive. Age and gender distribution of study subjects with reference to their life and death are shown below in table 1. A p value of ≤ 0.05 was found to be significant in both genders among live and died patients.

Table 2 shows demographic characteristics of all the study subjects. Predominantly 86 (86.0%) patients were married, having lower economic status. Records shown that most of the patients (62%) have family history of TB, furthermore 71 (71%) of the total patients had previous history of anti-tubercular treatment. Of 35 death cases 23(65%) had previous history of anti-tubercular treatment.

Table 3 shows the problems faced by the patients during treatment. A total of 22(33.8%) patients who were taking anti-tubercular treatment were also visiting traditional healers among live patients while only few patients had financial assistance. Most of the alive patients had good compliance while most of the death cases had bad or no compliance. Only few patients used extra supplements during anti-tubercular treatment. Chronic disabilities due to anti-tubercular treatment were observed in 41.5% of alive cases while 57.1% of death cases. Predominantly deafness was observed in both groups. A high number of 25/35 (71.4%) relapse cases were died.

Table 4 shows the co-morbidities among the study subjects. Hypertension and Cardiac disorder were most prominent comorbidities followed by diabetes, hepatitis B&C, lung cancer and renal disorders. Sputum samples of all 65 alive patients were collected for smear microscopy and culture. Result showed that all 65 patients have negative smear and culture. A p value of ≥ 0.05 was found in history of TB, primary education, good compliance and co-morbidities shows insignificant relation of both groups with these variables.

Table 1: Age and gender distribution of study subject

		Patient alive		Total N=100	
		Yes n(%) N=65	No n(%) N=35		
Gender	Male	51 (78.5)	20(57.1)	71	(P = 0.0252)
	Female	14(21.5)	15(42.9)	29	
Age	Mean	46	45	45.5	
	Standard Deviation	17	18	17.5	
	Minimum	16	17	16	
	Maximum	80	80	80	

Table 2: General characteristics of study subjects

Characteristics	Response	Patient Alive			
		Yes (n=65)		No (n=35)	
		N	%	N	%
Marital Status	Married	54	83.1	32	91.4
	Unmarried	11	16.9	3	8.6
	Total	65	100.0	35	100.0
Economic Status	Lower Rs. 7000-15000	35	53.8	13	37.1
	Middle Rs. 15001-25000	30	46.2	19	54.3
	Higher above Rs. 25000	0	0.0	3	8.6
Family History	yes	39	60.0	23	65.7
	No	26	40.0	12	34.3
Family Size (Binned)	<= 4	1	1.5	0	0.0
	5 - 8	25	38.5	10	28.6
	9 - 12	33	50.8	21	60.0
	13+	6	9.2	4	11.4
Education	≤ Primary	37	56.9	20	57.1
	Matriculation	24	36.9	13	37.1
	Higher above	4	6.2	2	5.7

Column wise percentages are calculated. P-value for history of TB = 0.58, Primary education = 0.98

Table 3: Problems Faced During Treatment

Study Question	Response	Patient Alive			
		Yes (n=65)		No (n=35)	
		N	%	N	%
Traditional Healer	Yes	22	33.8	11	31.4
	No	43	66.2	24	68.6
Type of Traditional Healer	None	43	66.2	24	68.6
	Hakim	18	27.7	6	17.2
	Homeopathic	0	0.0	2	5.7
	Spiritual Leader	4	6.2	3	8.6
Financial Assistance	Yes	3	4.6	3	8.6
	No	62	95.4	32	91.4
Medicines Available Easily	Yes	30	46.2	18	51.4
	No	35	53.8	17	48.6
Completion of Treatment	cured	15	23.0	3	8.6
	Relapsed	0	-	25	71.4
	treatment completed	50	76.9	7	20.0
Compliance Treatment	Good compliance*	36	55.4	14	40.0
	Bad Compliance**	29	44.6	19	54.3
	Non Compliance***	0	0.0	2	5.7
Gap in Medicine	No Gap	34	52.3	14	40.0
	<1 month	5	7.7	0	0.0
	>1 month	15	23.1	6	17.1
	1-2 months	11	16.9	13	37.1
	>2 months	0	0.0	2	5.7
Extra Supplements	Yes	8	12.3	1	2.9
	No	57	87.7	34	97.1
Chronic Disability Due to anti-tubercular treatment	Yes	27	41.5	20	57.1
	No	38	58.5	15	42.9
Complication	No Disorder	38	58.5	15	42.9
	Renal Disorder	0	0.0	2	5.7
	Deafness	12	18.5	7	20.0
	Blindness	6	9.2	4	11.4
	Hepatotoxicity	5	7.6	5	14.3
	Others	4	6.2	2	5.7
	Total	65	100.0	35	100.0

