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Original article:

Various clinical risk factors influencing development of drug resistance among multidrug resistant tuberculosis patients

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ABSTRACT

Introduction: Tuberculosis has been a major cause of suffering and death since times immemorial, thought to be one of the oldest human diseases. Multidrug Resistant Truberculosis (MDR-TB) has emerged as a significant global health concern. Aim: To assess the various Clinical Risk Factors Influencing Development of Drug Resistance among Multidrug Resistant Tuberculosis patients. Method: It was a hospital basded observational study carried out from 1st June, 2015, to completion of 100 diagnosed cases of Multidrug Resistant Pulmonary Tuberculosis at PMDT site at Department of Respiratory Medicine, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner. Results: The overall male female ratio was 3:1 and mean age was about 39 years, 79% were rural, 56% had addiction history, 66% patients had per capita income <3000, 61% patients were illiterate. The prior anti-tuberculosis medication, inadequate dose, compliance to ATT, default in previous treatment, wrong categorization were strongly associated with development of MDR TB in our study. (P value <0.0001). Conclusion: Development of drug resistance in tuberculosis patients in our study is the result of a complex web of biomedical, socio-cultural and behavioral interactions, and the reporting of individual risk factors would be an oversimplification.

Keywords: Multidrug Resistant Truberculosis, Risk Factors.

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 effect diagnostic, preventive and curative strategies, remains as the second leading cause of death from an infectious agent worldwide, after the human immunodeficiency virus (HIV).[2] Multidrug Resistant Truberculosis (MDR-TB) has emerged as a significant global health concern.[3,4] There are alarming reports of increasing drug resistance from various part of globe which potentially threaten to disrupt the gains achieved in truberculosis (TB) control over the last decade.[5] Globally, 3.7% (2.1 - 5.2%) of new cases and 20% (13-26%) of previously treated cases are estimated to have MDR-TB. By the end of 2011, India and the Russian Federation, which combined with China, contribute to almost 60% of the estimated global burden of MDR-TB.[2] In India 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 proportion of MDR-TB are

lesser in India.[2] DRS survey have show that there is no XDR amongs new cases and the prevalence amongs re-treatment cases is 0.5%. The prevalence of XDR among MDR-TB patients was estimated 3.2% (95% CI, 1.2-6.6%).[6] The drug resistant tuberculosis results largely from a poorly managed case of TB.[6] Drug-resistant TB has microbial, clinical, and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug infective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutant to become the dominant strain in a patient infected with TB. However it should be stressed that MDR-TB is a man-made phenomenon- poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.[7] Previous treatment for TB is the strongest risk factor for development of MDR-TB (4-7 times).[8] Adherence to long terms therapy is a multidimensional phenomenon determined by the interplay of five sets of factors (dimensions) namely; social and economic factors, health care team and system related factor, condition related factor, therapy related factors and patients related factors.[9]

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. Thus we planned this study to analyze the various factors influencing development of drug resistance among MDR-TB patients attending PMDT site at Department of Respiratory Medicine, S.P. Medical College & Associated Group of Hospitals Bikaner, Rajasthan.

AIM

To assess the various Clinical Risk Factors Influencing Development of Drug Resistance among Multidrug Resistant Tuberculosis patients.

METHOD

It was a hospital based observational study carried out for 1 year started from june 2015 in which 100 diagnosed cases of Multidrug Resistant Pulmonary Tuberculosis were included attending at PMDT site at Department of Respiratory Medicine, Sardar Patel Medical College and Associated Group of Hospitals, Bikaner. Approval from institutional ethical committee was obtained for the thesis. The severely ill patients and that are registered from other PMDT site were excluded.

The confirmed cases of Multidrug Resistant Pulmonary Tuberculosis patients from various Tuberculosis Unit under PMDT site, Bikaner reporting to the DOTS Plus site Committee along with their DST result and PMDT referral for treatment form and after decision of DOTS Plus site Committee they were admitted for Pre-treatment Evaluation in the MDR ward at the Department of Respiratory Medicine, S.P. Medical College, Bikaner.

