# Drug Resistance in Re-treatment Cases of Pulmonary Tuberculosis by Using the Drug Sensitivity Test

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**Abstract**

**Background:** Drug resistant tuberculosis (TB), particularly multidrug resistant (MDR) represents a major global public health problem particularly in developing countries like Pakistan. Different studies have found that Drug resistant TB is associated with a higher risk of treatment failure and death. This study was done to determine the magnitude of drug resistance among retreatment cases. **Objective:** To determine the frequency of drug resistance in re-treatment cases of pulmonary tuberculosis by using the Drug Sensitivity Test (DST). **Material and methods:** Tubes containing LJ medium were separately supplemented with following drugs in each tube (Streptomycin 10 µg, Isoniazid 1 µg, Ethanbutaol 10 µg, Rifampicin 1 µg, Pyrazinamide 100 µg, Ethionamide 5 µg, Kanamycin 6 µg, Amikacin 6 µg, Ofloxacin 1 µg, Capremycin 10 µg). Any amount of growth observed in any tube with drug was considered as Resistant. If no growth observed in any of those tubes then it was Sensitive. **Results:** Of these 265 study cases, 157 (59.2) were male patients and 108 (40.8%) were female patients. Mean age of our study cases was $34.16 \pm 8.24$ years (with minimum age was 20 years while maximum age was noted to be 48 years). Mean weight of our study cases was $59.38 \pm 7.54$ Kg (with minimum weight was 48 Kg while maximum weight was 75 Kg). Of these 265 retreatment cases, 74 (27.9%) were of treatment failure, with relapse 53 (20%) and 138 (52.1%) were defaulters of the treatment. Drug resistance was noted in 170 (64.2%) of our study cases while 95 (35.8%) showed drug sensitivity. **Conclusion:** Very High frequency of drug resistance was observed among retreatment patients in our study. Failure to the compliance with treatment (defaulter of treatment) was major risk factor observed in our study. Drug resistance was significantly associated with increasing age, relapse of tuberculosis, defaulter of treatment and diabetes mellitus. More studies are required from different parts of Pakistan to generate database at National level to combat this menace. There is a need to design well directed massive awareness campaign to educate general public and to bring awareness among targeted population.

**Keywords:** Pulmonary tuberculosis, retreatment, drug resistance.

**Introduction:**

Global burden of Tuberculosis (TB) cases and drug resistance are increasing.[1] Most of this burden is in the resource poor and under developed countries where tuberculosis kills more people than any other single infection. Traditional sputum smear microscopy is the only laboratory test for TB that is accessible to most of the world's population. Smear microscopy is inexpensive and highly specific, so positive results almost always prompt treatment. However, smear microscopy has low sensitivity and cannot test for drug resistance, which is important because patients with drug resistant TB require prompt second-line treatment to prevent morbidity, mortality and thereby preventing dissemination of multi-drug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).[2,3]

An alarming increase in the global incidence of drug-resistant tuberculosis has created a critical need to detect tuberculosis and identify drug-resistant cases.[4] . The recent discovery of large numbers of cases of multidrug-resistant (MDR) TB and extensively drug-resistant (XDR) TB in South Africa likely represents an unrecognized and evolving epidemic rather than sporadic, localized outbreaks.[5] Failure to quickly and effectively recognize and treat patients with drug-resistant tuberculosis leads to increased mortality, nosocomial outbreaks, and resistance to additional anti-tuberculosis drugs.[6,7] . However, MDR and XDR tuberculosis can be treated and its spread can be prevented if properly identified at an early stage. This test uses the DST, which provides results after six weeks. Rifampicin resistance is an excellent marker for for multi drug resistant Mycobactarium tuberculosis, as 90% of rifampicin resistant Mycobacterium tuberculosi sstrains are also isoniazid resistant, and hence, are classified as multi drug resistant[8] Isoniazid (INH) and Rifampicin (RIF) are the backbone of the standard regimen for treating tuberculosis (TB), and resistance to these drugs indicates a necessity for alteration of the standard regimen. [9]. Ideally, a treatment regimen for drug resistant TB would be designed and initiated based on in vitro drug susceptibility test results for each patient's M .tuberculosis isolate

[10]The choice of drugs would be based on the pattern of drug resistance which drugs have been taken previously Whether  the patient has underlying medical conditions The adverse effects associated with the drug In order to treat patients properly and to reduce further spread of drug-resistant TB, it is clinically important to provide susceptibility results to health care providers. In a prevous study the frequency of drugs resistance in re-treatment cases is 52% [11] in Dehli, India. In another study at Haryana, India the frequency of drugs resistance in re-treatment cases is 75%.[12]  In a previous study the frequency of drugs  resistance in re-treatment cases is 45.6% in Istanbul ,Turkey.[13]  In another study conducted in Makassar Indonesia the frequency of drug resistance in re-treatment cases is 59.6%[14].

