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# Prevalence of adverse drug reactions among MDR-TB patients with different anti tubercular regimens

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***Abstract*---**Aim: The main aim of this study is to monitor the adverse drug reactions among the patients treated with different regimens for MDR-TB. Materials and Methods: Patients who were diagnosed with MDR-TB of either gender and with an age of above 18 years were included in this study. The causality assessment of the ADRs was done by using the Naranjo's scale and according to this scale, the ADRs were classified based on the scores into definite ADRs (≥9), probable ADRs (5-8), possible ADRs (1-4) and doubtful ADRs (0). Results: Among the 300 study participants, 129 (43%) were observed to be with various adverse drug reactions in this study. In this study, most of the ADRs were observed to be with gastrointestinal related (25.58%) followed by nausea & vomiting (20.92%), According to the Naranjo's scale, the causality assessment was done and it was observed that among the 129 cases. Conclusion: According to the Naranjo's causality assessment, most of the ADRs were possible ADRs followed by probable, most of the ADRs were observed to be with moderate severity followed by mild severity.

***Keywords*---**tuberculosis, adverse drug reactions, multidrug reaction.

## Introduction

Tuberculosis (TB) is a disease caused by the bacteria called Mycobacterium tuberculosis. In case of tuberculosis and drug resistant tuberculosis, India is one

of the high burden countries and as per the global tuberculosis report of 2015, an incidence of 4,80,000 cases were observed to be with MDR-TB (Multi Drug Resistant Tuberculosis) in India [1]. Providing the treatment for MDR-TB is quiet difficult and complex. Unacceptable adverse drug reactions can be observed frequently with the reserve drugs which may result in the frequent change of the regimen [2]. Patients with non-compliance towards the treatment and the prescribing errors during the treatment were the major reasons for drug resistance. The major source of new drug resistant cases can be ongoing transmission of established drug resistance strains in the clinical scenario [3]. When introducing the new anti-TB drugs and regimens, the national TB programmes that systematically monitor the adverse effects associated with the anti-TB drugs are better placed to safe guard the safety of the patient. In the aspect of addressing the safety of current and anti-TB drugs, pharmacovigilance will play a significant part of global and national policy [4,5]. Hence, we made an attempt to monitor the adverse drug reactions among the patients with MDR-TB and XDR-TB (Extensively Drug Resistant Tuberculosis).

**Aim and Objectives**

**Aim**

The main aim of the present study is to estimate the prevalence of ADRs among MDR TB patients treated with different regimens at Damien TB centre.

**Objectives**

- Identification of types and frequency of adverse drug reactions in Intensive and continuation phase.
- To evaluate the incidence of treatment discontinuation in relation to ADRs.
- To assess casualty and severity of the reported adverse drug reactions.
- To categorize the patients based on their demographic parameters.

**Methodology**

Study Design: It is a prospective observational cross sectional study
Study site: The present study was carried out at Damien Foundation Urban Leprosy & TB Centre, Nellore with prior approval of institutional Ethics Committee.
Study Duration: The study was conducted for a period of Twenty four months (June 2019 to June 2021)
Research Tool: Naranjo scale was used for causality assessment of the ADRs. ADRs were categorized into four types based on the scores as Definite ADRs (≥9), probable ADRs (5-8), possible ADRs (1-4) and doubtful ADRs (0).

**Inclusion criteria**

- Patient of either sex of age more than 18 years – 50 years with tuberculosis.
- Diagnosed cases of MDR- TB, enrolled under RNTCP(NTEP) program.
- Agreed to adhere tuberculosis treatment regime prescribed.
- Patient who provide written informed consent and ready to give follow up

**Exclusion criteria**

- History of Patients receiving ART Treatment
- Patients with deranged Liver and Kidney function tests.
- History of patient suffering from any other chronic disease condition requiring any concomitant medication.
- Patients those were transferred to diagnosis were changed.
- Pregnant Women.
- Not ready to give informed consent.
- Not ready to give follow up.

**Method of data collection**

Patients for this study were included from Damien Foundation Urban Leprosy & TB Centre, Nellore who were diagnosed to have MDR-TB (Isoniazid and Rifampicin resistance individually or both) admitted in Drug Resistance Tuberculosis Centre. All study subjects were evaluated after written informed consent was obtained. Thorough detailed history was taken regarding the demographic profile, present complaints, past history of tuberculosis, history of any addiction, family history of Tuberculosis was collected using a structured patient data collection form. Detailed general and systemic examination was done to find out any abnormalities. Pre-treatment investigations done included informed consent, urine for albumin, sugar and pregnancy test for female patients (if 18 to 50 yrs. old), complete haemogram, renal and liver function test, Thyroid function test, psychiatric evaluation, Audiometry (SOS), Vision Acuity Test (SOS).

