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Original Research Article

ASSESSMENT OF PATTERN OF RESISTANCE AND FACTORS AFFECTING ADVERSE DRUG REACTIONS AMONG PATIENTS WITH MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS: A TERTIARY HOSPITAL BASED STUDY

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Abstract

Background: Multidrug-resistant TB (MDR-TB) is a growing concern, affecting 3.3% of new cases and 18% of previously treated cases. This study aims to analyze resistance patterns and adverse outcomes among MDR-TB patients to improve treatment and pharmacovigilance. **Materials and Methods:** Hospital-based analytical observational study of 80 MDR-TB patients, with data collected through personal interviews and laboratory results. **Results:** High prevalence of resistance to both isoniazid and rifampicin (58.75%). The majority of patients were non-contact cases (87.5%). Previous Anti-Tubercular Treatment episodes were common (45 patients). Risk factors for Adverse Drug Reactions (ADR) included alcohol use, HIV status, and advanced disease progression. Among the 70 secondary patients, 41 patients (58.6%) were initially categorized as "Failure" before converting to MDR, followed by 14 patients (20%) in the "Relapse" category. The Line Probe Assay detected patterns of drug resistance, with 47 patients (58.75%) showing resistance to both isoniazid and rifampicin (HR), and 33 patients (41.25%) showing resistance to rifampicin alone (R). **Conclusion:** In conclusion, the study highlights that the majority of patients were non-contact cases, and a significant proportion had undergone previous Anti-Tubercular Treatment episodes. The Line Probe Assay results indicate a high prevalence of resistance to both isoniazid and rifampicin. These findings have important implications for the development of effective treatment strategies and public health interventions to combat MDR tuberculosis. Anemia, BMI <18.5, alcohol addiction history, HIV positivity status and are in risk to develop second line anti-tuberculosis drugs adverse reactions. Patients with these risk factors should be carefully monitored during the anti-tuberculosis drug treatment.

INTRODUCTION

Tuberculosis (TB) is one of the top 10 causes of death globally and has been the leading cause of death from a single infectious agent since 2007. In 2019, there were approximately 11 million new cases of tuberculosis (TB) worldwide, resulting in 1.3 million fatalities attributable to TB. Southeast Asia and Africa were responsible for 44% and 25% of these deaths, respectively.[1]

Multidrug-resistant tuberculosis (MDR-TB) is a kind of tuberculosis that is resistant to at least two important drugs, rifampicin and isoniazid. The worldwide prevalence of multidrug-resistant tuberculosis (MDR-TB) is 3.3% among individuals with newly diagnosed cases of tuberculosis, and 18% among those who have been previously treated for tuberculosis.[2]

The World Health Organization (WHO) defines an adverse drug reaction as a noxious and unintended response to a drug at normal doses, used for prevention, diagnosis, or treatment. Antitubercular drugs can cause various adverse reactions, affecting multiple systems, including gastrointestinal, liver, skin, nervous, and eyes. Monitoring and reporting these reactions were crucial to identify the culprit

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drug and tailor treatment regimens. Pharmacovigilance of antitubercular drugs is essential for successful tuberculosis treatment and its elimination, highlighting the importance of vigilance in drug safety to ensure effective treatment outcomes.[3] Hence, the present study aimed to analyze the Assessment of Pattern of resistance identify factors associated with adverse outcomes among MDR-TB patients.

MATERIALS AND METHODS

This hospital-based analytical observational study was conducted at the PMDT site in the Department of Respiratory Medicine at JLN Medical College and Associated Group of Hospitals in Ajmer, Rajasthan, after obtaining approval from the institutional ethical committee. The study included all diagnosed cases of Multidrug Resistant Pulmonary Tuberculosis patients who reported to the PMDT site and had documented evidence of sputum for Mycobacterial Culture & Sensitivity from an Intermediate Reference Laboratory. Mycobacterial Culture & Sensitivity was performed using Conventional solid egg-based Lowenstein-Jensen (LJ) media and Molecular Line Probe Assay. Patients who did not provide detailed history or documents, were severely ill, stopped treatment prematurely, died before the 6-month follow-up, or were unwilling to participate were excluded from the study.