All these patients were clinically examined in detail in the indoor patient department of our hospital and following routine investigations were done as mentioned in guidelines. 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 questions were design to evaluate all three possible aspects of development of drug resistance i.e. patient related, drug related and health care and system related aspects. These questions were asked to establish demographic and social characteristics, housing environment, health service experience, clinical characteristics, knowledge about TB/MDR-TB, and self-reported reason for defaulting.

RESULTS

Highest number of patients (38%) were from Ganganagar whereas 21% in Bikaner and Churu and minimum 20% in Hanumangahr. However there was no association observed between development of MDR tuberculosis and geographical distribution of the patients. The overall male female ratio was 3:1 and mean age was about 39 years. Most of the patients were farmer (32%) followed by manual laborers (14%) and minimum working in cotton factory (1%). 61% patients were illiterate, was found to be significantly associated with development of MDR TB in our study ($p < 0.0001$).

Table 1

Age Band (Years)	**No. of Patients**		**Percentage**
	Male	**Female**	
<15	0	2	2%
16-25	14	7	21%
26-35	21	10	31%
36-45	17	1	18%
46-55	8	4	12%
56-65	15	1	16%

70% patients were in the reproductive and economically productive age group of 16-45 years. Majority were male and had significant association ($p <0.001$). Most of the patients (79%) were from rural set up. majority of patients (34%) belonged to lower middle economic class of Agarwal's Classification. Total 66% patients belonged to the poor economic class ($P < 0.0001$). Twenty Four patients gave history of contact with a confirmed case of TB before they themselves got affected by TB. In such cases, 15(62.5%) were from family members followed by relatives 5 (20.83%), Household Neighbors 2 (8.33%) followed by Friends and Work place person 1 (4.16%). Fifty six patients (56%) had history of addiction and it was observed significant association of MDR TB with addiction habit ($P < 0.001$). Smoking induced co-morbid conditions such as COPD was found in most of the cases (25%). HIV/AIDS association was found in only 1% patients. History of prior anti-tuberculosis medication was observed in 99% (P value <0.0001). Fifty Nine patients (59.59%) received ATT from NRTCP in our study and it also suggests that supervised treatment under RNTCP was also significantly associated with development of MDR TB ($P < 0.005$). In our study population, 14(14.14%) patients received CAT-I regimen from RNTCP.13 (13.13%) patients started their anti-tuberculosis treatment from private health facilities. There were 86 (86.86%) retreatment cases, out of them 79 (79%) patients received retreatment from RNTCP and 7 (7.07%) patients from private health facilities. 19 (19.19%) patients had documented evidence of use of quinolones before DST results. There were 86 retreatment cases, out of which 69 (80.23%) case received injection streptomycin as single drug addition to previous anti-tuberculosis

treatment. DST results on Molecular LPA available for 34 patients. Out of 34, 24 (70.6) patients were HR resistant and 10 (29.4%) were Rifampicin Monoresistant.

S. No.	Possible Factors Responsible for Development of Drug Resistance		No. of patients	Percentage
1.	Previous History of ATT		99	99%
2.	Socio demographic factors N=99	Rural Population	79	79.79%
		Male sx	75	75.75%
		Age group (16-45 years)	70	70.70%
		Poor Economic Class	66	66.66%
		Illiteracy	61	61.61%
		History of Addiction	56	56.56%
3.	Patients related factors N=99	Default	43	43.43%
		Lack of enough knowledge about tuberculosis	42	42.42%
		Drug induced gastritis	17	17.17%
		Poor compliance	9	9.9%
		Lack of faith on free medicine	7	7.7%
4.	ATT Under RNTCP N=99	Retreatment CAT-II Regimen	79	79.79%
		CAT-I Regimen	14	14.14%
5.	ATT from Private Sector N=99	Private ATT in between DOTS	24	24.24%
		Retreatment Private ATT	21	21.21%
		Use of Quinolones	19	19.19%
		Initially Private ATT	13	13.13%
		Empirical use of 2nd Line ATT	8	8.8%
		Only Private ATT	6	6.6%
6.	Physician's errors in prescriptions of ATT N=99	No use of Injectable Streptomycin in Retreatment Regimen	69	69.69%
		Wrong categorization of ATT under RNTCP	10	10.10%
		Inadequate drug dosages	7	7.7%
7.	Contacts of TB Cases N=100	Possibly Contact with MDR TB Case	23	23%
		Contact of Known MDR TB Case	1	1%

