Medico Research Chronicles
ISSN NO. 2394-3971
DOI No. 10.26838/MEDRECH.2024.11.6.749
Contents available at www.medrech.com

Rate and Pattern of Drug Reaction among Tuberculosis Patient During Antitubercular Drug Therapy

[1]Dr. Biswas Shaheen Hassan, [2]Prof. Biswas Akhtar Hossain, [3]Dr. Rezwana Pervin Nisa, [4]Syed E. Shaude

1. Associate Professor, National Institute of Diseases of the Chest and Hospital, Dhaka, Bangladesh.
2. Professor, Ex Head, Department of Respiratory Medicine, Dhaka Medical College, Dhaka, Bangladesh, Ex-Principal, Northern International Medical College Hospital, Dhaka, Bangladesh.
3. Coordinator, Department of Research and Development, International Network of Doctors Journal, Dhaka, Bangladesh.
4. Chief Coordinator, Department of Research and Development, International Network of Doctors Journal, Dhaka, Bangladesh.

ARTICLE INFO | **ABSTRACT** | **ORIGINAL RESEARCH ARTICLE**

Article History
Received: November 2024
Accepted: December 2024
Key Words:
Tuberculosis, Antitubercular drug therapy, Adverse drug reaction, Tuberculosis patients

Background: Tuberculosis (TB) treatment often involves multi-drug regimens that can lead to adverse drug reactions (ADRs). These ADRs may affect treatment adherence and outcomes. In the treatment of tuberculosis (TB), the use of multi-drug regimens has been linked to unfavorable adverse drug reactions (ADRs). This study aims to evaluate the rate of ADRs and their effects on TB treatment at National Institute of Diseases of the Chest and Hospital with a focus on patients with risk factors.

Objective: To assess the rate and pattern of adverse drug reactions (ADRs) caused by anti-TB medications in the infectious disease department throughout 12 months. To identify known adverse drug reactions (ADRs) that are severe and avoidable.

Methods: A retrospective study was conducted to evaluate the rate and pattern of drug reactions in tuberculosis patients receiving antitubercular therapy. This cross-sectional study was conducted via retrospective review of outpatients' medical records. Details regarding ADRs were identified by a pharmacist and verified by a consultant respiratory physician. Data were analyzed by SPSS software (version 25.0, IBM statistical product).

Results: Of the 50 patients, 88% were male with a mean age of 47.8 ± 14.18 years. Twenty percent of patients experienced ADRs, with gastrointestinal issues and skin rashes being the most common. Seventy percent of ADRs occurred within 3 weeks of starting the intensive phase of treatment. Diabetes mellitus was the most prevalent comorbidity (60% of patients). While not statistically significant, trends suggested

higher ADR rates in smokers and long-term diabetics. All ADRs were managed symptomatically without discontinuing antitubercular therapy.
Conclusion: The ADR rate in this study population was comparable to that reported in patients without comorbidities. Gastrointestinal ADRs were most common, and most ADRs occurred early in treatment. While comorbidities didn't significantly increase ADR risk, the high prevalence of diabetes underscores the need for integrated TB-diabetes care. Close monitoring for ADRs, especially during the initial weeks of treatment and in patients with risk factors, is crucial for successful TB management.

Corresponding author
Dr. B. S. Hassan*

2024, www.medrech.com

INTRODUCTION:

Tuberculosis (TB) is an infectious disease that most often affects the lungs and is caused by a type of bacteria. It spreads through the air when infected people cough, sneeze or spit. About a quarter of the global population is estimated to have been infected with TB bacteria. About 5–10% of people infected with TB will eventually get symptoms and develop TB disease.[1]