**Treatment regimen**

The standardized regimen consisted of an intensive phase (IP) of 6-9 months with 6 drugs, namely kanamycin (Km), Moxifloxacin (Mfx) ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and Clofazimine (Cfz) given daily. This was followed by a continuation phase (CP) of 18 months of 4 drugs, namely Lfx (levofloxacin), Eto, E and cycloserine (Cs). At the end of 6 months of treatment, if the fourth month culture remained positive, the IP was extended for a further 3 months. Doses of the drugs were chosen according the weight range to which patient belonged.

All patients enrolled to the study were treated with a daily supervised regimen. All patients were monitored daily for adverse drug reactions after starting regimen till the patients remains admitted in hospital and later followed up personally or telephonically at regular intervals of 2 monthly bases and will be asked questions regarding possible adverse drug reactions of the drug which are prescribed to them. In between the 2 monthly follow up in OPD, telephonic questioning regarding adverse drug reactions will be asked on the any day of first week of every month. Anticipated ADRs will be identified and assessed. The causality of adverse drug reactions will be assessed as per Naranjo's causality assessment scale, at the end of the study, these adverse event records will be analyzed and statistically interpreted.

**Statistical analysis**

Prevalence of ADRs among patients treated with MDR-TB was estimated by using the formula

Prevalence = Number of cases / Population * 100

All the data analysis was done by using Microsoft excel spreadsheet, version-2009, we used only descriptive statistics like, mean and simple percentage.nAll the demographics parameters, graphs, tables were generated, the tool used assess the severity of ADR was analyzed by using Naranjo's scale.

**Intensive phase (IP) 6-9 Months**

| Drugs | | 16-29 kgs | 30-45 kgs | 46-70 kgs | >70 kgs |
|---|---|---|---|---|---|
| $Mfx^h$ | Moxifloxacin | 400mg | 600mg | 800mg | 800mg |
| Km | Kanamycin | 500mg | 750mg | 750mg | 1000mg |
| Eto | Ethionamide | 375mg | 500mg | 750mg | 1000mg |
| Cfz | Clofazimine | 50mg | 100mg | 100mg | 200mg |
| Z | Pyrazinamide | 750mg | 1250mg | 1750mg | 2000Mg |
| E | Ethambutal | 400mg | 800mg | 1200mg | 1600mg |

**Continuation Phase 18-20 Months**

| Drugs | | 16-29 kgs | 30-45 kgs | 46-70 kgs | >70 kgs |
|---|---|---|---|---|---|
| $Lfx^h$ | Moxifloxacin | 400mg | 600mg | 800mg | 800mg |
| Eto | Ethionamide | 375mg | 500mg | 750mg | 1000mg |
| Cfz | Clofazimine | 50mg | 100mg | 100mg | 200mg |
| E | Ethambutal | 400mg | 800mg | 1200mg | 1600mg |
| $H^h$ | $INH^h$ | 300mg | 600mg | 900mg | 900mg |

**Results**

The prevalence of ADRs was 43% among the MDR TB patients treated with different regimens. All the study subjects were categorized based on gender and represented in table 1, among the total sample of 300 males were 196 (65.33%) and females were (104) 34.66%.

Table 1: Categorization of subjects based on Gender

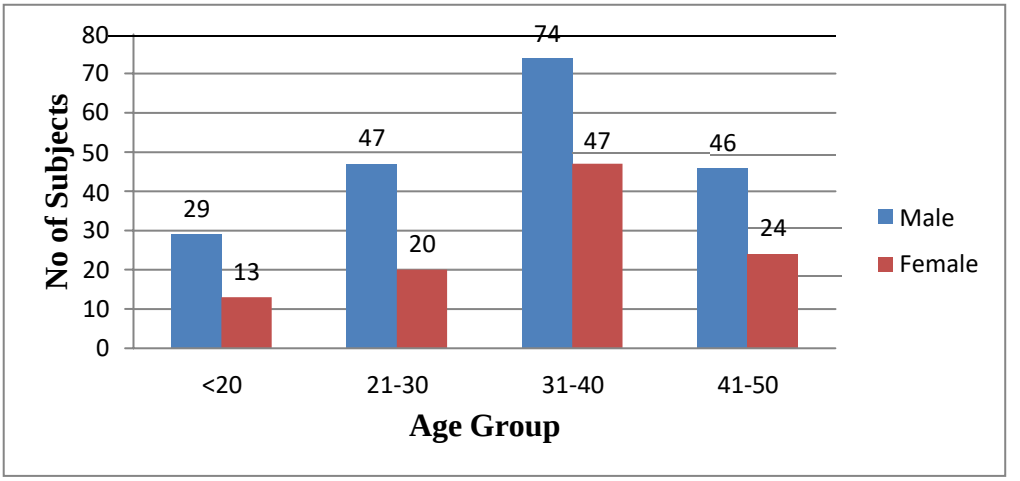
| S. No | Gender | No. of subjects | Percentage (%) |
|---|---|---|---|
| 1. | MALE | 196 | 65.33 |
| 2. | FEMALE | 104 | 34.66 |
| 3. | TOTAL | 300 | 100 |

