

## To Study the Pattern of Drug Resistance in Microbiologically Confirmed Cases of Tuberculosis and Risk Factors Associated with Drug Resistance

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### Abstract

### Original Research Article

This is an observational prospective study, which included 200 microbiologically confirmed cases of tuberculosis (TB) which came to outpatient department or got admitted in the wards. Clinico-diagnostic profile of these cases was determined. The collected data were documented, compiled, tabulated and statistically analysed to reach a valid conclusion. Out of 200 microbiologically confirmed cases of TB, 25% of the cases were in the age group of 21-30 years, 147 (73.5%) were drug susceptible (DS) and 53 (26.5%) were drug resistant (DR). Amongst DR-TB cases, 21 (18.7%) were new and 32 (36.4%) were previously treated cases. Rifampicin mono-resistance was higher in both new (47.6%) and previously treated (37.5%) drug resistance cases. The majority of the patients with DR-TB had previous history of ATT i.e., (p value <0.5). Risk factors associated with DR-TB are female gender and previous history of Anti-tubercular therapy (ATT) (p value <.05).

**Keywords:** Drug resistant Tuberculosis; Mycobacterium tuberculosis; Anti-tubercular therapy; Rifampicin.

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## INTRODUCTION

Tuberculosis remains a worldwide public health problem despite the fact that the causative organism was discovered more than 100 years ago [1]. Emergence of drug resistance has further worsened the situation and has become a significant health problem world over creating an obstacle to effective tuberculosis control as the treatment is much more toxic and much more expensive than the one of patients with sensitive organisms [2].

The burden of DR-TB is of major interest and concern at global, regional and country levels. In 2018, there were approximately half a million (range, 417 000–556 000) new cases of rifampicin-resistant TB (RR-TB) of which 78% had MDR-TB. The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (9%). Globally, 3.4% of new TB cases and 18% of previously treated cases had MDR/RR-TB, with the highest proportions (>50% in previously treated cases) in countries of the former Soviet Union. Currently, the WHO estimated incidence of R and MDR TB in India is estimated to be around 130 000. This translates to around 9.6 patients per 100 000 population annually as per the Global TB Report, 2019 [3].

MDR-TB mirrors the functional state and efficacy of tuberculosis control programs and realistic attitude of the community towards the implementation of such programs in the country [4]. Good treatment is pre-requisite to the prevention of emergence of resistance. India has one-fifth of the world's multidrug resistant tuberculosis burden- the largest number for any country globally after China [6]. MDR-TB is a man-made phenomenon- Poor treatment, poor drugs and poor adherence lead to the development of MDR-TB [5].

Most of the studies found that cavity was the most common radiological lesion of multidrug resistant tuberculosis patients on chest x-rays. The limited drug penetration into the cavity that harbor large mycobacterial load and a greater number of Acid fast bacilli (AFB) in moderately advanced or far advanced disease is believed to contribute to drug resistance [6].

The treatment of DR-TB is extremely challenging owing to the complexity of chemotherapy regimens, the toxicity of alternative drugs, and the high cost of these drugs. Therefore, it is particularly important to identify the risk factors associated with DR-TB. Judicious use of drugs, supervised individualized treatment, focused clinical, radiological and bacteriological follow up, use of surgery at the

appropriate juncture are key factors in the successful management of these patients.

This research is believed to contribute to the pattern of drug resistance and to identify the potential risk factors for DR-TB, so that the management of patients will also be strengthened through preventing these factors, alongside patient treatment which will have a positive impact on the successful treatment outcome, and decrease the burden of the disease as a whole.

## MATERIALS AND METHODS

This study was carried out in the Department of Chest and Tuberculosis, Government Medical College, Amritsar. This is an observational prospective study, which included 200 microbiologically confirmed cases of tuberculosis, which came to outpatient department or got admitted in the wards over a period of 18 months. The approval of institutional thesis and ethics committee was taken before the start of the study. Participants who met the inclusion criteria was recruited after giving information regarding the study in their vernacular language and written informed consent was obtained.

### Inclusion Criteria

- All consenting new and previously treated microbiologically confirmed cases of tuberculosis of any age and gender visiting chest and TB hospital Amritsar was included in the study.

### Exclusion Criteria

- Patients with tuberculosis not confirmed by microbiology.
- Critically ill / moribund patients.
- Patients not willing to participate in the study.
- Patient not capable of giving consent (psychiatric patient).

All diagnosed Patients of MDR-TB referred to DR-TB-Centre were admitted for Cat-IV treatment under the programmatic management of drug-resistant tuberculosis (PMDT)- revised national tuberculosis programme (RNTCP) in directly observed treatment, short course (DOTS) Plus ward, department of TB & Chest, Government Medical College, Amritsar for pre-treatment evaluation for a minimum duration of seven days. The protocol was clearly explained to the patient/care provider before enrolment and informed consent was taken from each patient. A pre-structured proforma will be filled in those cases which are included in the study.