8.	Associated Co-morbid conditions N=100	DM-2	4	4%
		HIV/AIDS	1	1%
9.	N = 100	Genetic Basis of M. tuberculosis	39	39%

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 our study, the ganganagar is district comprise highest no of patients (38%). In the study subject, most of cases were males (75%) 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. The case-series study by Pant et al in Nepal also observed that 70% of the patients were male and male sex significantly co-relates with MDR TB.

Most of the patients (70%) were in the reproductive and economically productive age groups and mean age was about 38 years. In epidemiological study [10] at Ahmadabad, 83.7% 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.

Around 51% of patients were addicted to tobacco and/or alcohol any time during their disease state. An epidemiological study in Ahmedabad also showed that around 57% of MDR TB patients were addicted to tobacco and/or alcohol.[10] Studies in Russia showed alcohol abuse/dependence[11] and smoking were associated with drug resistance.

Dual addiction with alcohol and smoking was observed in 27% patients in our study. A case-control study[12] by Barroso et al suggested that 39% of the patients with dual addition of smoking and alcohol were associated with development of MDR TB.

About 66% an overwhelmingly large number of the patients in our study were from lower economic class Furthermore more than half of the patients (61%) were illiterate. The case-series study by Pant et al in Nepal observed that about 87% of the patients belonged to lower socioeconomic class and about 77% of the patients were illiterate. However the European meta-analysis found no linkage between low socioeconomic class or literacy and MDR.[8] In a study in Turkey however, patient's education and MDR TB were found to be inversely related.[13]

As more than 2/3rd of patients belonged to lower economic classes, the nutrition status might be poor in these patients and studies suggested[14] that malnourished patients have delayed recovery and higher mortality rate when compared to well-nourished patients. Furthermore tuberculosis itself causes anorexia leading to decreased food intake, malabsorption, anabolic block and wasting. These chronic patients may be a source of infection for others. Studies suggested that the prolonged infectiousness of patients in the community remains a hurdle to the success of the tuberculosis control programme.[15,16,17]

In our study, most of the patients (79%) belong to rural area where approach by health care workers was difficult in tracing of MDR suspect patients and collection of sputum sample and then the transportation of sputum to IRLs, CBNAAT for DST. This whole procedure was time consuming and during this period the fate of patient was unknown. Studies suggested that the average time delay for processing the sputum sample and getting back the DST

results is at least 3 months.[18] During this time patients may be inappropriately treated, drug resistant strain may continue to spread, amplification of resistance may occur and patient may even die while waiting for DST results but now due to incorporation of CBNAAT there is much more possibilities to detect patient at risk of MDR .

About 24 (n=24) patients showed the history of contact with TB case and most of them were family members (n=15, 62.5%) showing the fact that. TB usually spread with close contacts. An epidemiological study[10] in Ahmadabad observed positive history of contact with TB case in about 50% patients. Most of them were also among family members and treatment outcome was death in 60% of cases which was similar to our study.

The present study also revealed that previous treatment of tuberculosis (n=99, 99%) was strongly associated with MDR TB. Similarly study by Faustini et al has shown that previous anti-TB treatment was the strongest determinant of MDR-TB in Europe. 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.[17] " 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[12] et al also observed that about 92% (134 out of 146) of the MDR TB patients having previous history of anti-tuberculosis treatment.

