Study of Multi-Drug Resistance Associated with Anti-Tuberculosis Treatment by DOT Implementation Strategy in Pakistan

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Abstract: *Purpose*: The present prospective cross sectional study was aimed to access the prevalence and trend of Multi-Drug Resistant Tuberculosis (MDR-TB) in different age groups and gender, in the city of Lahore, Pakistan. Tuberculosis is a disease of poverty affecting mostly young adults in their most productive years; however, all age groups are at risk.

Method: The study population consisted of patients under DOT program with MDR-TB among males and females and in different categories of age groups. The data was collected from 100 MDR-TB patients from 7800 TB patients that were admitted in duration of 6 months and analyzed to evaluate the drug resistance associated with patient's noncompliance. Moreover, drugs resistance ratio was also calculated from the data.

Results: TB is a specific infectious disease, caused by *M. tuberculosis* strains, which is becoming resistant to anti-tuberculosis agents especially to Isoniazid and Rifampicin that are two key drugs of TB treatment and are termed as MDR-TB. The disease was seen in 66% males and 34% in female. The highest drug resistance ratio was in found in adults (age group).

Keywords: Multi Drug Resistance, Tuberculosis, DOT, Lahore, *M. tuberculosis.*

INTRODUCTION

TB is a treatable and curable disease that is treated with a standard six-month course of four antimicrobial drugs that are provided with information, supervision and support to the patient by a health worker or trained volunteer. Without proper supervision and support, adherence to treatment can be difficult, therefore disease can spread. On the other hand if medicines are provided and taken properly, the majority of TB cases can be cured [1]. According to DOT program, the treatment of the patient should be started with the combination of Isoniazid (INH)-Rifampicin (RIF)-Pyrazinamide (PZA)-Ethambutol (ETB) for two months, followed by INH-RIF co-administration for four months; this therapy is only suitable for those patients who are susceptible for INH and RIF. The treatment of MDR-TB should be based on patient's status and result of susceptible studies. Mostly patients are resistant to INH and RIF therefore at least three sensitive regimens should be given until sputum is clear, then two sensitive regimen should be given for another twelve months [2].

According to an estimates given by WHO, 3.3% of the cases of TB had MDR-TB in 2009 [3]. MDR-TB mostly develops when a doctor gives an inappropriate treatment to the patients [4]. Moreover, patient's poor compliance during the treatment is also a contributing factor in increasing the risk of MDR-TB in the continent [5]. In some cases the developed resistance to the drugs is very severe, which gives rise to extensively MDR-TB. Extensively Drug-Resistant TB (XDR-TB) responds to very few medicines [1].

Pakistan is ranked 8th in terms of global estimated burden of TB cases despite of widely spread BCG vaccination, [6]. In Pakistan, around 161 million people live in an area of 803,490 square kilometers (WHO, 2009). Every year, approximately 70,000 deaths and about 270,000 people fall sick due to TB. According to WHO Pakistan stands amongst 27 most affected states; moreover this is also true for MDR-TB [7]. MDR-TB also poses significant challenges to TB control programs both in terms of clinical management and infection control [8].

The present study was a retrospective cross-sectional study among the patients having TB with a resistance to first line anti-TB drugs therapy according to DOT program. In duration of six months, 7800 TB patients were registered in Gulab Devi Hospital Lahore, Pakistan from which 100 patients were diagnosed as resistant to treatment. These MDR-TB patients were studied according to seven parameters; to check prevalence, trend of MDR-TB due to patient's non-compliance and developing adverse effects in our

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developing country. The study parameters included age, gender, poverty, literacy, history of TB, previous treatment and nutritional status. The data was collected over duration of 6 months (March to August, 2013) for evaluation. The data was evaluated statistically using SPSS software.

MATERIAL AND METHOD

Study Design

The research was performed to quantify and compare published studies related to MDR causing hindrance in treatment of TB by DOT implementation strategy due to patients pervasiveness, non-compliance, developing adverse effects in males and females and different categories of age groups.

Inclusive Criteria

The study population consisted of patients under DOT program with MDR-TB among males and females and in different categories of age groups.