*Patient did not missed medicine at all during anti-tubercular treatment, ** Missed medicine when not available due to limited resource, Missed medicine without any reason. Column wise percentages are calculated. P value for good compliance = 0.144

Table 4: *Comorbidities among study subjects*

Type of Co-morbidity	Patient Alive			
	Yes (n=65)		No (n=35)	
	N	%	N	%
Diabetes	5	7.6	3	8.6
Hepatitis C Virus	3	4.6	1	2.8
Hepatitis B Virus	2	3.0	1	2.8
Cardiac Disease	6	9.2	2	5.7
Lung Cancer	0	-	3	8.6
Hypertension	7	10.8	4	11.4
Renal Disorders	0	-	1	2.8

Column wise percentages are calculated. $P = 0.37$

Discussion

In present study a high proportion of 35% of MDR-TB patients died during or short after completion of anti-tubercular treatment confirms the statement that higher trends of treatment failure and or relapse are associated with MDR-TB¹⁵. In current study shows 25 out of 35 death cases (71.4%) undergoes relapse, 3 patients (8.57%) were cured and 7 patients (20%) died after completion of anti-tubercular treatment however treatment success rate remained 65%. This study is not comparable with a similar study conducted in Peru has showed that 20% MDR TB patients were died before the completion of treatment, 8% were defaulted and 1% had failed treatment however the success rate remained 51.8%¹⁶. Another study conducted in South Africa in King George Hospital situated in Durban had shown an approximate success rate of 45% with default rate of 15% during year 2000 to 20068.

Due to retrospective analysis actual default rate could not be calculated in present study however 42% of the study subjects have more than one month gaps in their medicine and most of which 21/35 (60%) were among death cases. In another study done by Tugela Ferry during 2005-7 reported mortality rate of 75% among MDR-TB cases after treatment of one year⁸ is far more than this study. A study in Karachi reported mortality rate of 4.6% in

hospitalized MDR TB patients, 14.3% defaulted and a high rate of 41.2% were lost on follow up¹⁷.

Results of present study reveal that patients with MDR-TB are lack in education and high rate of poverty are associated with higher risk of death during treatment. Lower education level may be linked with associated low funds, over population and uncertainty. A higher number of earlier presentations about anti-tubercular treatment may also be associated to the greater risk of mortality as unleashed by the present study where 65% subjects who died had also previous history of anti-tubercular treatment. Overall results are comparable to the research that listed reasons of mortality in MDR-TB patients include late presentation of disease, poor compliance to anti-tubercular treatment, longer duration of illness before starting the anti-tubercular treatment and low body weight¹⁸.

Co-morbidities among MDR-TB patients includes diabetes, hypertension, hepatitis B&C, lung cancer and renal disorders among them diabetes and hypertension were the most prominent. And results are in agreement with a similar kind of study conducted in Peru¹⁵. Tendency of MDR-TB patients to take the treatment from traditional healers which include hakim is 24%, homeopathic 2% and spiritual leader 7% remained low as compared to the previous study among TB patients under same circumstances where 14% patients were taking medicine from hakim and 8% were taking from homeopathic treatment providers¹⁹. Before the launching of programmatic management of drug resistant TB (PMDT) sites there was no record keeping and hence no treatment of MDR patients available therefore such studies were difficult to conduct. Now it has opened the new horizon for initiating such studies.

Conclusion

High mortality rate of patients after initiation of MDR TB treatment was observed in present study revealed associated risk of death during or after completion of treatment. Lower education level, previous history of TB, delay in taking medicines,

co-morbidities like diabetes, hypertension, renal and cardiac diseases, were associated with mortality in MDT-TB. Timely diagnosis which is essential for proper detection of MDR-TB and management must be followed especially in resource limited countries.