A total of 1.3 million people died from TB in 2022 (including 167 000 people with HIV). Worldwide, TB is the second leading infectious killer after COVID-19 (above HIV and AIDS). In 2022, an estimated 10.6 million people fell ill with tuberculosis (TB) worldwide, including 5.8 million men, 3.5 million women and 1.3 million children. TB is present in all countries and age groups. TB is curable and preventable. Multidrug-resistant TB (MDR-TB) remains a public health crisis and a health security threat. Only about 2 in 5 people with drug resistant TB accessed treatment in 2022. Global efforts to combat TB have saved an estimated 75 million lives since the year 2000. US$ 13 billion is needed annually for TB prevention, diagnosis, treatment and care to achieve the global target agreed at the 2018 UN high level-meeting on TB. Ending the TB epidemic by 2030 is among the health targets of the United Nations Sustainable Development Goals (SDGs).[1]

The WHO South-East Asia (SEA) Region is home to around one-fourth of the world's population with more than 45% burden of annual TB incidence (new patients developing the TB disease). It is estimated that in 2022, more than 4.8 million people fell ill with TB and more than 600 000 died (excluding HIV+TB mortality) because of the disease which is more than half of global TB deaths. Treatment success for new and relapse TB cases was 88% (2021 cohort). Six of global high TB burden countries are in the SEA Region: Bangladesh, Democratic People's Republic of Korea, India, Indonesia, Myanmar and Thailand while for RR-/MDR-TB burden, Nepal replaces Thailand in the high-burden list for the Region. [2]

The key component of antitubercular therapy (ATT) is the standard directly observed treatment, short course (DOTS) chemotherapy regimen, which requires taking drug combinations of isoniazid, rifampicin (RFP), pyrazinamide, ethambutol, and/or streptomycin (SM). Despite the positive therapeutic effects, studies have shown that utilization of multidrug regimens can cause undesirable adverse drug reactions (ADRs) of varying degrees of severity such as hepatotoxicity, gastrointestinal disorders, allergic reactions, and arthralgia. ADRs may play a role in treatment nonadherence, which may therefore contribute to the development of drug-resistant tuberculosis. medication resistance can be prevented by improving patient compliance, increasing the number of patients who complete their

therapy, identifying adverse medication reactions early on and managing them promptly. Studies on ADR of ATT in adult patients are numerous. Still, those on ADR of ATT in specific populations, like pediatric TB, and TB with comorbidities like diabetes mellitus, liver disorders, renal disorders, thyroid disorders, psychosis, seizure disorders, undernutrition, and social behaviors such as alcohol and tobacco use, are scarce. This research aims to learn more about the rate and pattern of drug reaction among TB patient during antitubercular drug therapy in these unique populations.[3]

Treatment non-adherence is frequently most commonly caused by ADR. According to studies, the biggest treatment interruption with ATT happens in the second and third months. Early improvement and the occurrence of adverse drug reactions were determined to be the two most frequent causes.[4] Drug-resistant forms of tuberculosis (TB) are more common, which could reduce the effectiveness of treatment, and TB tolerance brought on by adverse effects from anti-TB medications is a major concern. [5]

Risk factors and concomitant diseases affect the frequency of ADR and the results of TB treatment. The incidence of ADRs is higher in patients with diabetes mellitus and TB than in those with TB alone. In addition, individuals diagnosed with diabetes mellitus had a lower sputum conversion rate and a higher likelihood of experiencing a poor course of treatment compared to those without the condition. [6] Smoking increase ADRs, sputum culture-positive rate at the end of the 2nd month, and failure rate of pulmonary TB patients.[7]

MATERIALS AND METHODS

Study design, population, sampling and data collection

This retrospective study looked at the cases of outpatient department, National Institute of Diseases of the Chest and Hospital from June 2022 to May 2023. The study population included adult patients diagnosed with tuberculosis and initiated on a standard four-drug antitubercular regimen in this hospital The information was obtained from patients' medical report, TB booklet and in-patient record (if they had been admitted previously). Demographic characteristic, causative drug and management were recorded and analyzed. The study successfully enrolled 41patient during this study's defined data collection period and convenience sampling technique was adopted in this study. Data analysis was done using SPSS software. Mean, percentages, Fisher's exact test, Chi-square test, and *P*-values were calculated. $P < 0.05$ was taken to denote statistically significant relationship. A univariate analysis was carried out to test the association between risk factors and occurrence of ADR.

