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A Study to Assess Association of Previous Treatment with Development of Multi Drug Resistance among TB Patients of Tertiary Care Hospital of India

(ORIGINAL ARTICLE)

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Abstract

Background: *Tuberculosis has been a major cause of suffering and death since times immemorial, thought to be one of the oldest human diseases. Drug resistance is a threat to TB control programs worldwide. One of the core factors in development of multi drug resistance is previous treatment received by the patient. Therefore we planned this study to find the various previous treatments correlates influencing development of drug resistance among MDR-TB patients*

Objective:

1. *To assess socio economic distribution of MDR cases reported at hospital*
2. *To find out association of previous treatment and its correlates with MDR cases reported at hospital*

Method: *It was a hospital based observational study. Informed consent of the patient was taken for the study. Approval from institutional ethical committee was obtained for the thesis. All information to accomplish objectives was collected by personal interview of each of the study subjects for about 30 to 45 minutes at PMDT site using pre-designed and pre-tested Proforma.*

Results: *MDR TB can affect all the age groups. In the study population, 214 (74.30%) patients were in the reproductive and economically productive age group of 16-45 years. The history of prior anti-tuberculosis medication was observed in 98.95% and it was strongly associated with development of MDR TB in our study.*

***Key words**: MDR cases; previous treatment.*

Introduction

Tuberculosis has been a major cause of suffering and death since times immemorial, thought to be one of the oldest human diseases.[1] Tuberculosis, despite the availability of effective diagnostic, preventive and curative strategies, remains as the second leading cause of death from an infectious agent worldwide, after the human immune-deficiency virus (HIV).[2] In 1993, the World Health Organization recognized the lethal impact of this disease and declared it a "Global Emergency".[3]

Multidrug Resistant Tuberculosis (MDR-TB) has emerged as a significant global health concern.[4, 5] There are alarming reports of increasing drug resistance from various part of globe which potentially threaten to disrupt the gains achieved in tuberculosis (TB) control over the last decade.[6] The prevalence of MDR-TB mirrors the functional state and efficacy of tuberculosis control programs and realistic attitude of the community towards implementation of such programs in the country.[7]

Drug resistance is a threat to TB control programs worldwide. Patients infected with multiple-drug resistant strains are less likely to become cured [8], particularly if they are infected by HIV or suffer from another immune disease. The treatment is much more toxic and much more expensive (about 700 times) than the one of patients with sensitive organisms.[9]

Based on the results of Gujarat, Maharashtra and Andhra Pradesh DRS Survey, Estimated proportion of MDR-TB is 2.1% (1.5% - 2.7%) in New TB cases and 15% (13%-17%) in previously treated cases. As compared to global rates, the proportions of MDR-TB are lesser in India.[2]

It is crucially important to recognize the individual and collective factors responsible for the heterogeneous global distribution of drug resistance, and to identify those populations at highest risk, in order to be able to develop the most appropriate case finding strategies. One of the core factor in development of multi drug resistance is previous treatment received by the patient.

Therefore we planned this study to find the various previous treatments correlates influencing development of drug resistance among MDR-TB patients attending PMDT site at Department of Respiratory Medicine, JLN Medical College & Associated Group of Hospitals Ajmer, Rajasthan, from 1st January 2012 to 31st December 2012.

Objectives

1. To assess socio economic distribution of MDR cases reported at hospital
2. To find out association of previous treatment and its correlates with MDR cases reported at hospital.

Material and Methods

Study Design: It was a hospital based observational study. Informed consent of the patient was taken for the study. Approval from institutional ethical committee was obtained for the thesis.

Study Duration: This study was carried out from 1st January 2012 to 31st December 2012 at PMDT site at Department of Respiratory Medicine, JLN Medical College and Associated Group of Hospitals, Ajmer, Rajasthan.

Study Population: All diagnosed cases of Multidrug Resistant Pulmonary Tuberculosis patients reporting to PMDT site at the Department of Respiratory Medicine, JLN Medical College, Ajmer were form the study population.

Inclusion criteria

The patients with documented evidence of sputum for Mycobacterial Culture & Sensitivity from an Intermediate Reference Laboratories were included in the study population. 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).

Exclusion criteria

- Those patients who did not give detailed history or documents were excluded from study group.
- Severely ill patients who are unable to understand the questionnaires.
- The patients that are registered from other PMDT site and reporting at PMDT site at the Department of Respiratory Medicine, JLN Medical College, Ajmer due to treatment related issue were also excluded from the study so that the results are not biased.