**Materials and methods:**

The patients were enrolled from the outpatient department of Mayo  Hospital, Lahore. Patient with co-morbid diseases like Chronic liver disease, chronic renal failure and congestive cardiac failure and pregnant women were excluded from our study. The demographic data like age, sex and weight of the patients was collected. Patients fulfilling inclusion and exclusion criteria were included in study. Tubes containing LJ medium were separately supplemented with following drugs in each tube (Streptomycin 10 μg, Isoniazid 1 μg, Ethanbutaol 10 μg, Rifampicin 1 μg, Pyrazinamide 100 μg, Ethionamide 5 μg, Kanamycin 6 μg, Amikacin 6 μg, Ofloxacin 1 μg, Capremycin 10 μg). Any amount of growth observed in any tube with drug was considered as Resistant. If no growth observed in any of those tubes then it was Sensitive. Re-treatment Cases:  included relapse / treatment failure and defaulter cases. Treatment failure was defined as a patient whose sputum smear was positive at fifth month or later during treatment. A patient previously treated for TB who has been declared cured or treatment completed, and was diagnosed with bacteriologically positive (smear or culture) tuberculosis was defined as relapse. Defaulter was defined as a patient who returned to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.          Sputum samples were collected as per WHO instructions. The sputum sample were sent to Provincial Reference laboratory of the Hospoital for culture and DST. The report was assessed for detection of MTB and drugs resistance. All the data was entered in a specifically designed   proforma. Descriptive statistics was applied. Data was entered using software SPSS version 10. Numerical data like age and weight were described in terms of mean and standard deviation. The nominal data like gender and drugs resistance detection on drug sensitivity were described as frequencies and percentages.

**Results:**

Our study included a total of 265 patients re-treatment cases of pulmonary TB meeting inclusion and exclusion criteria of our study. Of these 265 study cases, 157 (59.2%) were male patients and 108 (40.8%) were female patients. Mean age of our study cases was 34.16 ± 8.24 years ranging from 20 years to 48 years. Mean age of the male patients was 32.43 ± 7.75 years while that of female patients was 36.69 ± 8.33 years (p=0.000) while 140 (52.8%) were less than 35 years of the age. Mean weight of our study cases was 59.38 ± 7.54 Kg ranging from 48 Kg to 75 Kg while 171 (64.5%) had weight ranging from 40 to 60 kilograms. Of these 265 retreatment cases, 74 (27.9%) were of treatment failure, with relapse 53 (20%) and 138 (52.1%) were defaulters of the treatment. Of these 265 study cases, 52 (19.6%) were diabetic patients and 48 (18.1%) had history of hypertension. Drug resistance was noted in 170 (64.2%) of our study cases while 95 (35.8%) showed drug sensitivity.

**Table No. 1**
**Stratification of gender with regards to drug resistance**

| Gender | Drug Resistance | | P- value |
|---|---|---|---|
| | Resistant (n=170) | Sensitive (n=95) | |
| Male (n=157) | 95 | 62 | |
| Female (n=108) | 75 | 33 | **0.153** |
| **Total** | **265** | | |

**Table No. 2**
**Stratification of age with regards to drug resistance**

| Age groups | Drug Resistance | | P- value |
| --- | --- | --- | --- |
| | Resistant (n=170) | Sensitive (n=95) | |
| 18-36 Years (n=140) | 75 | 65 | |
| 36-50 Years (n=125) | 95 | 30 | 0.000 |
| Total | 265 | | |

**Table No. 3**
**Stratification of treatment failure with regards to drug resistance**
**(n=265)**

| Treatment failure | Drug Resistance | | P – value |
| --- | --- | --- | --- |
| | Resistant (n=170) | Sensitive (n=95) | |
| Yes (n=74) | 52 | 22 | |
| No (n=191) | 118 | 73 | 0.253 |
| Total | 265 | | |