- Detailed clinical history and clinical examination.
- Complete blood count.
- Blood sugar to screen for diabetes mellitus.
- Liver function test.

- Blood urea and serum creatinine to assess the Kidney function test.
- Urine examination- routine and microscopic.
- Pregnancy test (for all women in child bearing age group).
- Chest X-ray.
- All DR-TB cases will be offered a referral for human immunodeficiency virus (HIV) counselling and testing at the nearest center if the HIV status is not known or the HIV test is found negative with results more than 6 months old. If the patient is HIV positive, he /she will be referred to anti-retroviral therapy (ART) centre (if not on ART).

Demographic characteristics, socioeconomic status, complete detailed clinical history regarding total duration of illness, smoking history, drug/alcohol abuse, mental illness, diabetic history, previous anti tuberculosis therapy, family history of anti- tuberculosis therapy and any contact with tuberculosis patients will be taken from the patients. All sputum positive patients will be subjected to chest radiograph.

The collected data was documented, compiled, tabulated and statistically analysed to reach a valid conclusion.

## RESULTS

In our study, out of 200 patients taken for the study maximum number of patients were present in the age group of 21-30 years i.e. 25%. Mean age was 40.15 years. There was an overall male preponderance in the study with 60% being males, 40% being females. 110 (55%) patients were from urban population and 90 (45%) patients belonged to rural areas.

Most of the patients were Laborers 63 (31.5%). The most common symptom was cough with expectoration which was present in 185 (92.5%) of cases followed by fever, which was present in 155 (77.5%) cases. Pallor, clubbing and lymphadenopathy were present in 155 (77.5%), 37 (18.5%), 46 (23%) of the patients respectively. 33 (16.5%) patients were Diabetic, 6 (3%) were diagnosed cases of HIV. Most common addiction was smoking present in 79 (39.5%) of study subjects, followed by alcohol which was present in 72 (36%) of the cases. 87 (43.5%) patients were having a previous history of ATT, 113 (56.5%) patients were not having any previous history of ATT. History of exposure was present in 50 (34%) cases in drug susceptible cases and 16 (30.1%) in drug resistant cases.

147 (73.5%) were drug susceptible and 53 (26.5%) were drug resistant. Total no. of new and previously treated cases were 91 (82.1%) and 56 (63.6%) in drug susceptible and 21 (18.7%) and 32 (36.4%) in drug resistant cases.

Out of 21 drug resistant new cases, 10 (47.6%) patients were Rifampicin mono resistant, 5 (23.8%) were multi-drug resistant, 4 (19%) were isoniazid resistant and 2 (9.5%) were rifampicin plus fluoroquinolone resistant. Among 32 previously treated drug resistant cases, 12 (37.5%) patients were Rifampicin mono resistant, 9 (28.1%) were multi-drug resistant, 5 (15.6%) were isoniazid mono resistant 4 (12.5%) were rifampicin plus fluoroquinolone resistant, 1 (3.1%) each of extensive drug resistant and isoniazid plus fluoroquinolone resistant ( p value >.05 which is not significant).

Majority of the patients 83 (56.4%) has unilateral disease in drug susceptible cases and bilateral disease 23 (43.4%) in drug resistant cases. Among drug susceptible cases, 37 (25.1%) patients were having minimal disease 53 (36%) and 48 (32.6%) patients were having moderate and far advanced disease respectively. Among drug resistant cases, 5 (9.4%) were having minimal disease, 8 (15.1%) and 38 (71.7%) patients were having moderate and far advanced disease. Risk factors associated with drug resistance TB are female gender and previous history of ATT (p value <.05) while other factors such as age less than 40 years, contact history, HIV status, smoking and alcoholism are not associated with Drug resistance TB.

## DISCUSSION

There were total of 200 microbiologically confirmed cases of TB, which included 194 sputum positive, 1 broncho-alveolar lavage (BAL) and 5 others (pleural fluid, pleural pus, fine needle aspirate) who were detected through smear microscopy and molecular methods i.e. line probe assay (LPA) or cartridge based nucleic acid amplification (CBNAAT). We evaluated patterns of drug resistance in these cases and risk factors associated with drug resistance.

There were 120 males and 80 were females in our study (Table-1) Peter *et al.*, [7] and Fandinho *et al.*, [8] have also reported male to female ratio of 1.8:1 and 1.6:1 respectively. This may be due to our male dominating society in which males have more access to health facilities as compared to female. Out of 200 patients, 110 (55%) patients were from urban population and 90 (45%) patients belonged to rural areas. Study by Kliiman *et al.*, also showed that 61.7% patients were from urban areas and 38.3 % patients were from rural areas [9]. Among the urban population narrow living spaces, poorly ventilated houses, overcrowding and unhealthy food habits could be cause of tuberculosis.