All the study subjects were categorized based on their age groups as represented in table 2, among them majority of the subjects were in the age group of 31-40 years with 40.33% followed by 41-50 years with 23.33%.

Table 2: Distribution of subjects based on age groups

| S. No | Age group | Male | Female | Percentage (%) |
|---|---|---|---|---|
| 1. | <20 | 29 | 13 | 14.00 |
| 2. | 21-30 | 47 | 20 | 22.33 |
| 3. | 31-40 | 74 | 47 | 40.33 |
| 4. | 41-50 | 46 | 24 | 23.33 |
| 5. | TOTAL | 196 | 104 | 100 |

Fig:1 Graphical Representation of Subjects based on age groups




All the subjects were divided based on weight band into four categories as shown in the table 3 as the main stay in the treatment of tuberculosis is weight of the patient.

Table 3: Distribution of Subjects based on weight band

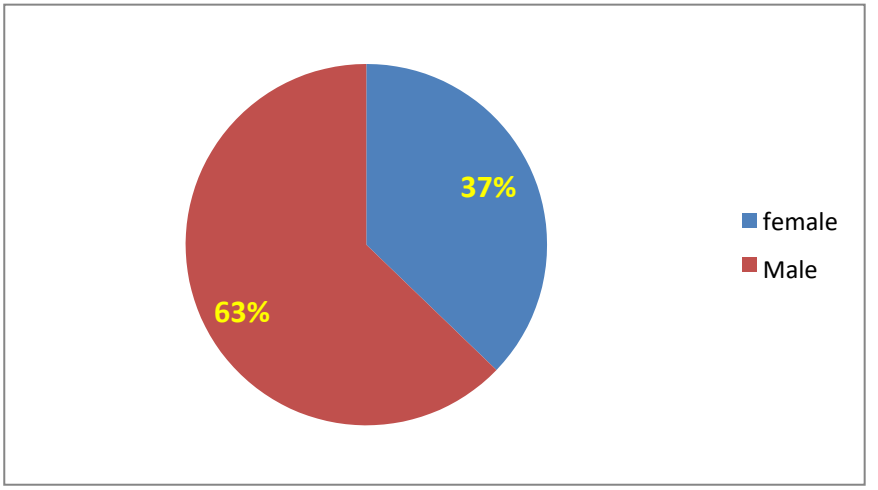
| S. No | Weight (In Kg) | Male | Female | Percentage (%) |
|---|---|---|---|---|
| 1. | 16-25 | 00 | 00 | 00 |
| 2. | 26-45 | 69 | 22 | 30.33 |
| 3. | 46-70 | 85 | 61 | 48.66 |
| 4. | >70 | 42 | 21 | 21.00 |
| 5. | Total | 196 | 104 | 100 |

A total of 129 Adverse drug Reactions were observed during the study period, were 81(62.79%) of males and 48 (37.2%) females experienced ADRs.

Table 4: Distribution of adverse drug reactions based on gender

| Gender | Number of Subjects | Percentage (%) |
|---|---|---|
| Male | 91 | 62.79 |
| Female | 38 | 37.20 |
| Total | 129 | 100 |

Fig 2: Graphical Representation of Adverse drug reactions based on gender




In the present study ADRs experienced by different subjects were categorized based on the anatomical site affected as shown in the table 5. The most predominant system affected was gastro intestinal tract with 25.58%.

