DOI: https://doi.org/10.53350/pjmhs21155959

**ORIGINAL ARTICLE**

# Frequency of Pre-Extensively Drug Resistant Tuberculosis and Extensively Drug Resistant Tuberculosis in Patients with Multi Drug Resistant Tuberculosis

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## ABSTRACT

**Aim:** To determine the frequency of pre-extensively drug resistant tuberculosis, extensively drug resistant tuberculosis in patients with multi-drug resistant tuberculosis.
**Study design:** Retrospective/observational
**Place and duration of study:** Department of Medicine, Bolan Medical College Quetta from 1st July 2019 to 31st December 2020.
**Methodology:** One hundred and eighty patients of both genders presented with multi drug resistant tuberculosis were enrolled in this study. Patient's detailed information including age between 20-70 years, sex, body mass index were recorded. Sputum samples were taken from all the patients and then drug sensitivity testing (DST) for 1st and 2ndline drugs. Frequency of pre-XDR TB and XDR tuberculosis were recorded.
**Results:** There were 100 (55.56%) males and 80 (44.44%) patients were females and mean age was 37.38±10.75 years. Mean body mass index was 24.18±2.41 kg/m$^2$. Among all the multi-drug resistant tuberculosis patients, pre extensively drug resistant tuberculosis was found in 62(34.44%) patients and extensively drug resistant tuberculosis was found in 8(4.44%) patients. All 62(100%) patients of pre-XDR tuberculosis were resistant to fluoroquinolone while among XDR tuberculosis patients 4 were resisted to amikacin, 2 were resisted to kanamycin and fluoroquinolone, 1 patient was resisted to amikacin and kanamycin.
**Conclusion:** Frequency of pre-extensively tuberculosis among multi drug resistant tuberculosis was high while only 4% patients had extensively drug resistant tuberculosis.
**Keywords:** Tuberculosis, Multi-drug resistant, Pre-extensively drug resistant, Extensively drug resistant

## INTRODUCTION

Tuberculosis is one of the leading infectious diseases in the world and is responsible for more than two million deaths and nine million new cases annually. World Health Organization (WHO) statistics for 2013 giving an estimated incidence figure of 2.1 million cases of TB for India out of a global incidence of 9 million. The estimated TB prevalence for 2013 is 2.6 million[1].

In the 2018 update of the World Health Organization (WHO) treatment guidelines for multidrug- and rifampicin-resistant TB (MDR-/RR-TB),[2] Some medicines of the anti-TB injectable group (kanamycin and capreomycin) were deleted from the list of recommended DR-TB drugs, and only amikacin (Am) and streptomycin (S) were retained. These latter drugs have been placed lower in the hierarchy (to Group C from Group B previously) to be considered only if drug susceptibility test (DST) results confirm susceptibility and if high-quality audiology monitoring for hearing loss can be ensured. S is to be considered only if Am cannot be used (due to suspected or documented resistance or unavailability) and if phenotypic DST results confirm susceptibility.

Received on 03-01-2021
Accepted on 28-04-4041

The incidence of tuberculosis (TB) increases rapidly in 4 settings where TB control is poor, patients are immuno compromised and also among those with HIV/AIDS or malnutrition.[3] Globally an estimated 20 % 5of patients with TB default or fail to respond to therapy and develop MDR-TB.[4-6] These include programmatic and patient factors such as poor adherence of patients to first line anti-TB drugs, inappropriate treatment regimen, dosage and duration for treatment and non-compliance to national guidelines and TB treatment protocol by clinicians among others. The inappropriate use of second line anti-TB drugs in MDR-TB patients will lead to amplification of resistance and the development of XDR-TB[7].

## MATERIALS AND METHODS

This retrospective/observational study was conducted at Department of Medicine, Bolan Medical College Quetta from 1st July 2019 to 31st December 2020. A total of 180 patients of both genders with ages 20 to 70 years presented with drug resistant tuberculosis were enrolled in this study. Patient's detailed demographics including age, sex, residence and body mass index were recorded after taking written consent. Drug resistance TB diagnosis has been carried out using GeneXpert MTB/RIF assay, genotypic and phenotypic drug susceptibility testing (DST).

Patients who had used the aminoglycoside for a month or more in the past six month prior to the start of study, patients with renal failure, patients who received concomitant administration of other ototoxic drugs, and uncooperative patients were excluded from this study. Complete previous history of anti-tuberculosis drugs was explored from the patients and all the samples underwent gene expert and then drug sensitivity testing (DST) for 1st and 2ndline drugs. All the data was analyzed by SPSS 24.

## RESULTS

There were 100(55.56%) males and 80(44.44%) patients were females. Mean age of patients was 37.38±10.75 years. Mean body mass index was 24.18±2.41 kg/m$^2$. Thirty (16.67%) patients had diabetes mellitus, 24 (13.33%) patients had hypertension (Table 1).

Among all the multi-drug resistant tuberculosis patients, pre extensively drug resistant tuberculosis was found in 62(34.44%) patients and extensively drug resistant tuberculosis was found in 8(4.44%) patients (Fig. 1).