Exclusive Criteria

Patients taking treatment other than DOT program and patients on first line drug therapy of TB.

Plan of Work

The data collection form consisted of close ended questions. These were designed according to drug resistant prevalence and developing side effects in patients of pulmonary tuberculosis receiving DOT therapy under NTP (National TB Control Program).

The patients were analyzed for following data.

- Demographical data of patients, name, age, gender, qualification, occupation, socio-economic status and material status.
- Types of resistance; primary or secondary.
- Duration of disease, family history, previous treatment and if patient has taken medicines regularly.
- Sputum conversion test or AFB smear culture was studied to access effectiveness of the therapy.
- Causes of drug resistance such as irregular intake of medicines due to adverse effects and irregularity due to poor adherence of patient to treatment.
- Study of main adverse effects (neuropathy and jaundice) developed due to anti-tuberculosis drugs and is responsible for termination of therapy.
- Drug susceptibility testing (DST) was studied to find out the resistance ratio in percentage of all first line anti-tuberculosis drugs.

RESULTS

In duration of six months 7800 patients were registered, out of which 100 (1.3%) were resistant cases in the Lahore city. Among these 1.3%; males were 66% as compared to females which shows the ratio of 34%. Amongst males; 67% were adult, 18% children and 15% were geriatrics. Among females; 65% were adult, 17.5% children and 17.5% were geriatrics. Moreover MDR was seen mostly in adults (66%) as compared to child (18%) and geriatrics (16%) as shown in Figure **1**.

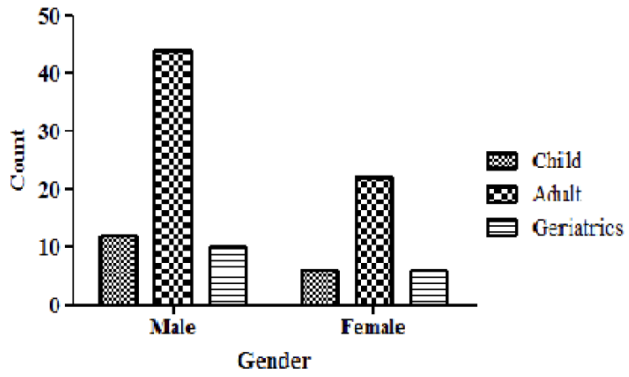


Figure 1: MDR-TB in Gender vs. Age group.

Treatment irregularity rate was lower (47.8%), which can be the cause of resistance, while regularity rate was comparatively high (52.2%).

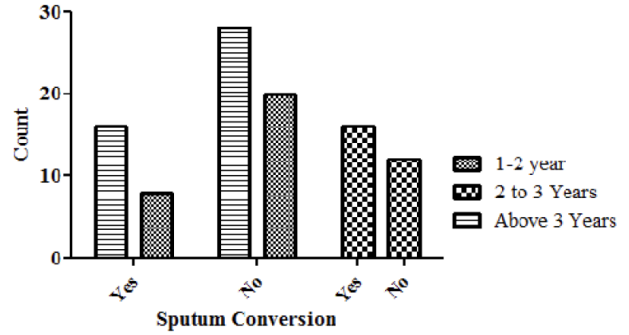


Figure 2: Sputum conversion in relation to duration of disease.

It was observed that 40% of the patients showed conversion of sputum during their course of treatment

(Figure **2**), i.e. the sputum conversion was low with longer duration of disease condition [2]. This rate of sputum conversion was greater in males (70%) as compared to females (30%) as given in Figure **3**.

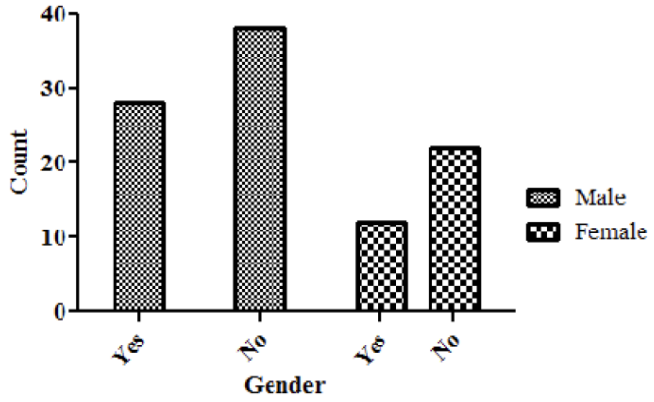


Figure 3: Sputum conversion in relation to gender.