Study criteria

Inclusion criteria

All patients of either gender aged 18 years and above who are under the treatment of tuberculosis with anti-tuberculosis drugs.

Exclusion criteria

Pregnant patients mentally challenged and who presented with hepatic dysfunction and subjects who were not willing to participate were excluded from the study.

RESULTS

Out of the 50 enrolled patients, 42 were diagnosed as pulmonary TB and 8 patients with extra-pulmonary TB. Four patients were having RFP-resistant TB, identified by CBNAAT, and were getting SM. Three patients had a history of previous ATT intake but were found to be with drug-sensitive TB and were on FDC with first-line drugs.

In this study, the study population was predominated by males (n = 44, 88%) [Table 1]. Only one patient was 20 years aged. The average age of the adult patient was 47.8 ± 14.18 years and of pediatric patient was 9 years [Table 2].

Table 1: Gender distribution of TB patients and ADR (*n*=50)

Gender	Total Patients n (%)	Frequency of ADR	Significance
Male	44 (88%)	8	P>0.05
Female	6(12%)	2	

ADR: Adverse drug reaction, TB: Tuberculosis

Table 2: Age-wise distribution of patients and ADR

Age in years	Total patients, *n* (%)	Frequency of ADR, *n* (%)	Significance
20	1 (2)	0	P>0.05
21-40	12 (24)	4(40)	
41-60	27 (54)	4(40)	
>60	10 (20)	2(20)	

ADR: Adverse drug reaction

All the subjects with the habit of only alcoholism gave a history of former smoking. Including them as smokers, the no. of smokers was 40 (80%). The most common risk factor was found to be combined diabetes and hypertension [Table 3].

Out of 50 patients, 10 ADRs were reported, out of which seven ADRs were reported by males and two were reported by females ($P > 0.05$). All ADRs were from patients with pulmonary TB. No ADR was reported from drug-resistant TB patients on second-line drugs. The most common ADRs were gastrointestinal problems such as loss of appetite, symptoms suggestive of gastritis such as heart burns and abdominal pain [Figure 1]. Loss of appetite was seen most frequently. Seven ADRs developed during the intensive phase (2–3 weeks after the start of intensive phase of the treatment) and three developed during the continuation phase (during the 4th month of the treatment). Out of the 10 ADRs reported, 4 were in non-smokers, 6 in current or former smokers ($P > 0.05$) 50% of the patients who developed ADR had diabetes as a comorbidity ($\chi 2 = 0.5208$, $P > 0.05$), and all were having diabetes for more than 5 years duration. Most of the ADR occurred in patients with sputum positivity of 2+, which was not statistically significant [Table 5].

All of the patients who experienced adverse drug reactions were managed symptomatically, and none of them needed to stop taking ATT. Eight of the ten ADRs had outpatient treatment. Peripheral neuropathy was a months-long condition that needed hospitalization for the two individuals. An analysis of the result was not possible for one patient who contracted hepatitis and was transported out. After receiving symptomatic treatment, the remaining patients recovered. Gastritis and skin rashes were two side effects that reappeared but did not necessitate stopping ATT.

Table 3: Prevalence of risk factors (*n*=50)

Risk factors	Frequency	Percentage
Diabetes mellitus	30	60
Hypertension	23	46
Asthma	13	26
Thyroid disorder	10	20

Seizure disorder	7	14
Renal disorders	5	10
Pediatric	1	2
Smoking	39	78

Table 4: Relationship between number of risk factors and ADR

No. of risk factors	Frequency (%)	Significance
1	18 (36)	P>0.05
2	26 (52)	
>2	6 (12_)	

ADR: Adverse drug reaction

Table 5: ADR in relation to sputum positivity

No. of risk factors	Frequency (%)	Significance
1+	2 (30)	P>0.05
2+	5 (50)	
3+	3 (30)	

