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Assessment of Risk Factors in MDR TB Patients. The Reasons behind Their Admission to DOTS plus Centres. Will They Pass Through?

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ABSTRACT

Adherence to MDR-TB treatment remains a pressing public health problem to address. It requires enhanced efforts towards resolving medical problems like adverse drug effects, developing short duration treatment regimens, reducing pill burden, motivational counselling, and flexible timings for DOT services, social support, and family support for patients and improving awareness about disease. Further implementing research is needed for devising strategies to address these issues and to document practices for improvement in adherence to MDR-TB treatment. A questionnaire-based case control study amongst 50 MDR-TB cases and 25 Non-MDR TB controls was conducted. Information was collected from cases and control on a wide range of potential host related, environmental and health service related risk factors for MDR TB. The patients were interviewed using semi constructed questionnaire developed to ascertain potential risk factors. Regarding factors of non-compliance, 22 out of 50 patients were not adhered to treatment due to side effects. 19 out of 30 males, who were alcoholic, were not adhered to treatment. Distance of the health centres from the patients' home was definitely not a determinant of non-compliance. Socio economic status, occupation, migration, and literacy were also not determinants of non-compliance. Regarding the risk factors of MDR TB, out of 50 cases, 47 cases were previously exposed to TB and this is a major risk factor for developing MDR TB. 19 out of 30 males were smokers and eventually developed MDR TB and this is a major risk factor. Knowledge regarding MDR TB and DOTS Plus was significantly high amongst MDR TB patients. A perception of MDR-TB being more harmful to one's health was particularly evident among all patients and was willing to alter their lifestyles to complete this course of treatment without interruption.

Introduction

Good adherence to Tuberculosis (TB) treatment is crucial to cure patients, to limit the development of drug resistance and to reduce TB transmission in the community. For years, World Health Organization (WHO, 2006) has been recommending the

administration of drugs through directly observed therapy short course (DOTS) as a part of the control strategy.

Irregular, incomplete and inadequate treatment is the most common means of acquiring drug resistant organism. The current threat is multidrug-resistant tuberculosis (MDR- TB) due to the emergence of strains resistant to the two most potent anti-tuberculosis drugs — Isoniazid (H) and Rifampicin (R) (Sharma SK, 2004) According to the 2008 estimates, there were 440.000 cases and 150.000 deaths of MDR-TB globally. (WHO, 2010) Due to the emergence of MDRTB, the WHO developed a directly observed therapy short course (DOTS) Plus strategy in 2000. (WHO, 2011) This strategy aims at ensuring correct identification and proper management of MDR-TB patients.

In 2008, the WHO reported that the global weighted mean rate of MDR was 2.9% among new patients and 15.3% among previously treated patients. (WHO, 2008) In addition, gender, age, poor living conditions, the presence of a cavity on the patient's chest, unemployment, poor medical management of the patient's treatment, lack of directly observed treatment, abandonment of treatment, seeking initial care at a non-professional health care facility and limited or interrupted drug supplies, association with HIV/AIDS etc are found to be associated with MDR-TB. (Songhua C *et al.,* 2013)

The risk factors that had led to the development of multidrug resistance will persist and may pave the way for development of Extensive Drug resistance (XDR-TB) which is a forthcoming serious threat. XDR-TB is resistant to these first line anti-tuberculous agents, as well as to at least one Fluoroquinolone and at least one injectable agent. This phenotype emerges from MDRTB, with the acquisition of further drug resistance

mutations, and was first described in the United States followed by the Tugela Ferry outbreak. (Gandhi NR *et al.,* 2006)With this background, the present study was conducted in DOTS plus centre, Tirunelveli Medical College Hospital to explore the risk factors for development of drug resistance.

Materials and Methods

This study was conducted at DOTS PLUS centre, Department of Thoracic Medicine, Tirunelveli Medical College which covers the three districts of Tirunelveli, Tuticorin and Kanyakumari for the period of 6 months. The study protocol was carried out after approval by the Institutional Scientific and Ethics Committee.

Study population

Inclusion criteria

Men and women > 19 years of age who are newly started on Category IV anti-TB treatment at the DOTS PLUS centre.

Men and women > 19 years of age who are already on Category IV anti-TB treatment, attending the DOTS PLUS centre for follow up.

Exclusion criteria

Patients < 20 years of age
Patients too ill to be interviewed
Unwilling to participate in the study

Study Design

A questionnaire-based case control study amongst 50 MDR-TB cases and 25 Non-MDR TB controls was conducted. The source of control constituted hospital controls who are free from MDR tuberculosis i.e. sputum positive tuberculosis patients who had

undergone DOTS treatment for at least five months with negative findings on sputum microscopy. Information was collected from cases and control on a wide range of potential host related, environmental and health service related risk factors for MDR TB. The patients were interviewed using semi constructed questionnaire developed to ascertain potential risk factors. Additionally, information related to Diabetes mellitus and HIV status, was also collected.