**Table No. 4**
**Stratification of relapse with regards to drug resistance**
**(n=265)**

| Relapse of TB | Drug Resistance | | P – value |
| --- | --- | --- | --- |
| | Resistant (n=170) | Sensitive (n=95) | |
| Yes (n=53) | 42 | 11 | |
| No (n=212) | 128 | 84 | 0.011 |
| Total | 265 | | |

**Table No. 5**
**Stratification of defaulter of treatment with regards to drug resistance**
**(n=265)**

| Defaulters | Drug Resistance | | P – value |
| --- | --- | --- | --- |
| | Resistant (n=170) | Sensitive (n=95) | |
| Yes (n=138) | 76 | 62 | |
| No (n=127) | 94 | 33 | 0.001 |
| Total | 265 | | |

**Discussion:**

Male gender predominance has been reported to occur more frequently in retreatment cases of pulmonary TB in different parts of the world. Our study included 157 (59.2) male patients and 108 (40.8%) were female patients. A study conducted by Anyama et al [15] also reported higher proportion of male patients (75%), similar to that of

our study results. Abdella et al [16] reported 60.8 % male patients with retreatment of pulmonary TB, these findings are similar to that of our study results. Similar results have been reported in other studies as well [17, 18]. Our study results are in compliance with that of reported by

Mean age of our study cases was 34.16 ± 8.24 years (with minimum age was 20 years while maximum age was noted to be 48 years). Mean age of the male patients was 32.43 ± 7.75 years while that of female patients was 36.69 ± 8.33 years (p=0.000). Abdella et al [16] reported 31.67 ± 10.02 years, close to our results. Similar results have been reported by Anyama et al [15]. Mean weight of our study cases was 59.38 ± 7.54 Kg (with minimum weight was 48 Kg while maximum weight was 75 Kg). Our study results have indicated that majority of our study cases i.e. 171 (64.5%) had weight ranging from 40 to 60 kilograms.

Of these 265 retreatment cases, 74 (27.9%) were of treatment failure. Abdella et al from Ethiopia reported 43 % treatment failure among retreatment cases. These values are quite higher than that of our study results. [16] In our study patients with relapse were 53 (20%) while a study conducted by Abdella et al [16] reported fairly high proportion of relapse to be 46 %.  In our study, 138 (52.1%) were defaulters of the treatment. Singhai et al from India [18] reported 46 % frequency of defaulters which predominated relapse, these findings are in compliance to our study results. Meskel et al [19] also reported  defaulters predominantly in high proportion which is consistent with our findings while Abdella et al reported only 10 % defaulter rate in their study. A study conducted by Chiang et al [20] reported same findings as ours.

Of these 265 study cases, 52 (19.6%) were diabetic patients. Anyama et al [16] reported 20 % frequency of diabetes in retreatment cases in 2 hospitals, these findings are close to that of our study results. In our study, 48 (18.1%) had history of hypertension.

In literature different studies have reported high proportions of drug resistance among retreatment cases. Drug resistance was noted in 170 (64.2%) of our study cases while 95 (35.8%) showed drug sensitivity. Abdella et al [16] reported 58.6 % rate of drug resistance in their study, our study results are in compliance with that of Abdella et al. a study conducted by Chiang et al [20] reported 43 % drug resistance among retreatment cases. An Indian study conducted by Janmeja et al [12] reported 75 % drug resistance among treatment failure patients which is close to our findings while Singhai et al [18] from India reported 47 % drug resistance among retreatment cases. Sevam et al [13] from Turkey reported 45.6 % frequency of drug resistance among retreatment cases. Meskel et al [19] reported 53.6% drug resistance among retreatment patients.

**Conclusion:**

Very High frequency of drug resistance was observed among retreatment patients in our study. Failure to the compliance with treatment (defaulter of treatment) was major risk factor observed in our study. Drug resistance was significantly associated with increasing age, relapse of tuberculosis, defaulter of treatment and diabetes mellitus. More studies are required from different parts of Pakistan to generate database at National level to combat this menace. There is a need to design well directed massive awareness campaign to educate general public and to bring awareness among targeted population.

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