All MDR-TB patients were referred to the ICTC under the Department of Medicine and Microbiology for HIV counselling and testing. Female patients received additional counselling on family planning. For pre-treatment evaluation of XDR TB patients, an EKG, serum electrolytes, and surgical evaluation were also conducted, all free of cost. Symptomatic medications were prescribed to all patients, provided free of cost by the Rajasthan state government under the MNDY scheme. Once the pre-treatment evaluation results were approved by the DOTS Plus site Committee, patients were treated with the RNTCP Category IV regimen, which includes second-line anti-TB drugs. All information to accomplish objectives was collected by personal interview of each of the study subjects for about 30 to 45 minutes at PMDT site using pre-designed Proforma.

A detailed history of contact with pulmonary tuberculosis/Multidrug Resistant tuberculosis patients and any death due to pulmonary tuberculosis/Multidrug Resistant tuberculosis in family was elicited. History of any other co-morbid conditions such as Diabetes mellitus, HIV etc. was taken. A detailed personal history of Occupation, Educational and Socioeconomic status, addiction habit and religion was also assessed. Detailed interaction was undertaken with each patient, to understand the problems faced by them during and after the treatment and preventive practice adopted by the patients. This helped a lot in gaining the faith of the patients, and family members to elicit the relevant information.

General impression regarding DOTS was also assessed, by inquiring about the difficulties faced by them in approaching health care provider at corresponding health facility, behavior of DOT provider or other health personnel and about their overall feeling about the efficacy or otherwise of treatment.

The results for HIV reactivity, sputum smear and culture and drug susceptibility testing (DST) were obtained from the available records of the patients.

This study was conducted using face to face administered questionnaires. The questionnaires consisted of a mixture of open ended, multiple choice, and yes/no questions. These questions were asked to establish demographic and social characteristics, housing environment, health service experience, clinical characteristics, knowledge about TB/MDR-TB, and self-reported reason for defaulting.

Adverse drug reactions were seen after completion of 1 month, 3 months and 6 months of the beginning of treatment.

Data thus collected was entered into Microsoft excel 2010 worksheet in the form of master chart. Then data were tabulated and analysed as per the aims and objectives with help of appropriate statistical software. Microsoft word and Excel have been used to generate graphs, tables etc. To find out significance of difference in proportions in various groups Chi square test was applied and for the significance cut off P value.

RESULTS

Table 1 shows age wise distribution with maximum patients 32.5% aged 41-50 years followed by 31.25% aged 31-40 years, 21.25% aged 21-30 years. Table 2 reveals 70 (87.5%) patients were non-contact cases. Table 3 shows details of patients with previous anti tubercular treatment (ATT) episodes. Table 4 shows total duration of past ATT in months with 45 (12.5%) patients were treated for >12 months and 25 (31.3%) were treated for <=12 months. Table 5 shows the initial category in secondary MDR patients before MDR conversion out of 70 secondary patients. Table 6 shows pattern of resistance as detected by Line Probe Assay. Table 7 shows several potential risk factors for Adverse Drug Reactions (ADR) and discovered that alcohol use was a notable risk factor, with a clear statistical distinction between individuals who consume alcohol and those who do not. On the other hand, tobacco use, anemia, low albumin levels, and diabetes did not demonstrate a significant impact on ADR occurrence. In stark contrast, having HIV and advanced disease progression showed a strong correlation with ADR, with a highly significant statistical difference. These results indicate that

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specific factors, including alcohol consumption, HIV status, and disease severity, BMI significantly contribute to the development of ADR, whereas others do not.