Data collection

All information to accomplish objectives was collected by personal interview of each of the study subjects for about 30 to 45 minutes at PMDT site using pre-designed and pre-tested Proforma. The Proforma contained questions for detailed history of previous anti-tuberculosis treatment including treatment cards, drug-o-gram and its side effects, adequacy of doses and combinations of drugs, addition of injection streptomycin in retreatment cases, use of quinolones before DST, empirical use of second line ATT without DST, duration of treatment, clinical outcome and radiological assessment of the disease.

Statistical Analysis

Data thus collected was entered into Microsoft excel 2010 worksheet in the form of master chart. Then data were tabulated and analysed as per the aims and objectives with help of appropriate statistical software (Primer statistical software version 6). 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.

Results

MDR TB can affect all the age groups. In the study population, 214 (74.30%) patients were in the reproductive and economically productive age group of 16-45 years. The overall male female ratio was 4.43: 1 and mean age was about 38 years. (table 1)

Majority of cases were males (n=235, 81.59%). There was significant association observed between MDR TB and male patients. (P value <0.001)

*All these 3 patients are contacts of known MDR TB patients and presented with Sputum AFB smear positive. So their sputum samples were also subjected to Molecular LPA for DST.

Case 1 was HR resistant and the index case was SHRE resistant.

Case 2 was HR resistant and the index case was HR resistant.

Case 3 was HR resistant and the resistance pattern of index case was not known.

The history of prior anti-tuberculosis medication was observed in 98.95% and it was strongly associated with development of MDR TB in our study. (P value <0.0001 considered extremely significant, Chi-square test) (table 2)

One hundred sixty three (57.19%) patients received ATT from RNTCP in our study and it also suggests that supervised treatment under RNTCP was also significantly associated with development of MDR TB. (P value <0.005 considered extremely significant, Chi-square test) Therefore we should also consider other factors regarding growth of MDR TB. Sixteen patients (5.61%) received ATT from private health facilities while one hundred four (36.39%) patients from both RNTCP as well as private health facilities. There were 2 (0.70%) patients who used other systems of medicine for TB treatment. (table 3)

In our study population, 51 (17.89%) patients received CAT-I regimen from RNTCP. 72 (25.26%) patients started their anti-tuberculosis treatment from private health facilities. There were 230 (80.70%) retreatment cases, out of them 188 (65.96%) patients received retreatment from RNTCP and 42 (14.73%) patients from private health facilities. (table 4)

Seventy nine (27.71%) patients firstly received ATT from RNTCP then from private health facilities and then they procured ATT from RNTCP. 23 (8.07%) patients received empirically second line ATT without DST from private health facilities. (table 5)

Forty three (15.08%) patients had documented evidence of use of quinolones before DST result. Fifty four (18.94%) patient's status was not known about use of quinolones as they have no documented evidence while they received ATT from private health facilities. (table 6)

The dosage of anti-tuberculosis drug taken by the patients under RNTCP or private health facilities were known for 226 patients while in 59 patients the dosage of ATT were not known. Inadequate dosage of ATT was found in 1 and 50 patients respectively under RNTCP and private health facility. The difference in proportions was statistically significant. (P value < 0.0001 considered extremely significant, Chi-square test) (table 7)

The compliance of ATT was regular in 256 (89.82%) patients, out of which 158 patient received ATT from RNTCP while 98 patients from private health facilities. Twenty nine (10.17%) patient had taken irregular ATT, out of which 4 patient taken from RNTCP and 25 patients taken from private health facilities. The difference in proportions was statistically significant. (P value < 0.0001 considered extremely significant, Chi-square test) (table 8)

The most common cause of treatment interruption in our study was social stigma (75.76%) followed by drug induced gastritis (58.62%), no improvement of symptoms (55.16%) and improvement of symptoms (37.93%).

Nine patients interrupted their treatment due to financial problem while 4 patients interrupted due to alcoholism. Three patients forget to visit at DOTS Centre and thereby default treatment. The difference in proportions was statistically significant. (P value < 0.05)

Poor adherence to anti-tuberculosis treatment was found in 112 (39.29%) patients of whom 27 patients received ATT under RNTCP while 85 patients received ATT under private health facilities. The difference in proportions was statistically significant. (P value < 0.0001 considered extremely significant, Chi-square test) (table 9)

TABLE NO. 1 AGE & SEX WISE DISTRIBUTION OF MDR TB CASES

Sr. No.	Age Band (Years)	No. of Patients			Percentage
		Male	Female	Total	
1.	<15	1	2	3	1.04%
2.	16-25	43	9	52	18.04%
3.	26-35	62	21	83	28.81%
4.	36-45	68	11	79	27.43%
5.	46-55	36	7	43	14.93%
6.	56-65	21	3	24	8.33%
7.	>65	4	0	4	1.38%
	Total	**235**	**53**	**288**	**100%**