Statistical analysis

For comparison of categorical variables, significance testing is done by Pearson chi square test and using 2-sided Fisher's exact test as appropriate. Associations between selected factors are estimated by computing odds ratios (ORs) and their 95% confidence intervals (CIs) from an unconditional logistic regression model. The criterion for significance is set at $P < 0.05$ based on a two-sided test.

Results and Discussion

Socio-demographic characteristics

A total of 50 patients who were newly started on Category IV anti-TB treatment or came for follow up at the DOTS PLUS centre, Department Of Thoracic Medicine, Tirunelveli Medical College Hospital were analysed, of which 30 were males and 20 were females. Age distribution data shows that maximum number of cases was seen in age group above 50 (Figure 1). Among the 50 cases, 5 cases had a secondary or more level of education (10%). 45 patients (90%) had less than secondary level of education. Patients who resided within the Tirunelveli Corporation limits were taken as urban population and the others as rural population. 86% of the cases from the rural areas are under treatment for MDR-TB. The type of

occupation among the study group is tabulated. Majority of them (48%) were workers and daily labourers (Table 1).

TB treatment adherence status (Table 2)

Distance

It was found that distance is a main factor for non-adherence. About 70 % (35) of MDR TB and 60% (15) of Non MDR TB patients have to walk a long distance to avail the medicine (OR 1.5556; 95% CI 0.5705-4.2414). Significant association have been found between non-adherence and distance.

Side effects

Among the MDR-TB patients, 44% (22) had side effects during TB treatment in comparison to 0% (0) of the non-MDR group (OR 40.2632; 95% CI 2.3221-698.1242). Statistical analysis showed that there is a significant association between side effects and adherence to the TB treatment.

Migration

Among the MDR-TB patients, 58% (29) migrate to distant places for work or other cause in comparison to 60% (15) of the non-MDR group (OR 0.9206; 95% CI 0.409-2.887) thus disrupting the treatment. This leads to the development of drug resistant TB (p value=0.868).

Alcoholism

Out of 30 male patients of MDR TB and 19 male patients of Non MDR TB, 19 Patients of MDR TB are alcoholic in comparison to 9 patients of Non MDR TB (OR 3.4286; 95% CI 1.0304-11.4078). During statistical analysis a strong association is shown between alcoholism and risk of becoming ill with MDR-TB (p value=0.0445). The finding of

this study showed that those with the habit of alcoholism are more likely to become ill with MDR-TB in comparison to those who are non-smokers.

Knowledge on MDR TB and DOTS PLUS

Out of 50 patients of MDR TB and 25 patients of Non MDR TB, 19 Patients of MDR TB do not have sufficient knowledge on MDR TB treatment and duration in comparison to 16 patients of Non MDR TB (OR 2.9006; 95% CI 1.0708-7.8572). Inadequate knowledge leads to the discontinuation of treatment paving way for the development of DR TB.

Missed doses of anti-TB drugs during intensive phase of previous treatment

Of 50 MDR-TB who had history of previous TB treatment, 90 % of MDR-TB patients missed dose of ATT during intensive phase. 10% of MDR-TB cases patients didn't miss anti-TB treatment during intensive phase of previous treatment.

Previous history of TB treatment

Among the MDR-TB patients, 94% (47) have previously been treated for TB in comparison to 0% (0) of the non-MDR group (OR 692.1429; 95% CI 34.3891-13930.6417). Similarly, during multivariate analysis by Pearson chi square test strong association is shown between previous history of TB treatment and risk of becoming ill with MDR-TB (p value=<0.0001). The finding of this study showed that those with history of previous TB treatment are more likely to become ill with MDR-TB in comparison to those who had no previous history of TB treatment.
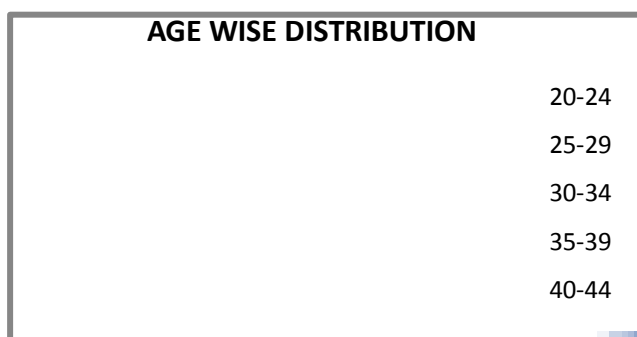
Smoking

Out of 30 male patients of MDR TB and 19 male patients of Non MDR TB, 26 Patients of MDR TB are smokers in comparison to 11 patients of Non MDR TB (OR 4.7273; 95% CI 1.1751-19, 0168). During statistical analysis a strong association is shown between smoking and risk of becoming ill with MDR-TB (p value=0.0287). The finding of this study showed that those with the habit of smoking are more likely to become ill with MDR-TB in comparison to those who are non-smokers.