Table 5: Frequency of individual ADRs noted during treatment of MDR-TB patient

| Type of ADR | No. of patients | Percentage (%) |
|---|---|---|
| GIT | | |
| Gastrointestinal | 33 | 25.58 |
| Nausea, vomiting | 24 | 20.93 |
| Diarrhea | 07 | 5.42 |
| Hepatitis | 06 | 4.65 |
| Psychological Disorders | | |
| Tinnitus +Vertigo | 06 | 4.65 |
| Insomina+Suicidal Tendencies | 06 | 4.65 |
| Depression | 02 | 1.55 |
| Altered behavior | 02 | 1.55 |
| Peripheral neuropathy | 08 | 6.20 |
| ENT | | |
| Ototoxicity | 07 | 5.42 |
| Vision defect Impaired visual acuity | 02 | 1.55 |
| Skin | | |
| Pruritus with rash | 05 | 3.87 |
| Pruritus without rash | 03 | 2.32 |
| Injection site pain and swelling | *08* | *6.20* |
| *Renal* | | |
| Renal dysfunction Deranged RFT | *02* | *1.55* |

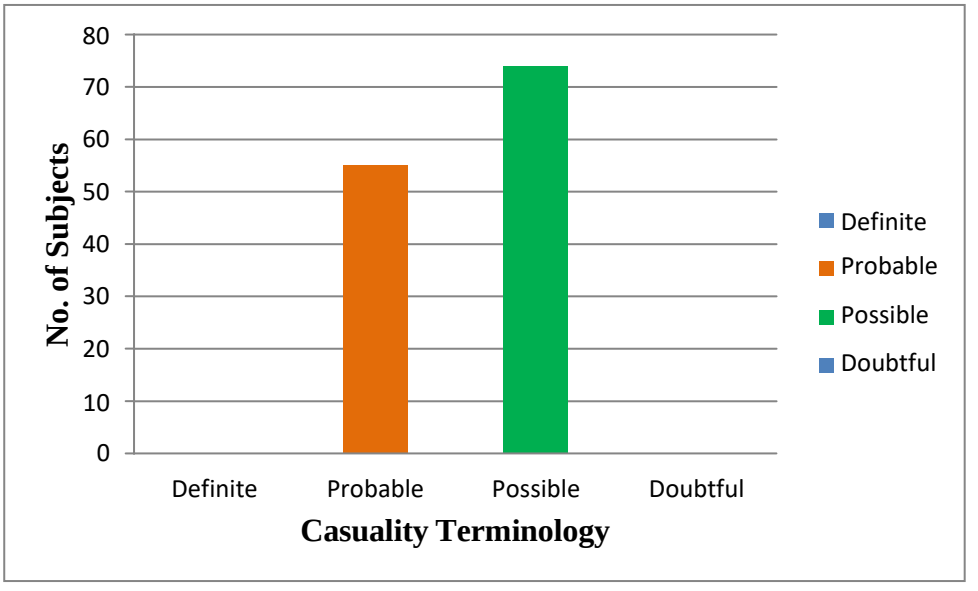
| *Other* | | |
|---|---|---|
| Musculoskeletal Arthralgia | *08* | *6.20* |
| Total | *129* | *100* |

All the observed adverse drug reactions observed were assessed for causality assessment using Naranjo scale as shown in the table 6. As per the Naranjo scale in the present study only probable and possible ADRs were observed with possible ADR predominance of 57%.

Table 6: Causality of ADRs induced by anti TB drugs according to Naranjo algorithm

| S.No | Type | No. of patients | Percentage |
|---|---|---|---|
| 1 | Definite | 04 | 3.10 |
| 2 | Probable | 53 | 41.08 |
| 3 | Possible | 69 | 53.48 |
| 4 | Doubtful | 03 | 2.32 |
| Total | | 129 | 100 |

Fig 3: Graphical Representation of Causality of ADRs according to Naranjo Scale




## Discussion

The present observational study has evaluated a DOTS- Plus program, with special reference to Adverse Drug effects in which standard treatment of drug resistant tuberculosis cases as per RNTCP (NTEP) guidelines has been started in this DR-TB Centre. In the present study of 300 patients, the age group ranged from 20 to 50 years. Maximum number of cases was in the age group 31-40 yrs (40.33%) followed by 41-50yrs (23.33%). The median age of the patients in present

study was 31.83 years, as compared to the reports in which the median age was 28 years.[6] And in another study it was reported as 26 years respectively[7]. In the present study, majority of the patients were males 196 (65.33%) and Females 104 (34.66%). similar observations were noted by authors in a study (males 65.33%and females 34.66%).and proportion of males to females was 65.33% and 34.66% respectively.