In our study most of the patients were laborers (31.5%). Laborers belong to lower socioeconomic status and as we know tuberculosis affects especially those from lower socioeconomic background. Poverty could be a major predisposing factor, ranging in them

from poor overall hygiene, poor living conditions, poor nutrition and immune status.

Among 200 patients taken in the study, the most common symptom was cough with expectoration present in 92.5% of cases followed by fever in 77.5%. Breathlessness was present in 77.5%. Loss of appetite was present in 66% and weight loss was present in 45% of patients and hemoptysis in 10% of cases. Among drug susceptible cases history of contact with pulmonary TB case was present in 44 (29.9%) and MDR-TB case in 6 (4.1%) of the study subjects. Among drug resistant cases history of contact with pulmonary TB case was present in 12 (22.6%) and MDR-TB case in 4 (7.5%) of the study subjects.

Most common drug addiction in our study was smoking present in 79 (39.5%) of study subjects, followed by alcohol, which was present in 72 (36%) of the cases. Study done by Mishra *et al.*, [10] also reported that smoking was commonest drug addiction followed by alcohol. HIV positive patients in our study were 6 (3%) and the rest were HIV negative. 33 (16.5%) were diabetic and 167 (82.5%) were non diabetic. Diabetes was commonest comorbidity. Among other comorbidities after diabetes COPD was commonest comorbidity. COPD present in 14 (7%) which was smoking related, followed by Hypertension in 10 (5%), Hypothyroidism and depression in 3 (1.5%).

Out of 200 patients 147 (73.5%) were drug susceptible and 53 (26.5%) were drug resistant in our study. Total no. of new and previously treated cases were 91 (82.1%) and 56 (62.5%) in drug susceptible and 21 (18.7%) and 32 (36.4%) in drug resistant cases. Out of 21 drug resistant new cases, 10 (47.6%) patients were Rifampicin mono resistant, 5 (23.8%) were multi-drug resistant, 4 (19%) were isoniazid resistant and 2 (9.5%) were rifampicin plus fluoroquinolone resistant. Among 32 previously treated drug resistant cases 12 (37.5%) patients were Rifampicin mono resistant, 9 (28.1%) were multi-drug resistant, 5 (15.6%) were isoniazid mono-resistant 4 (12.5%) were rifampicin plus fluoroquinolone resistant, 1 (3.1%) each of extensive drug resistant and isoniazid plus fluoroquinolone resistant (Table-2).

Findings similar to our study were reported by Dr. Nirmalya Manna, 53.7% patients were found to be resistant to Rifampicin only, 46.3% to both Rifampicin and Isoniazid [11]. In our study, out of 53 drug resistant cases majority 32 (60.4%) cases have previous history of ATT (p value <.05). A study done by Sudhakar W. more reported out of 86 cases, the majority of the patients with drug-resistant TB had acquired drug resistance, i.e., 66 (68.75%) [12].

Our study also showed that females were affected more than males in MDR-TB Cases (p value <.05). The reasons for the association between female

and MDR-TB might be related to the fact that women spend more time caring their family members with MDR- TB both in households and healthcare settings. Previous history of treatment was present in 55 (37.4%) cases in drug susceptible and 32 (60.4%) in drug resistant cases (p value <.05 which is statistically significant). Risk factors associated with drug resistance TB are female gender and previous history of ATT (p value <.05) while other factors such as age less than 40 years, contact history, HIV status, smoking and alcoholism are not associated with Drug resistance TB (Table-3).

The majority of the patients 83 (56.4%) has unilateral disease in drug susceptible cases and bilateral disease 23 (43.4%) in drug resistant cases. Among drug susceptible cases, 37 (25.1%) patients were having minimal disease 53 (36%) and 48 (32.6%) patients were having moderate and far advanced disease respectively. Among drug resistant cases, 5 (9.4%) were having a minimal disease, 8 (15.1%) and 38 (71.7%) patients were having moderate and far advanced disease. Another retrospective cross-sectional study done by Icksan *et al.*, [13] which compares chest X-ray findings of two groups of patients, involving 183 DS-TB patients and 183 MDR-TB patients. MDR-TB group have 177 (96%) patients with large lesions, 6 (4%) with medium lesions, and no small lesions. DS-TB group have 55 (30%) patients with small lesions, 78 (43%) with medium lesions, and 50 (27%) with large lesions.

## CONCLUSION

The prevalence of drug resistance was found to be high in previously treated patients as compared to new cases. Risk factors associated with DR-TB are female gender and previous history of ATT (p value <.05) Immediate therapeutics and more surveillance are necessary to combat the threat of DR-TB. Knowledge of drug resistance patterns for new and previously treated cases and risk factors associated with drug resistance are critical for effective control of MDR-TB in different regions of the country. Prompt and accurate detection of drug resistance will be critical to timely initiation of treatment hence prevent further transmission and allows selection of a drug regimen to which the infecting strain is susceptible.

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