ADR: Adverse drug reaction

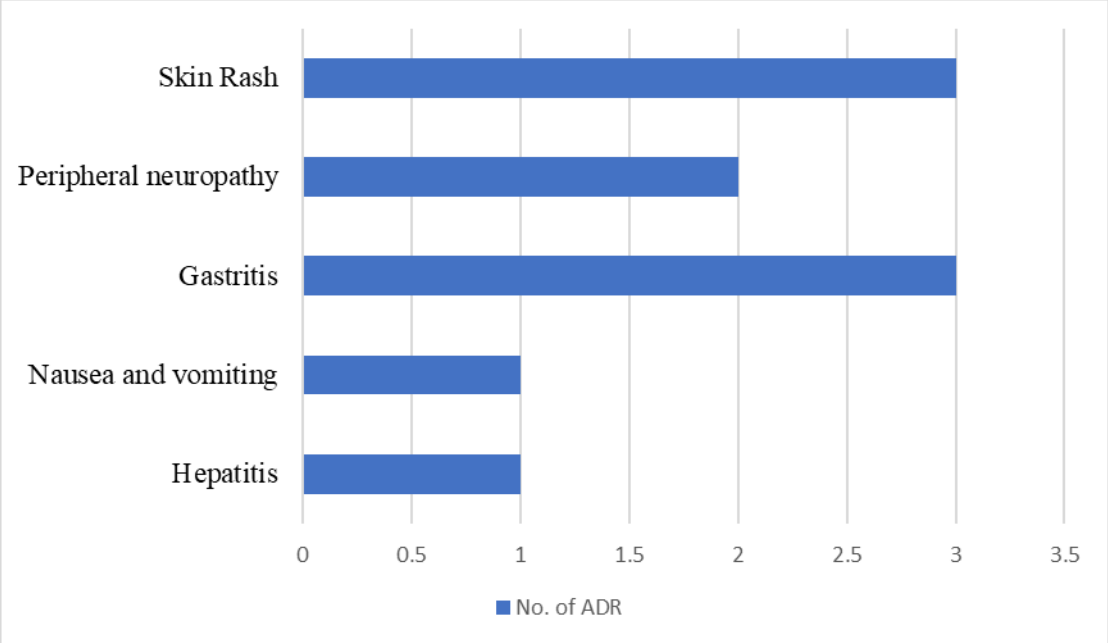

Fig 1: Pattern and frequency of ADR

DISCUSSION

To determine the frequency and pattern of adverse drug reactions (ADRs) in this unique demographic, fifty patients who were using DOTS ATT in addition to comorbidities and risk factors were included. According to our study, 20% of TB patients had ADR, which is comparable to other studies on ADR in individuals without concomitant illnesses.[8] From this, we can infer that there is not much increase in the incidence of ADR in patients with comorbid conditions. The study population was predominated by males (*n* = 44, 88%). Males are more vulnerable to

TB infection than females as they are exposed to several risk factors such as smoking and alcohol.[8] The most common comorbidity was found to be combined diabetes and hypertension (15 patients, 30%) and 30 patients (60%) had diabetes. This implies that all diabetic patients should be screened for TB and vice versa, especially in those with diabetes of longer duration.

Out of 10 reported ADRs, eight ADRs were reported by males and two ADRs were reported by females which are contrary to the article by Athira *et al*. [9] which says that the female gender is one of the predisposing factors for ADR. However, this may be due to the predominance of males in our study population. The prevalence of ADRs was determined by sputum positivity in the study by Dhingra *et al*.,[10] but in our study, it was not statistically significant. According to the study by Gholami *et al*.,[11] the incidence of ADRs is influenced by genetic differences in the population and the regimen followed by patients. The most common form of ADR is gastrointestinal problems and dermatitis was the second most common ADR. In our study, both gastritis and skin rash were equal in number (three each, 30%). This difference may be because of the difference in sample size between the two studies. The ADRs developed more in patients with pulmonary TB which is in correlation with a study by Athira *et al*. [9] where the ADRs were most frequently developed by the patients who had pulmonary TB than the patients with extra-pulmonary TB. About 70% of the ADRs occurred within 3 weeks of starting intensive phase of ATT. Similar results are seen in both studies by Sivaraj *et al*. [12] and Athira *et al*. [9] About 60% of the ADRs developed in smokers. In another study done on antiretroviral drugs, it was found that 89% of patients developed ADRs.[13]