References

1. World Health Organization. Tuberculosis Fact Sheet N 104, 2015. [Updated in October 2015, Cited on Nov 2015] Available from: <http://www.who.int/mediacentre/factsheets/fs104/en/>
2. World Health Organization. Global tuberculosis report 2014. ISBN 978 92 4 156480 9.
3. Surveillance and epidemiology, 2006. [Updated 2006 Cited Nov 2015] Available from website. http://www.who.int/GlobalAtlas/predefinedReports/TB/PDF_Files/pak.pdf.
4. Sonya S. Shin, Jennifer J. Furin, Felix Alcantara, Jaime Bayona, Epifanio Sanchez, Carole D. Mintnick. Long-term follow-up for multidrug-resistant tuberculosis. Available at www.cdc.gov/eid. 2006; 12;4: 687-88.
5. The Global Fund. Scaling up effective management of drug-resistant Tuberculosis 2011 available from: <http://www.who.int/tb/dots/InfoNoteMDRTB2011.pdf>
6. Multi drug resistant tuberculosis. A policy framework on decentralized and deinstitutionalized management for South Africa 2011. Available from website: http://www.inpracticeafrica.com/~media/Guidelines/SA_NDOH_MDR_TB.pdf
7. Mlambo C, Warren R, Poswa X, Victor T, Duse A, Marais E. Genotypic diversity of extensively drug-resistant tuberculosis (XDR-TB) in South Africa. *Int J Tuberc Lung Dis* 2008; 12(1):99-104.
8. Marra C. Tuberculosis MDR/XDR: The Msinga Experience - Lessons learnt from South Africa 2005–2009. Pietermaritzburg 2009.
9. Raviglion M, Zignol M. Centre for global development. Global MDR and XDR-TB Situation and Trends. [Updated March 2010, cited in 2015] Available from website : <http://www.cgdev.org/article/global-mdr-and-xdr-tb-situation-and-trends>.
10. AamerIkram, Sakhawat Ali, Wajid Ali, M Amin Wiqar. Latest pattern-tubercle treatment of multi-drug resistant tuberculosis in Pakistan. *Inf Dis J Pak*. 2008; 17(1):14-7.
11. Irfan S, Hassan Q, Hasan R. Assessment of resistance in multi drug resistant tuberculosis patients. *J Pak Med Assoc*. 2006; 56(9):397-400.
12. RizwanIqbal, IffatShabbir, SaulatUllah Khan, Shumaila Saleem, KashifMunir. Multidrug resistance tuberculosis in Lahore. *Pak J Med Res*. 2008; 47(1):22-25.
13. Denholm JT, Leslie DE, Jenkin GA, Darby J, Johnson PD, Graham SM. Long-term follow-up of contacts exposed to multidrug-resistant tuberculosis in Victoria, Australia. *Int J Tuberc Lung Dis*. 2012; 16(6):1320-5.
14. International standard verbal autopsy questionnaire. Available from website: http://www.who.int/healthinfo/statistics/verbal_autopsy_standards2.pdf
15. Delgado CD, Bravo SG, Montag AR, Cayla ABOJA. Mortality among MDR TB cases: Comparison with drug susceptible tuberculosis and associated factors. *PLoS One*. 2015; 10(3): e0119332.
16. Asencios L, Quispe N, Mendoza-Ticona A, Leo E, Vasquez L, Jave O, et al. National surveillance of anti-tuberculosis drug resistance, Peru 2005–2006. *Rev Peru Med Exp* 2009; 26(3):278-88.
17. Rao NA, Irfan M, Mahfooz Z. Treatment outcome of multi-drug resistant tuberculosis in a tertiary care hospital in Karachi. *J Pak Med Assoc*. 2009; 59(10): 94-8.
18. Haque G, Kumar A, Saifuddin F, Ismail S, Rizvi N, Ghazal S. et. al. Prognosis factors in tuberculosis related mortalities in hospitalized patients. *Tubercu Res Treat*. 2014; Article ID 624671, 6 pages.
19. Munir MK, Iqbal R, Shabbir I, Chaudhry K. Factors responsible for failure to initiate the tuberculosis treatment among smear positive tuberculosis patients. *Pak J Med Res*. 2012; 51(2): 34-7.

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