Table 1: Age distribution

Age	No of patients	Percentage
15-20	2	2.5
21-30	17	21.25
31-40	25	31.25
41-50	26	32.5
51-60	4	5
>60	6	7.5

Table 2: Pattern of MDR disease

MDR	No of patients	Percentage
MDR contact case	10	12.5
Non-contact cases	70	87.5

Table 3: Previous Anti Tubercular Treatment (ATT) episodes

No of previous ATT episodes	No of patients	Percentage
0	10	12.5
1	11	13.75
2	20	25
3	31	38.75
4	5	6.25
5	3	3.75

Table 4: Total duration of past ATT in months

Total duration in months	No of patients	Percentage
<=12 months	25	31.3
>12 months	45	56.3
nil	10	12.5

Table 5: Initial category in secondary MDR patients before MDR conversion out of 70 secondary patients

Category	No of patients	Percentage
Failure	41	58.6
Relapse	14	20
Default	15	21.4

Table 6: Pattern of resistance as detected by Line Probe Assay

Pattern (HR/R)	No of patients	Percentage
HR	47	58.75
R alone	33	41.25

Table 7: Assessment of Adverse drug reaction in comparison to various parameters

Parameters		With ADR	Without ADR	P value
Alcohol	Yes	50	4	Chi square= 4.67, p<0.05
	No	7	4	
Tobacco	Yes	40	5	Chi square=0.001, p>0.05 sig
	No	17	3	
Tobacco chewing and alcohol intake	Yes	14	4	Chi square = 1.175, p>0.05 n.s
	No	43	4	
Anaemia	Yes	56	8	Chi Square= 5.541, p < 0.05
	No	10	6	
Hypoalbuminemia	Yes	6	4	Chi square=2.424, p> 0.05 N.S
	No	60	10	
BMI	<18.5	62	10	Chi square 4.242, p value<0.05, significant
	Normal	4	4	
Diabetes mellitus	Yes	12	2	Chi square= 0.121, p>0.05 N.S
	No	54	12	
HIV status	Positive	20	3	Chi square = 6.84, p value <0.01 very significant
	Negative	30	27	
Radiological extent of disease	FAR ADV	59	8	Chi square= 8.827, p value < 0.01 very significant
	MOD ADV	7	6	

DISCUSSION

A study investigated various risk factors for Adverse Drug Reactions (ADR) and found that alcohol consumption was a significant risk factor, with a statistical difference between alcoholics and non-alcoholics. However, tobacco addiction, anemia, low albumin levels, and diabetes did not show a

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significant difference in ADR occurrence. In contrast, HIV-positive status and far-advanced radiological extent of disease were strongly associated with ADR, showing a highly significant statistical difference. These findings suggest that certain factors, such as alcohol consumption, HIV status, and disease severity, play a crucial role in the development of ADR, while others do not.

In this study, 86 patients were initially enrolled, but 6 were lost to follow-up and excluded, leaving a total of 80 patients. Among these, 66 patients (82.5%) experienced Adverse Drug Reactions (ADRs). The study assessed ADRs associated with second-line anti-TB drugs listed in the WHO Model List of Essential Drugs, including amikacin, capreomycin, ciprofloxacin, cycloserine, ethionamide, kanamycin, ofloxacin, para-aminosalicylic acid, and prothionamide. For analysis, drugs were grouped by pharmaceutical class: aminoglycosides (amikacin and kanamycin), thioamides (ethionamide and prothionamide), and fluoroquinolones (ciprofloxacin and ofloxacin).

Effective management of adverse drug reactions (ADRs) is crucial for treatment adherence and patient compliance, particularly in the context of increasing drug resistance to antitubercular drugs and the emergence of newer variants like XDR tuberculosis. The primary cause of resistance is poor adherence to treatment regimens, which can be addressed by minimizing risk factors for ADRs and providing adequate treatment for ADRs associated with highly toxic second-line antituberculous drugs. However, there is a paucity of studies focused on monitoring risk factors for ADRs in MDR TB cases, as well as their ADR profiles, severity assessment, and impact on treatment adherence.

Our study considers all possible risk factors for ADR and their statistical significance of association with the ADR. We have also taken into account the prevalence of adverse drug reactions among patients treated with category IV RNTCP regimen at Dots Plus site, patterns of adverse drug reactions, severity of adverse drug reactions and its impact on therapy, impact of adverse drug reactions on treatment adherence and possible outcome.