CONCLUSION

The majority of ADRs can be controlled without stopping therapy, however they are still a major problem in TB treatment. Careful observation is necessary for effective TB care and to stop the emergence of drug-resistant TB, particularly during the first few weeks of treatment and in patients who have risk factors. The significance of thorough patient assessment and risk factor evaluation in tuberculosis treatment is underscored by these results. ADRs must be closely watched, particularly in individuals with numerous risk factors and in the first few weeks of treatment. The study also highlights how important it is for tuberculosis patients to receive integrated care.

References:

[1] Tuberculosis 2023. https://www.who.int/news-room/fact-sheets/detail/tuberculosis.

[2] Tuberculosis SEARO 2019. https://www.who.int/bangladesh/health-topics/tuberculosis.

[3] B J, Antony L, V B, A D. Pattern of adverse drug reactions of antitubercular drugs in tuberculosis patients with comorbidities and risk factors in South Indian government health-care facilities. National Journal of Physiology Pharmacy and Pharmacology 2021:1. https://doi.org/10.5455/njppp.2021.11.07220202105072021.

[4] Sinha K, Marak IT, Singh W. Adverse drug reactions in tuberculosis patients due to directly observed treatment strategy therapy; experience at an outpatient clinic of a teaching hospital in the city of Imphal, Manipur, India. J Assoc Chest Physicians 2013; 1:50.

[5] Dedun A, Borisagar G, Solanki R. Impact of adverse drug reaction of first line anti-tuberculous drugs on treatment outcome of tuberculosis under revised national tuberculosis control programme. Int J Adv Med 2017; 4:645.

[6] Singh A, Prasad R, Balasubramanian V, Gupta N, Gupta P. Prevalence of adverse drug reaction with first-line drugs among

patients treated for pulmonary tuberculosis. Clin Epidemiol Glob Health 2015;3: S80-90.

[7] Ma Y, Che NY, Liu YH, Shu W, Du J, Xie SH, *et al*. The joint impact of smoking plus alcohol drinking on treatment of pulmonary tuberculosis. Eur J Clin Microbiol Infect Dis 2019; 38:651-7.

[8] Pant R, Pandey K, Joshi M, Sharma S, Pandey T, Pandey S. Risk factor assessment of multidrug-resistant tuberculosis. J Nepal Health Res Council 1970; 7:89-92.

[9] Athira B, Manju CS, Jyothi E. A study on adverse drug reactions to first line anti-tubercular drugs in DOTS therapy. Int J Pharmacol Clin Sci 2015; 4:7-11.

[10] Dhingra VK, Rajpal S, Aggarwal N, Aggarwal JK, Shadab K, Jain SK. Adverse drug reactions observed during DOTS. J Commun Dis 2004; 36:251-9.

[11] Gholami K, Kamali E, Hajiabdolbagh M, Shalviri G. Evaluation of anti-tuberculosis induced adverse reactions in hospitalized patients. Pharm Pract (Granada) 2006; 4:134-8.

[12] Sivaraj R, Umarani S, Muralidhar P, Parasuraman S. Revised national tuberculosis control program regimens with and without directly observed treatment, short-course: A comparative study of therapeutic cure rate and adverse reactions. Perspect Clin Res 2014; 5:16-9.

[13] Sadiq S, Gupta S, Khajuria V, Tandon VR, Mahajan A, Gupta M. Adverse drug events due to antiretroviral therapy in a Northern Indian tertiary care institution. Natl J Physiol Pharm Pharmacol 2016; 6:205-8.