About 59% (n=59) 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. A study by Granich et al[20] 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.

About 6% (n=6) 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." 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.[21]

In our study inadequate drug dosage (99%) and combination (60%) 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 7.7% (n=7) 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 9 (9.9%) patients interrupted and 43 (43.43%) patients defaulted to anti-tuberculosis treatment and these were significantly associated with development of MDR TB in our study. A case-control study 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.

improvement of symptoms were the most common cause of default (76.7%) and irregular (88.88%) treatment in our study. social stigma is second most common cause of irregular treatment(66.66%). A pilot study[22] by Marahatta et al observed that about 62% (34 out of 55) of the patients interrupted or default their treatment due to social stigma and social commitments and suggested that social stigma significantly associated with MDR TB.

Our study reveals that patients with ATT induced gastritis (n=17, 39.5%) were put on only isoniazid and ethambutol with or without injectable streptomycin without supervision till gastritis subside. This inadequate and unsuccessful treatment may lead to development of drug resistance.

About 20% (n=17) of retreatment cases in our study did not receive injection streptomycin and about 10.1% (n=10) of patients were put on CAT-I ATT instead of CAT-II ATT for retreatment. Inadequate drug dosage and inadequate drug combination were observed in about 7.7% (n=7) and 15.15% (n=15) cases respectively mostly in the patients taken ATT from private health facilities. These physician's related errors may contribute in development of drug resistance. Professor Michael Iseman, the US "guru" of MDR-TB, has shown that two to four errors are needed to turn a fully susceptible organism in to a case of MDR-TB.[23]

In our study, the documented evidence of previous use of quinolones and injectable agents (other than streptomycin) were observed in 19.2% (n=19). Astudy by Deutschendorf C et al suggested that previous quinolone use was significantly associated with first-line anti-TB drugs resistance.[24]

Smoking induced co-morbid condition such as COPD was found in 25%(n=25) cases and these co-morbid conditions may be due to sequels of tuberculosis. Study by Barroso[12] et al found COPD in 12 (9%) MDR TB patients and observed that COPD did not increases risk for MDR TB.

Diabetes patients constituted about 4% (n=4) of cases in our study and diabetes is known for immunosuppressive condition. Diabetes patients constituted about 4% (n=4) of cases in our study and diabetes is known for immunosuppressive condition.

Only 1 (1%) out of the 100 patients in our study were positive for HIV. The number fits with findings elsewhere- a Peruvian study also found only 1.5% of MDR TB patients to be infected with HIV.[50] Similar results were found in drug resistance survey [25] in Donetsk Oblast, Ukraine in 2006 and the case-series study by[11] Pant et al in Nepal that positive HIV status was an independent predictor for MDR-TB.

About 42.42% (n=42) of the patients were unaware about tuberculosis and the programs. A pilot study[22] by Marahatta et al also observed that about 51% (28 out of 55) of the patients were unaware about tuberculosis and its treatment and suggested that lack of enough knowledge about tuberculosis and the programme were significantly associated with development of MDR TB. Given the kind of living condition the patients have, they can easily be a source of infection to their family members. Therefore disclosure and positive prevention have an important role in the preventing further transmission. Furthermore family support is crucial if these patients are to satisfactorily complete their treatment, thereby preventing the development of MDR and XDR TB. There is enough scope for better counseling and surveillance so that these patients do not transmit their infection to others.

CONCLUSION

Development of drug resistance in tuberculosis patients in our study is the result of a complex web of biomedical, socio-cultural and behavioral interactions, and the reporting of individual risk factors would be an oversimplification. Health care worker ignorance, the wide misuse of TB drugs, lack of laboratory standardization and delay in laboratory results, all contribute to the emergence of drug resistance. Drug resistance has emerged as a major cause of failure of anti-tubercular therapy. The risk of infection with resistant Mycobacteria is increasing, posing a threat to control and eradication of this disease. Unless effective step are taken to treat and limit resistance, it may soon assume alarming proportions.

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