Diabetes mellitus

Among the MDR-TB patients, 15 patients have previous history of diabetes in comparison to 7 patients of the non-MDR group (OR 1.1020; 95% CI 0.3810-3.1876).But analysis by Pearson chi square test shows that the development of MDR TB and previous history of diabetes mellitus is not significant (p value=0.8577).

Fig.1

AGE WISE DISTRIBUTION

20-24
25-29
30-34
35-39
40-44

Table.1 Association of socio-demographic factors with MDR-TB

Variables	MDR TB CASES N= 50		NON-MDR TB CASES N= 25 (CONTROLS)		TOTAL N=75	PERCENTAGE
	N	%	N	%	N	%
Age in years						
≤ 30	4	8%	1	4%	5	6.65
> 30	46	92%	24	96%	70	93.1
Gender						
Male	30	60	19	76	49	65.17
Female	20	40	6	24	26	34.58
Marital status						
single	13	26	5	20	18	23.94
married	37	74	20	80	57	75.81
Family size						
≤ 6	31	62	16	64	47	62.51
> 6	19	38	14	56	33	43.89
Occupation						
Employed	42	84	21	84	63	83.79
Unemployed	8	16	4	16	12	15.96
Literacy						
Literate	39	78	19	76	58	77.14
Illiterate	11	22	6	24	17	22.61
Residence						
Rural	42	84	22	88	64	85.12
Urban	8	16	3	12	11	14.63

Table.2 Comparison of the characteristics of MDR-TB and control cases

Group		MDR TB	Non MDR TB	OR (95% CI)	p-value
History of Prior Tuberculosis	Yes	47	0	692.1429	<0.0001*
	No	3	25	(34.3891-13930.6417)	
Smoking N=30 (MDR TB)	Yes	19	9	4.7273	0.0287*
N=19 (non MDR TB)	No	11	10	(1.1751-19, 0168)	
Alcoholism N=30 (MDR TB)	Yes	19	9	3.4286	0.0445*
N=19 (non MDR TB)	No	11	10	(1.0304-11.4078)	
Diabetes Mellitus	Yes	15	7	1.1020	0.8577
	No	35	18	(0.3810-3.1876)	
Distance	Yes	35	15	1.1556	0.3879
	No	15	10	(0.5705-4.2414)	
Side Effects	Yes	22	0	40.2632	<0.0001*
	No	28	25	(2.3221-698.1242)	
Migration	Yes	29	15	1.086	0.868
	No	21	10	(0.409- 2.887)	
Social stigma	Yes	27	7	2.1801	0.1550
	No	23	18	(0.7448-6.3818)	
Knowledge on MDR TB and DOTS PLUS 0.0362*	Yes	31	9	2.9006	
	No	19	16	(1.0708-7.8572)	
History of contact with TB	Yes	5	2	1.6429	0.5721
	No	35	23	(0.2935-9.1946)	

The study predominantly discussed about two factors like non-compliance and risk factors for the development of MDR TB. The fact that the distance of the health care centre from patient's home and non- adherence to treatment is not significant in the present study (p value=0.3879). Travel-related factors were major determinants of non-adherence among the newly diagnosed patients. This study found strong association between the side effects and the discontinuation of treatment (OR: 40.2632 (2.3221-698.1242); p value=<0.0001). Side effects of the drugs given in the DOTS like Vomiting, Drowsiness, and Loss of appetite are one of the major factors for non-compliance of the

patients a study from Bihar and West Bengal reported that intolerance to drugs accounted 20% of drop out cases (Chattergee *et al.,* 2003). In another study in Pakistan done by Khan *et al.,* factors, side effects of drugs in 13% cases, was the attributed cause of discontinuation of treatment (Khan *et al.,* 2004). Drug related factors like adverse drug reaction and toxicity contributed the highest role in non-compliance of tuberculosis.

The present study found that some degree of association between the improvement of symptoms and discontinuation of treatment. It is noted that the patient take the drugs for first one month properly as scheduled. Then he feels that his symptoms get improved and so he discontinues his treatment thinking that his disease is cured. A study from Bihar and West Bengal reported that improvement in symptoms as reason for 40% drop outs (Chattergee *et al.,* 2003). This study did not find strong association between the migration and non-compliance. Occupation of the patient and its related migration contributes to the discontinuation of the treatment. The inability to work due to treatment side effects, the relationship between financial constraints and having adequate nutrition, and the threat of job loss were all intertwined factors that present challenges for patients to complete treatment (O'Boyle *et al.,* 2000).