According to the collected data, 82% of the observed patients got side effects during the course of treatment. All the observed children were affected which might be possible due to low immunity. Moreover adult ratio was greater (65.8%) in developing side effects as compared to geriatrics (Figure **4**). The side effects were mostly observed in males (70.7%) while only 29.3% females showed signs of side effects (Figure **5**).

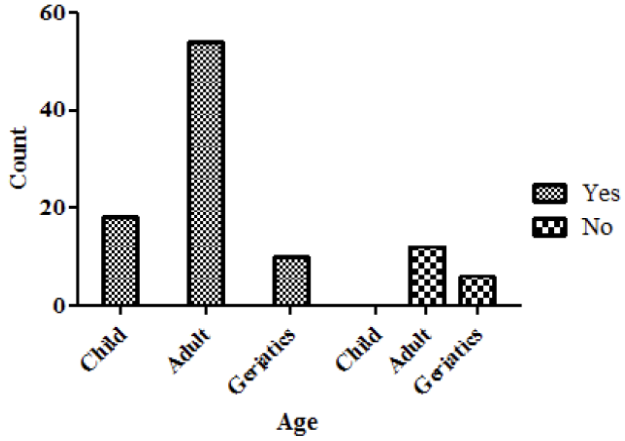


Figure 4: Side Effect developed during treatment with respect to age.

While studying the side effect further, commonly observed side effects of anti-tuberculosis drugs are neuropathy and liver dysfunction (hepatitis) [9, 10]. Neuropathy was observed in 48% of patients; 70.8% were males while 29.3% females got neuropathy during the course of their treatment (Figure **6**). Neuropathy was observed in 79.2% adults while ratio in child and geriatrics was low as shown in Figure **7**.

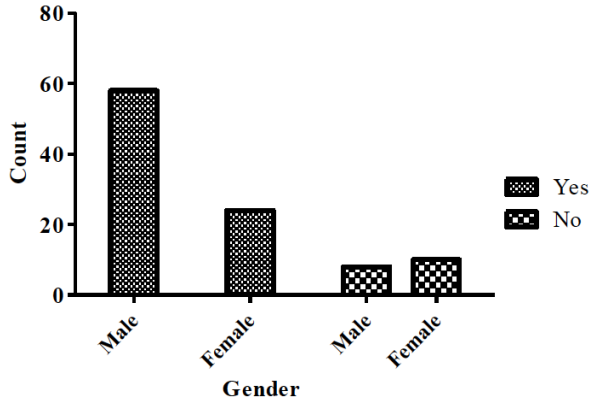


Figure 5: Side effect developed during treatment with respect to gender.

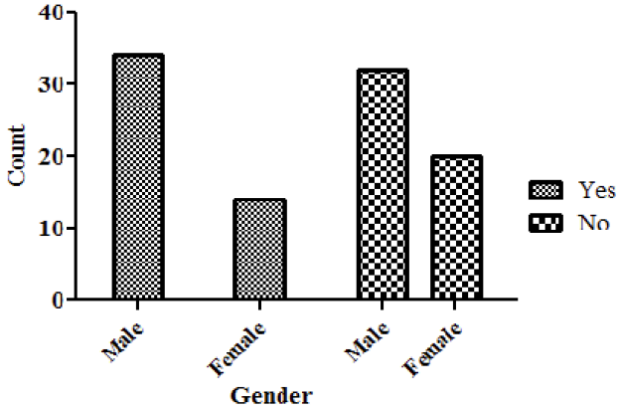


Figure 6: Development of neuropathy during treatment with respect to gender.