Table 1: Demographic information of the patients

| Variable | No. | % |
|---|---|---|
| Mean age (years) | 37.38±10.75 | |
| Mean BMI (Kg/m) | 24.18±2.41 | |
| **Gender** | | |
| Male | 100 | 55.56 |
| Female | 80 | 44.44 |
| **Co-morbidity** | | |
| Diabetes | 30 | 16.67 |
| Hypertension | 24 | 13.33 |

Fig. 1: Frequency of pre-XDR and XDR tuberculosis

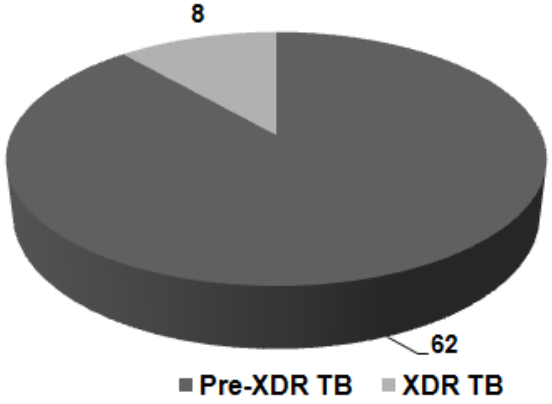


Table 2: Drug resistance among pre-XDR and XDR tuberculosis patients

| Variables | No. | % |
|---|---|---|
| **Pre-XDR tuberculosis (n=62)** | | |
| Flouroquinolone | 62 | 100.0 |
| Amikacin | - | - |
| Kanamycin | - | - |
| Capreomycin | - | - |
| **XDR tuberculosis (n=8)** | | |
| Amikacin | 4 | 50.0 |
| Kanamycin and fluoroquinolone | 2 | 25.0 |
| Amikacin and kanamycin | 1 | 12.5.0 |
| Capreomycin | 1 | 12.5.0 |

Sixty two (100%) patients of pre-XDR tuberculosis were resistant to fluoroquinolone while among XDR tuberculosis patients 4 were resisted to amikacin, 2 were resisted to kanamycin and fluoroquinolone, 1 patient was resisted to amikacin and kanamycin and 1 patient was resisted to capreomycin (Table 2).

## DISCUSSION

In this study we found the pattern of drug resistance tuberculosis in multi-drug resistance TB patients. Drug sensitivity test were performed for amikicin (AM), kanamycin (KM), capreomycin (CM) and fluoroquinolone (FQ). In present study the prevalence of XDR TB in MDR Tuberculosis patients was 4.44% while pre-XDR TB was found in 62(34.44%). All the patients of pre-XDR were resisted to fluoroquinolone (FQ) same as the study conducted by Manan et al[8] in 2018 showed results 32.2% and 3.4% in MDR TB patients. As compared to this similarity of results were showed by Rao et al[9], the prevalence of Pre XDR and XDR TB were found 39.5% and 2% respectively.

Compared to our findings, majority of studies reported higher rate of pre-XDR TB in India (56%), China (34%), Pakistan (24%), Bangladesh (16%), Nigeria (17%) and South Africa (17%).[10-14] The resistance of FQ in our study was 34.44% and it was similar to other several studies, reported as 10%, 13%, 24%, 35% and 57%.[15-19] Data from previous studies suggests that the incidence of FLQ resistant MDR-TB (pre-XDR-TB) is increasing worldwide.[20] The reason for the higher number of FLQ resistant pre-XDR-TB cases found in this study maybe due to the fact that FLQs are used indiscriminately in most of the common infections, including pneumonia and pyrexia of unknown origin, in addition to its use in MTB infection in Bangladesh. When FLQs are used as antibiotics they have two detrimental effects, first they have anti mycobacterial action which can delay the diagnosis of TB. Secondly, when these antibiotics are previously used for treatment, they can lead to selection of FLQ resistant MTB mutants. The exposures to FLQ antibiotics are more common than ISLs, as FLQ antibiotics are oral drugs, which are readily available in pharmacies without prescription in Pakistan.

Identification of pre-XDR TB patients will assist clinicians to monitor these patients closely and prevent the progression to XDR-TB which is more difficult to treat and poor treatment success. Major problem observed in our society for the patients of MDR TB is availability and misuse of drugs like Levofloxacin, Moxifloxacin, Ofloxacin and Sparfloxacin in the markets. Fluoroquinolones in patients suspected of having TB or have failed the conventional 1st line anti tuberculosis treatment.

In present study we found that majority of patients were ages between 20 to 40 years. A study by Shibabaw et al[21] reported that 63% of patients were ages between 15 to 34 years who were presented with multi drug resistant tuberculosis.

The control of DR-TB depends on early diagnosis of resistance, appropriate therapy improve patient's awareness for TB treatment, and interrupting transmission chains. Therefore, future TB prevention, care and management efforts in these areas should focus on

strengthening health care infrastructure, increase laboratory capacity for early diagnosis and treatment, monitoring of individuals with TB symptoms.

## CONCLUSION

Patients admitted with MDR TB had high prevalence of pre-extensively drug resistant TB as compared to extensively drug resistant TB. The control of DR-TB depends on early diagnosis of resistance, appropriate therapy improve patient's awareness for TB treatment, and interrupting transmission chains. There is also a need to ban over the counter sale of anti-tuberculous drugs especially second line drugs.

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