In our study the pattern of resistance to antituberculosis drugs were mostly HR (58.8 %) and R (41.3%). Information available in some parts of India shows an increase in the level of IDR (initial drug resistance) to Isoniazid (H) & Rifampicin (R)8. The IDR as reported from India is 18% to 20% for H, 14% to Streptomycin (S), and 3% to HR. This level of IDR reflects the effect of previous TB Control programme with unsupervised SCC (short course chemotherapy) regimen. Resistance to R started appearing late and has remained at a low level of about 1%.[4]

As per the published data from Bangalore in the year 1985-86, IDR to any drug was 20.6% (INH 17.4%, Streptomycin 4.8%, Rifampicin 2.9%, HR 1.4%).5 These data pertain to patients attending the District TB Centre situated in Bangalore Mahanagara Palike (BMP).

According to our findings in this prospective cohort study, there is no increased risk of TB-drug adverse events when age increases. In previous reports, the occurrence of any major side effect has been associated with age, especially amongst the elderly. The frequency of adverse reactions has shown to increase in a progressive and direct form in relationship to age.[6,7] Overall, vulnerability to adverse reactions are more probable at older ages—especially hepatotoxicity—due to a significant reduction in clearance rate of metabolized drug agents by the cytochrome P450 enzyme, changes in the hepatic blood flow distribution, as well as other factors affecting liver function.[8,9] In our study this insignificance of age can be due to disproportionately more number of patients in the age group below 65 as compared to age group more than 65.

Anemia, a blood marker commonly related to chronic diseases,[10] was another risk factor found in our study. Although data on hemoglobin levels is not routinely recommended in the laboratory examination according to the International Standard for Tuberculosis Care (ISTC),[11] such assessment is usually taken during pretreatment evaluation in Indian context according to DOTS plus PMDT (programmatic management of drug-resistant tuberculosis) guidelines. Some studies qualify anemia and malnutrition as risk factors for the development of anti-tuberculosis drug adverse reactions.[12,13] Some additional nutrition factors have been associated such as mid-arm circumference and hypoalbuminaemia.[14] Thus, it is not surprising that anemia could be another potential predictor of adverse reactions. However, a direct causal relationship is far from being established. Some evidence suggests that anemia may not at all be a risk factor for the appearance of adverse effects, but rather the adverse reaction itself.[15] Isoniazid and rifampicin may directly cause hemolytic anemia, as can pyrazinamide cause sideroblastic anemia. Others have suggested that anemia is seen as part of the clinical manifestation of tuberculosis and as a consequence of a chronic disease (chronic disease induced anemia). In general, tuberculosis patients have a higher predisposition to develop gastrointestinal absorption problems, consequently leading to anemia as a secondary side effect—yet not a risk factor itself. In addition, a selection bias might have occurred due to the nutritionist selection of anaemic cases. Thus, further studies are needed in order to confirm and clarify these findings.

On the other hand, a body mass index less than 18.5 kg/m2 (underweight) was also associated with adverse effects as previously describe in other papers. The host protective immune mechanism of infection with Mycobacterium tuberculosis depends critically on the interaction and cooperation between monocyte-macrophages and T-lymphocytes and

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their cytokines. Substantial experimental evidence suggests that malnutrition can lead to secondary immunodeficiency that increases the host's susceptibility to infection. Increased risk of tuberculosis can result from alteration in the individual protective function of, or the interaction between T-lymphocytes and macrophages because of nutritional insult. Of notice, a BMI<18.5 kg/m2 is also reported as a risk factor for active TB.[17-18] Drug metabolism pathways including acetylation pathways have been shown to be deranged in states of protein energy malnutrition. On the other hand, a body mass index more than 25 kg/m2 (overweight and obesity) was also associated with adverse reactions. Limited information is available regarding this association, but a prior investigation reported that drug toxicity might result in obese patients receiving total body weight doses. Another study has overall reported that obesity can have some effects on drug metabolism which could increase possibility of adverse events.[19]

Finally, smoking and tobacco chewing was the last independent factor associated with TB-drug adverse reactions with relative risk of 1.058 for tobacco users and smokers but the association was statistically insignificant. A previous case-control study found a statistically significant association between smoking and liver toxicity due to pyrazinamide.[20] However, literature regarding this finding is limited and further studies are needed to corroborate results.