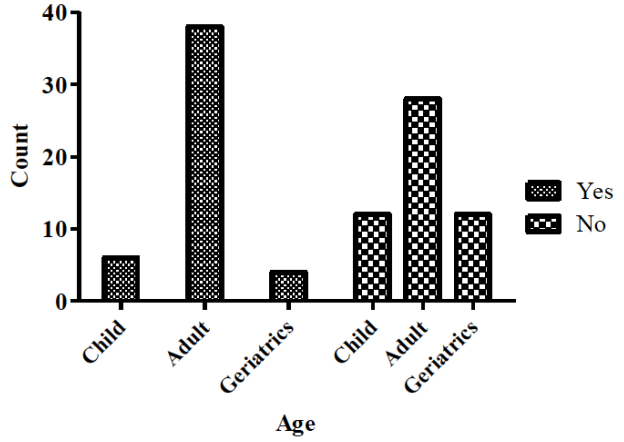


Figure 7: Development of neuropathy during treatment with respect to age.

The major problem with anti-tuberculosis drugs is (liver dysfunction) drug-induced hepatitis. INH, PZA and RIF are responsible drugs for possible liver dysfunction. Hepatitis maybe caused after the termination of therapy in most of the patients. It was observed that 74.3% males were experiencing hepatitis

while female ratio was only 25.7 % as shown in Figure **8**. On the other hand, according to the age group, jaundice was seen in most of the adults as depicted in Figure **9**.

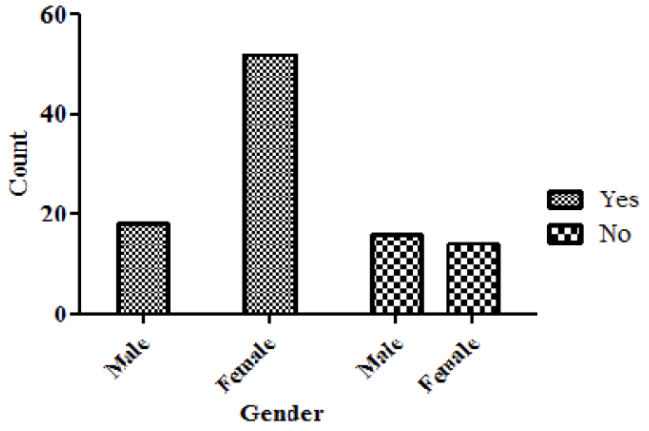


Figure 8: Development of jaundice during treatment with respect to gender.

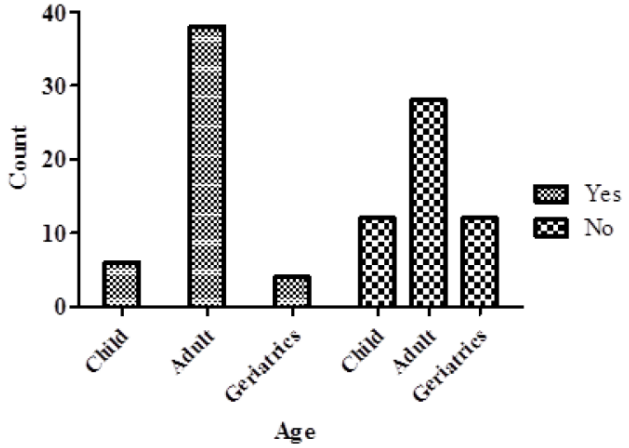


Figure 9: Development of jaundice during treatment with respect to age.

In our study, both the side effects (jaundice and neuropathy) were the cause of termination of therapy. Due to the possible disease, 48.5% of the patients terminated their therapy due to jaundice. The treatment remained terminated till liver transaminase enzymes returned to its normal range. On the other hand, the therapy was discontinued in 50% of the total patients due to neuropathy.