Weight band: Of the 300 drug resistance tuberculosis patients in this study, majority of patients were in the weight band of 26 to 70 Kg (78.99%). Whereas, a study observed that majority patients were above 45 Kg. Majority of the drug resistance tuberculosis patients were underweight before the start of treatment. In Present study, rifampicin mono resistance was found in 34.33%, while both isoniazid and rifampicin resistance were found in 65.67% patients when our DR-TB center started only solid cultures were available in the program due to which both rifampicin and isoniazid resistance was reported together. In this study ADRs were observed in 43.00% patient's, a finding comparable to present study reports notified in different studies. The ADR reported in present study were, Gastrointestinal, Ototoxicity, Injection site swelling/pain, Psychiatric manifestations, Arthralgia, Skin, Renal Involvement, Vision defect, peripheral neuropathy.

Gastro intestinal symptoms were most common adverse reaction observed in this study that is 33(25.58%) similar to other studies[9.11]. on the contrary other studies have found observed gastrointestinal ADRs in 42%, 60% and 100% patients respectively[7,8,12,13]. Hepatotoxicity was noted in 6(4.65%) patients only. Similarly findings were reported other authors[11,13]. They were mild but required immediate treatment. These gastrointestinal symptoms occurred mostly within a week of starting treatment. No patient required alteration in DOTS-Plus treatment due to gastrointestinal ADRs. Ototoxicity 7 (5.42%) was second most common ADR observed in this study of which decreased hearing 4 and tinnitus and vertigo in 2 patients These findings were similar to observations in a study which reported ototoxicity as second most common ADR after gastrointestinal ADR and frequency of ototoxicity[2,11,14]. Whereas another study reported ototoxicity in 5.92% patients[12]. Kanamycin was withdrawn in 80% of these patients and substituted with PAS (p- amino salicylic acid).

Psychiatric 16 (12.40%) manifestations were the third most common adverse reaction in this study of which insomnia was the most common followed by suicidal tendency, depression and altered behavior in descending order. Psychiatric ADRs were less common in this study as compared to 15.9%.[7] and 15%.[15] in other studies. All patients with psychiatric manifestation required withdrawal of cycloserine which was replaced with PAS (P-amino salicylic acid). Injection site swelling/pain 8 (6.20%) was fourth common ADR observed in this study. In contrast, it was reported in a study that injection site swelling/pain seen in 21.05% patients[8]. None of the patients required withdrawal of injection Kanamycin. Arthralgia 9 (5.92%) was fifth common ADR observed in this study. Similar observation was seen in 4.5% and 7.94% respectively.[9,11] In contrast, it was observed in the studies that arthralgia was seen in 31% and 23.68% patients.[8,14] Skin Adverse drug reactions ADR observed in this study was 5 (3.28%) of which pruritus without rash in 3 and pruritus with rash in 2 patient.

Frequency of skin reaction found in this study is similar 4%, 1.58% and 4.5%.[7,11,16] On the one of the study reported cutaneous reactions in 43.3% patients[13].

Renal involvement was seen 2(1.55%) patients in this study which is similar to observation noted in different other studies 1.58%, 2.7% and 2% respectively.[9,11,12] Renal involvements were seen in the form of borderline derangement of serum creatinine (2mg%) which improved in few weeks and none required withdrawal of injection kanamycin. Other ADR including Visual defect in 2 (1.55%), Peripheral Neuropathy 5(3.28%). similar findings seen in a study with frequency of visual disturbance 1(0.9%) and peripheral neuropathy 5 (3.87%)[9]. In present study Causality assessment of 129 ADRs was done by Naranjo's Causality Scale, out of 129 ADRs, 4(3.10) into definite category, 53(41.08%)into possible category, 69(53.48%) fall into Probable category and 3(2.32) Doubtfull category.. The distribution of 129 ADRs as Mild 43.40%, moderate 53.48% and sever 3.10%, as the study population the patients was hospitalized for ADRs, higher number of ADRs belonged to "Moderate "grade.

## Conclusion

In this study, about 43% of the study participants who were receiving the drug therapy for MDR-TB were observed with various adverse drug reactions. Most of the ADRs in the study were found to be with gastrointestinal issues followed by nausea & vomiting, swelling & pain at the injection site and ototoxicity. According to the Naranjo's causality assessment, most of the ADRs were possible ADRs followed by probable, most of the ADRs were observed to be with moderate severity followed by mild severity. Clinical pharmacists should take responsibility of the identification, management and prevention of adverse drug reactions especially in case of drug resistant tuberculosis patients in order to improve their health related quality of life.

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