Alcohol use can predispose and accelerate hepatotoxic effects caused especially by isoniazid,[21-22] due to enzyme induction changes. Alcohol use is independently associated with adverse reactions in MDR patients with a relative risk of 1.455 and the association was found to be statistically significant. Co-infection with hepatitis B or C has proven to be a high risk for adverse drug effects.[23] Unfortunately, our study did not assess hepatitis B or C infection status.

HIV infection was also a risk factor associated with drug reactions. Previous authors have reported that side effects are higher in HIV-positive than in HIV-negative patients,[24] especially due to parallel treatment with highly active antiretroviral therapy (HAART).[25,26] The interactions between the rifamycins (rifampicin, rifabutin and rifapentine).and the NNRTIs (Non-nucleoside reverse transcriptase inhibitors) and the PIs (Protease inhibitors) are complex. The PIs and NNRTIs are metabolized mainly through the cytochrome P450 (CYP) 3A4 enzymes. The rifamycins induce the expression of CYP3A4 isoenzyme in the liver and intestines, thereby greatly reducing the plasma concentration and exposure to the PIs and the NNRTIs when administered together. In addition, rifampicin (RMP) increases the activity of the efflux multidrug transporter P-glycoprotein (P-gp), which contributes to the elimination of the PIs. The reduction in plasma concentration of the PIs and NNRTIs during concurrent treatment with rifamycins can be associated with HIV treatment failure and emergence of drug resistance.[27]

Our findings are similar to Kocfa Chung-Delgado et al,[28] and Carreira et al,[29] as in our study we also did not find any significant difference between diabetes and adverse effects in MDR TB patients. DM causes dysfunction of the immune system, which can increase the susceptibility to TB. The main immunologic abnormalities are abnormal functions of polymorphonuclear cells, decreased peripheral monocytes with impaired phagocytosis, poor blast transformation of lymphocytes and defects in complement opsonic function. The pulmonary physiologic functions are also altered in diabetic patients.

At the same time, TB may increase the blood glucose levels and trigger a “latent diabetes” or be a factor in its decompensation. Fever, inactivity and malnutrition stimulate the stress hormones which raise the blood sugar level. Plasma levels of interleukin-1 and tumor necrosis factor-alpha are raised in severe TB, which can stimulate the anti-insulin hormones. The antituberculosis (anti-TB) drugs also influence the glycemic control. Pyrazinamide may cause hypoglycemia with difficulty in controlling blood sugar levels.[30,31]

DM is known to modify the clinical features of pulmonary TB.[32] and it has also been associated with increased risk of TB treatment failure or relapse and of increased risk of mortality. The radiographic patterns of TB in diabetic patients may also be different from those found in nondiabetics, as was initially reported by Sosman and Steidl.[33] These authors found a higher rate of lower lung field (LLF) involvement in their diabetic patients.

CONCLUSION

In conclusion, the findings highlight that the majority of patients were non-contact cases, and a significant proportion had undergone previous Anti-Tubercular Treatment episodes. The study also reveals that a substantial number of patients had a total ATT duration of more than 12 months, and a significant proportion were initially categorized as "Failure" before converting to MDR. The Line Probe Assay results indicate a high prevalence of resistance to both isoniazid and rifampicin. These findings have important implications for the development of effective treatment strategies and public health interventions to combat MDR tuberculosis. Anemia, BMI <18.5, alcohol addiction history, HIV positivity status are in risk to develop second line anti-tuberculosis drugs adverse reactions. Patients with these risk factors should be carefully monitored during the anti-tuberculosis drug treatment. A comprehensive clinical history (smoking and body mass index) and additional exams, including hemoglobin, hematocrit, HIV-ELISA, might be useful to identify these patients.

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