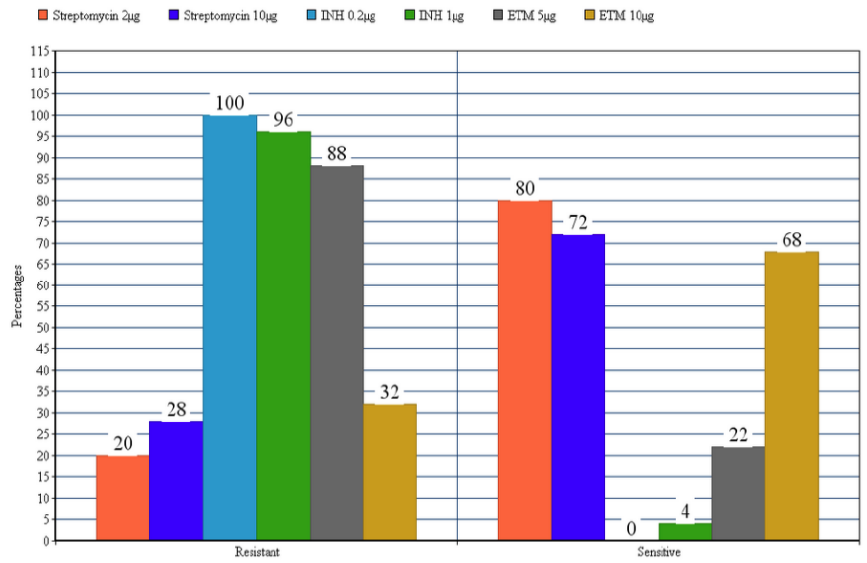
DST report was observed and studied for every patient in order to access the resistant pattern of first line TB drugs. Resistant to both INH and RIF was seen in the patients as the cause of MDR-TB. Moreover ETM (88%) and PZA (80%) resistant ratio was also high. Only streptomycin showed 72% sensitivity amongst the first line drugs while other drugs were highly resistant in most of the patients. After signs of resistance to first line drugs, patients were shifted to second line drugs in which ETM, Kanamycin, and Amikacin showed greater sensitivity towards *M. tuberculosis*, calculated to be 80%, 96% and 96% respectively (Table **1**). Among flouroquinolones; Ofloxacin showed 28% sensitivity while 72% resistance was observed in patients as shown in Table **1** and Figure **10A**, **B** and **C**.

Table 1: Resistance of Anti-TB Drugs; First Line Therapy and Second Line Therapy

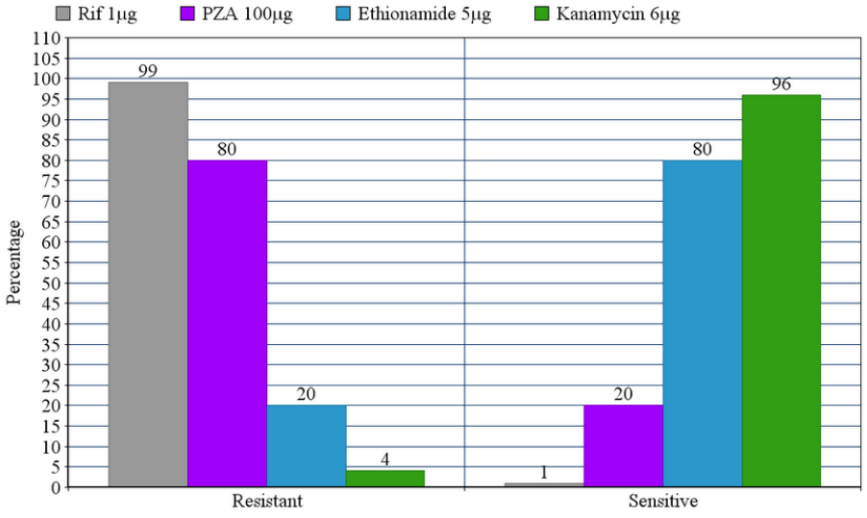
DRUGS	Resistant	Sensitive
First Line Anti Tuberculosis Drugs		
Streptomycin 2µg (S)	20	80
Streptomycin 10µg (S)	28	72
Isoniazid 0.2µg (INH)	100	0
Isoniazid 1µg (INH)	96	4
Ethambutol l5µg (ETM)	88	12
Ethambutol 10µg (ETM)	32	68
Rifampicin 1µg (RIF)	99	1
Pyrazinamide 100µg (PZA)	80	20
2nd Line Anti Tuberculosis Drugs		
Ethionamide 5µg (Eto)	20	80
Kanamycin 6µg (K)	4	96
Amikacin 6µg (A)	4	96
Ofloxacin (Ofx)	72	28
Capreomycin	12	88