It is easy to understand that those with poor education, low income, and small living space are more susceptible to TB, because infectious disease and poverty often go hand in hand. Lack of access to the health facility to pick up medications due to distance to the facility could lead to poor adherence to treatment (Gopi *et al.,* 2007). There was the association between having an alcohol drinking habit and having MDR TB. Most interviewed patients themselves did not note alcohol addiction as a factor for not adhering to treatment but alcohol abuse was expressed

as a major barrier to treatment adherence noted by their providers and attenders. In a multivariable analysis, alcohol consumption during treatment was found to be the strongest predictors of poor treatment outcome for MDR TB (Fleming *et al.,* 2006).

Literacy of the community plays a great role in the development of MDR TB. Kaona *et al.,* in their study on assessment of factors contributing to TB treatment adherence in Ndola, Zambia showed that feeling well was the major reason for patient stopping treatment (Kaona *et al.,* 2004). Educational status had a positive impact on adherence. Possible explanations for such findings include, as the level of education increases, the understandings about the importance of adherence to treatment increases. But we did not find any significance between literacy and the compliance.

Majority of patients in the present study belonged to the older age group (more than 30 years), of which 32 cases were than 50 yrs. of age group. The risk of MDR-TB has been seen to be higher among elderly individuals (age > 45 years) by Kimerling and colleagues (Kimerling *et al.,* 2003). Of the 50 MDR TB cases 30 cases (60%) were males and 20 cases (40%) were females. Of the 25 controls 19 (76 %) were males and 6 (24%) were females. Gender difference was not found to be a significant risk factor for the development of drug resistance in the present study. Studies in Western Europe and the Samara region of Russia revealed that males had a significantly higher risk of MDR-TB (Ruddy *et al.,* 2005).

In the current study, association between social stigma and having MDR TB was high with OR 2.1801 (95% CI 0.7448-6.3818) (p=0.1550), though not significant. Social stigma and lack of scientific awareness about the disease and social commitments are stated reasons for interrupting and defaulting TB

treatment. This study revealed that previous treatment of tuberculosis was strongly associated with MDR TB; OR =692.1429 (95 % CI 34.3891-13930.6417) (p=<0.0001). The prevalence of drug resistance in previously treated cases was higher than new cases for each drug alone as well as for all six drugs, as reported previously (Zhao *et al.,* 2012; Yu *et al.,* 2010; Shao *et al.,* 2011). This suggests that retreatment is deficient and poses a threat to continued transmission, which has not yet manifested itself among new patients although three of the MDR patients failed to reveal the previous treatment particulars.

The present study revealed that the association between having a history of smoking and MDR TB was significant with OR 4.7273 and 95%CI ranging from 1.1751-19, 0168 (p=0.027). We found smoking to be positively associated with non-adherence, and hence to drug resistance amongst the MDR TB patients. Cigarette smoking had been shown to be associated with interruption with treatment similar to findings in Turkey and India although the mechanism is not well understood (Balbay *et al.,* 2005; Bagchi *et al.,* 2010). This study had no significant association between Diabetes and TB (OR 1.120 and CI ranging from 0.3810-3.1876, p value=0.8577). There is growing evidence that Diabetes mellitus is an important risk factor for TB and might affect disease presentation and treatment response (Dooley and Chaisson, 2009; Alisjahbana *et al.,* 2007).

Tuberculosis remains an important problem in Human immunodeficiency virus (HIV) infected patients worldwide. In the present study none of the cases and controls had HIV infection, hence it was unable to assess the significance of HIV as a risk factor. Literature suggests that, appropriate management of HIV-associated TB remains extremely challenging due to diagnostic difficulties, adherence concerns, the overlapping drug side effects, drug-drug interactions, and the occurrence of immune reconstitution inflammatory syndrome. Concomitant treatment also leads to a higher pill burden this may lead to poorer adherence among these patients. Poor adherence to anti-TB drugs can lead to an increased risk of drug resistance, including multi-drug and extensively drug resistant TB, which is difficult to treat and contribute to increased mortality (Padmapriyadarsini, 2011). But we could not suggest anything related to this issue since all the patients in our study are non-HIV patients.

Smoking and alcoholism are major risk factor and determinant of non-compliance to treatment respectively, in the treatment of MDR TB. Though these two factors are modifiable by the patient himself, this study highlights other two important factors- Side effects of the treatment and previous TB exposure as a determinant of non-compliance and the latter a potential risk factor for developing MDR TB. Unfortunately these two factors are non-modifiable. Thereby, this study concludes that the patients on DOTS plus treatment for MDR TB, due to the side effects of drugs and the previous TB exposure, have a risk of developing further drug resistance.

Acknowledgement

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