TABLE NO. 2: PREVIOUS HISTORY OF ANTI-TUBERCULOSIS TREATMENT

Sr. No.	Previous History of ATT	No. of Patients	Percentage
1.	Yes	285	98.95%
2.	No	3*	1.04%
	Total	**288**	**100%**

TABLE NO. 3: SOURCE OF ANTI-TUBERCULOSIS TREATMENT

Sr. No.	Source of ATT	No. of Patients	Percentage
1.	Under RNTCP	163	57.19%
2.	Private sector	16	5.61%
3.	Both Govt& Private sector	104	36.49%
4.	Traditional healer	2	0.70%
	Total	**285**	**100%**

TABLE NO. 4 CLASSIFICATION OF PATIENTS AS PER HISTORY OF ANTI-TUBERCULOSIS TREATMENT AS RISK FACTOR FOR DEVELOPMENT OF MDR –TB

Sr. No	Type of ATT		No. of Patients	Percentage
1.	Under RNTCP	CAT-I regimen	51	17.89%
		Retreatment CAT-II regimen under RNTCP	188	65.96%
2.	Private sector	Private ATT only	16	5.61%
		Initially Private ATT	72	25.26%
		Retreatment Private ATT	42	14.73%
		Private ATT in between DOTS	79	27.71%
		Empirical use of 2ndLine ATT without DST	23	8.07%

TABLE NO. 5 USE OF QUINOLONES BEFORE DST

Sr. No.	Use of Quinolones	No. of Patients	Percentage
1.	Yes	43	15.08%
2.	No	188	65.96%
3.	Not Known	54	18.94%
	Total	**285**	**100%**

TABLE NO. 6 USE OF DOSAGE OF ANTI-TUBERCULOSIS DRUG DURING GOVT /PRIVATE TREATMENT

Sr. No.	Drug dosage	No. of Patients			Percentage
		Under RNTCP	Private sector	Total	
1.	Adequate	160	15	175	61.40%
2.	Inadequate	1	50	51	17.89%
3.	Not Known	1	58	59	20.70%
	Total	**162**	**123**	**285**	**100%**

TABLE NO. 7 COMPLIANCE OF ANTI-TUBERCULOSIS TREATMENT

Sr. No.	Compliance of ATT	No. of Patients			Percentage
		Under RNTCP	Private sector	Total	
1.	Regular	158	98	256	89.82%
2.	Irregular	4	25	29	10.17%
	Total	**162**	**123**	**285**	**100%**

TABLE NO. 8 PROBABLE REASONS FOR TREATMENT INTERRUPTION/IRREGULAR TREATMENT

Sr. No.	Reasons for irregular ATT	No. of Patients			Percentage
		Under RNTCP	Private sector	Total	
1.	Social stigma	2	20	22	75.76%
2.	Drug induced gastritis	1	16	17	58.62%
3.	No improvement of symptoms	0	16	16	55.16%
4.	Improvement of symptoms	3	8	11	37.93%
5.	Financial problem	0	9	9	31.03%
6.	Alcoholism	2	2	4	13.79%
7.	Forget to take ATT	1	2	3	10.34%
8.	Short term migration	1	0	1	3.44%
9.	Busy in job	0	1	1	3.44%

TABLE NO. 9 HISTORY OF DEFAULT IN PREVIOUS TREATMENT

Sr. No.	Default from previous ATT	No. of Patients			Percentage
		Under RNTCP	Private sector	Total	
1.	Yes	27	85	112	39.29%
2.	No	135	38	173	60.70%
	Total	**162**	**123**	**285**	**100%**

Discussion

We have undertaken an observational study to assess the various factors influencing development of drug resistance among 288 MDR TB patients in a tertiary care center in India, the first study to do so to date.

In the study subject, most of cases were males (n=235, 81.59%) and male sex co-relates well with MDR-TB in our study. This may be due to an increased awareness of health and increased care seeking tendency of males. It was sensed that women were more compliant with treatment and therefore less likely to receive inadequate treatment. The case-series study [10]by Pant et al in Nepal also observed that 70% (22 out of 31) of the patients were male and male sex significantly co-relates with MDR TB.

Most of the patients (n=214, 74.30%) were in the reproductive and economically productive age groups and mean age was about 38 years. In epidemiological study [11] at Ahmadabad, 83.7% (n=77) of the patients were in the reproductive age group of 16-45 years with mean age of about 34 years and these data were almost similar to our study.

Previous treatment of tuberculosis has been consistently reported as the risk factor within various clinical conditions and populations.[12, 13, 14, 15] The present study also revealed that previous treatment of tuberculosis (n=285, 98.95%) was strongly associated with MDR TB.