DISCUSSION

According to the present study, MDR-TB is mostly seen in males as compared to females (ratio of 34%). This possible lower reporting in females might be due to the ignorance to the female's health in our socio-economic setup. Moreover MDR was seen mostly in adults as compared to children and geriatrics. It can be assumed that BCG (Bacillus Calmette–Guérin) vaccine gave protection to most of the children but not to the people who were at high risk with low immunity [11, 12]. The treatment regimen of TB recommended under DOT program is associated with lot of side effects and also non-adherence to the treatment is the major problem in our community [9]. A maximum number of patients did not complete their course due to which treatment irregularity rate was greater which lead to the major cause of resistance. This rate of sputum conversion was greater in males as compared to the



A



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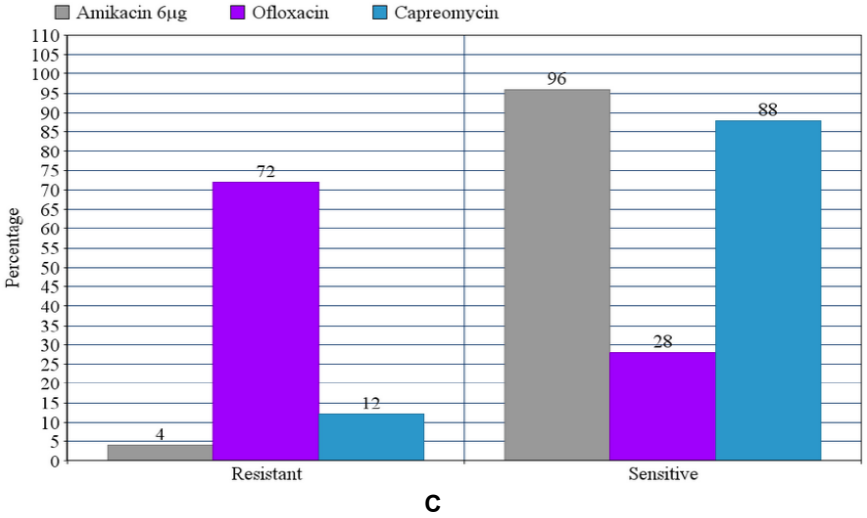

C

Figure 10: (**A**): Resistance against Anti-Tuberculosis Drugs (Streptomycin 2µg, Streptomycin 1µg, INH 0.2µg, INH 1µg, ETM 5µg and ETM 10µg).

(**B**): Resistance against Anti-Tuberculosis Drugs (RIF 1µg, PZA 100µg, ETM 5µg and Kanamycin 6µg).

(**C**): Resistance against Anti-Tuberculosis Drugs (Amikacin 6µg, Ofloxacin and Capreomycin).

females which can be due to the fact that females have lower immunity and in our community most of the females are facing malnutrition.

According to the results, it can be assumed that development of drug resistance might be due to the termination of treatment encountered due the progression of side effects. This termination of treatment can be encountered from the side of patient or doctor [4]. From our study it was observed that 82% of the patients got side effects during the course of treatment; hepatitis being the major cause of termination of therapy in most of the patients. It can be assumed that low immunity in diseased patients plays an important role. Neuropathy, one of the side effects of treatment regimen, occurs due to malnutrition for which diet can be made better and pyridoxine can be added to the treatment regimen. Therefore, only 50% patient's therapy is discontinued due to neuropathy.

CONCLUSION

According to DST report, first line drugs such as ISN, RIF and PZM were 100%, 99% and 80% resistant respectively, while second line drugs were sensitive. There should be at least two sensitive drugs added in therapy for effectiveness. Hence, Capreomycin, Kanamycin, and Amikacin are good choice as they show greater sensitivity towards *M. tuberculosis*.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

The funding sponsors had no role in design of study, in collection, analysis or interpretation of data, in writing of manuscript and in decision of publishing results.

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