A reported history of previous treatment of tuberculosis, although unconfirmed, suggests that MDR-TB was acquired during a previous treatment episode; such acquired drug resistance may indicate failure of TB control efforts due to inadequate case management, interruptions in drug supply, or inadequate drug regimens. Based on the results of Gujarat, Maharashtra and Andhra Pradesh DRS Survey, estimated proportion of MDR-TB is 2.1% (1.5% - 2.7%) in New TB cases and 15% (13%-17%) in previously treated cases.[2]

A study by Faustini et al has shown that previous anti-TB treatment was the strongest determinant of MDR-TB in Europe. MDR-TB patients were more likely to have received previous tuberculosis treatment in 22 studies, with a pooled risk estimate of being 10 times higher for treated cases than for new patients. [16]Furthermore, resistance to any drug was significantly higher in the previously-treated patients. The WHO/ International Union against Tuberculosis and Lung Disease Global Project on Anti-tuberculosis Drug Resistance Surveillance reported that retreatment status was significantly associated with both MDR-TB and any drug resistance. [17]Another study revealed that the risk of MDR in people previously given TB treatment was 10.54 times higher than in those who were not given treatment.[18] A study carried out in China found that patients with a previous treatment history was more than five times likely to have an increased risk of MDR-TB (adjusted OR: 6.14, 95% CI: 4.61-8.17), compared with those previously who had not been treated.[19]Study by Barroso[20] et al also observed that about 92% (134 out of 146) of the MDR TB patients having previous history of anti-tuberculosis treatment.

About 57% (n=163) of the patients had taken ATT from RNTCP and they were also presented as MDR TB patients instead of WHO recommended highly effective supervised treatment. Therefore other factors like default, poor compliance, inadequate and inappropriate treatment may also be associated for development of MDR TB in these patients. Significantly fewer cases were managed exclusively by private physicians (n=16, 5.61%) About 36% (n=104) of the cases managed both by private physicians and RNTCP. A study by Granich et al [15] on 367 MDR TB patients observed that about 58% (n=206) of the patients managed by public health department with supervised treatment were significantly associated with MDR TB. They also observed that about 14% (n=50) of the patients managed exclusively by private physicians and about 28% (n=101) of the cases managed both by private physician and public health department and these patients were significantly associated with development of

MDR TB. These findings were almost similar to our study.

The relationship between inadequate treatment and MDR TB are so widely recognized that MDR-TB is classified as being acquired due to previous treatment if the patient has been treated before, and attributed to an initial infection with an MDR strain of M. tuberculosis if detected in newly diagnosed patients.[9]About 25% (n=72) of the patients started their anti-tuberculosis treatment from private practitioners and, the initiation of an inadequate regimen using first line anti tubercular drugs in terms of inadequate drug dosage and drug combinations and variations in bioavailability of private anti-TB drugs may predispose the patient to the development of MDR-TB.[21]

Furthermore the prescription for tuberculosis may be wrong or improper by private practitioners. A study by Prasad et al on analysis of prescription for tuberculosis by 449 doctors found that 75 % of the doctors had committed some prescription error.[22]

It was observed that about 43% (n=122) of patients received ATT from private practitioners. Major cause for default and irregular treatment in these patients was improvement of symptoms, no relief of symptoms, drug induced gastritis and financial crunch. In our study inadequate drug dosage (98%) and combination (90%) were also found in majority of the patients taking ATT from private practitioners. Furthermore poor compliance (86%) and poor adherence (75%) were also more in patients taking ATT from private practitioners. One striking finding observed that about 8% (n=22) of the patients did not believe to take free medicine for TB treatment provided by RNTCP and they preferred private practitioners for their treatment. These findings suggest that private practitioners must be motivated to refer the patients to RNTCP so as their treatment can be supervised their by preventing default and further wandering of for treatment and consequent development of drug resistance.

There were 29 (10.17%) patients interrupted and 112 (39.29%) patients defaulted to anti-tuberculosis treatment and these were significantly associated with development of MDR TB in our study. A case-control study[20] by Barroso et al observed that about 21% (28 out of 134) patient interrupted and about 27% (37 out of 134) patients defaulted to anti-tuberculosis treatment during their first treatment and these were significantly associated with development of MDR TB. They also suggested that irregular treatment was more important than defaulted treatment in development of MDR TB because there is a 7.01 risk of developing MDR-TB for cases with irregular treatments, versus a 2.73 risk for cases which defaulted on treatment. These patients should be traced and followed by health care workers as soon as possible through telephonically contact or field visits and should be asked to resume treatment accordingly.

Conclusion

MDR is strongly denting all the strategies implied by the government for the prevention and control of tuberculosis. Effective development of data pool for MDR cases is the urgent necessity to combat this creeping malady effectively. This study was an attempt to conform the before mentioned approach and it also warrants and instigates other researchers to do some qualitative research to find out other factors associated with MDR cases more candidly with exorbitant external validity.

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