Section: Miscellaneous

Original Research Article

ADVERSE DRUG EVENTS FROM FIRST-LINE ANTI-TUBERCULOSIS DRUGS IN A TERTIARY MEDICAL CENTER

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ABSTRACT

Background: Tuberculosis (TB) has remained one of the top causes of morbidity and mortality in the Balangir, Odisha since 2018. However, adverse drug reactions (ADR) from first-line anti-tuberculosis medications such as rifampicin, isoniazid, pyrazinamide, and ethambutol cause significant impact on treatment adherence. The aim is to determine the incidence of ADRs among patients treated with first-line anti-tuberculosis medications at a Bhima Bhoi Medical College of Balangir District of Odisha a tertiary medical centre.

Materials and Methods: In this retrospective cohort study, rifampicin-susceptible patients undergoing first-line anti-TB treatment enrolled in the Tuberculosis-Directly Observed Treatment Strategy at the Balangir Bhima Bhoi medical college were included. Pertinent data obtained from chart review included sociodemographic factors, clinical characteristics, duration of treatment prior to the appearance of adverse drug reactions, type of ADRs, TB medication causing the ADR, and treatment outcomes.

Results: A total of 524 patients treated with first-line anti-TB treatment were identified, with 46 (8.78%) noted to have ADRs to the treatment regimen. Most reaction types included mild or localised skin reactions (34.8%), severe skin rash secondary to hypersensitivity (32.6%), and jaundice due to hepatitis (21.7%). Reaction to more than one medication was seen in 89.1% of patients with ADRs, with rifampicin having the highest frequency of ADR (4.3%) among the anti-TB medications.

Conclusion: The incidence of ADRs among patients treated with first-line anti-TB medications at Balangir Bhima Bhoi medical college in the Tuberculosis-Directly Observed Treatment Strategy is frequent and comparable to other relevant study populations. A larger sample size and exploration of other methodological studies are recommended to further expand on this study.

Keywords: Adverse drug reactions (ADR), directly observed treatment, tertiary medical centre, tuberculosis (TB).

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. It remains a major public health problem, especially in developing countries such as the Bhima Bhoi MCH Balangir.[1,2] TB treatment requires a prolonged multidrug regimen using first-line anti-TB medications: rifampicin (RIF), isoniazid (INH), ethambutol (EMB), and pyrazinamide (PZA). To improve treatment adherence, the World Health Organization (WHO) introduced the Directly Observed Treatment Strategy (DOTS).[3,4]

Although effective, these medications can cause adverse drug reactions (ADRs), which may lead to treatment interruption, poor adherence, or the need for second-line therapies. Information on the

prevalence and characteristics of ADRs in the data is limited.[5,6]

This study aimed to determine the incidence, characteristics, risk factors, and outcomes of ADRs among patients receiving first-line anti-TB drugs at a Department of Health tertiary medical center. The findings may help improve patient safety, treatment outcomes, and resource allocation for TB management.[7]

MATERIALS AND METHODS

Definition of Terms: Adverse drug reactions (ADRs) were classified based on the DOH National Tuberculosis Program Manual of Procedures, 6th Edition. Minor ADRs included gastrointestinal disturbances, mild skin reactions, orange-colored urine, peripheral neuropathy, arthralgia, and flu-like symptoms. Major ADRs included severe skin rash, hepatitis, optic neuritis, renal disorders, psychosis, convulsions, thrombocytopenia, anemia, and shock.

Research Design: This study used a retrospective cohort design. Data were collected through chart reviews from the Balangir Bhima Bhoi medical college TB-DOTS Department using records before 2021 until the required sample size was reached. An online data collection form was used to gather relevant sociodemographic data (age, sex), clinical characteristics, treatment history, comorbidities, ADR onset, suspected TB medications, and treatment outcomes. ADR diagnoses were based on physicians' assessments documented in patient charts. Recorded ADRs included gastrointestinal disturbances, hepatotoxicity, ototoxicity, nephrotoxicity, peripheral neuropathy, and cutaneous reactions. Participants were selected according to the study's inclusion and exclusion criteria.

Statistical Analysis

SPSS version 27.0 was used for data processing and analysis. Mann-Whitney U test was used to compare non-normal continuous variables, while Chi-square test was used to compare categorical non-continuous variables and, in cases where this was not applicable, Fisher's exact

test was used. To determine the factors associated with the presence of ADR, a simple logistic regression was used. $P \leq 0.05$ were considered statistically significant.

RESULTS

A total of 524 patients receiving first-line anti-tuberculosis treatment were included (Table 2). Among them, 46 patients (8.78%) developed adverse drug reactions (ADRs).

The male-to-female ratio was similar in both groups (ADR: 1.875; non-ADR: 1.795). Patient ages ranged from 19 to 85 years, with a median age of 42.5 years in the ADR group and 45 years in the non-ADR group.

Most patients had pulmonary TB, clinically diagnosed TB, and were new treatment cases. ADRs were more common in patients with diabetes compared to those with HIV.

The most common ADRs (Table 3) were:

- Mild or localized skin reactions (34.8%)
- Severe skin rash due to hypersensitivity (32.6%)
- Jaundice due to hepatitis (21.7%)

Most ADR cases (89.1%) involved reactions to more than one anti-TB drug. Among individual drugs, rifampicin had the highest association with ADRs (4.3%).

The majority of patients with ADRs completed treatment, and the difference in outcomes was not statistically significant.

Simple logistic regression was used to identify factors associated with ADRs; however, only selected variables showed significant associations

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Rifampicin susceptible patients undergoing Category 1 treatment before 2021.	Paediatric patients (aged ≤18 years). Patients with multidrug-resistant tuberculosis.

Table 2: Sociodemographic and clinical characteristics of patients with and without adverse drug reactions to first-line anti-tuberculosis medications in Balangir Bhima Bhoi medical college tuberculosis Directly Observed Treatment Strategy, from earlier than 2021

Variables		n (%) Patients with ADR (N=46)	n (%) Patients without ADR (N=478)
Sex	Male	30 (65.2)	307 (64.2)
	Female	16 (34.8)	171 (35.8)
Age Median (IQR)		42.5 (27.75)	45 (33.75)
TB case type	Pulmonary TB	36 (78.3)	414 (86.6)
	Extrapulmonary TB	10 (21.7)	64 (13.4)
TB diagnosis type	Clinically diagnosed TB	36 (78.3)	337 (70.5)
	Bacteriologically confirmed TB	10 (21.7)	141 (29.5)
TB treatment history	New case	37 (80.4)	448 (93.7)
	Retreatment	9 (19.6)	30 (6.3)
Comorbidities	Diabetes	7 (63.63)	6 (46.15)
	HIV	4 (36.36)	7 (53.85)
Mean duration of treatment prior to appearance of ADR (days)		35 (SD: 27.09)	n/a

Note: Other comorbidities not specified were not included. IQR: interquartile range; TB: tuberculosis.

Table 3: Frequency distribution and incidence of adverse drug reaction types among patients with adverse drug reactions to first-line anti-tuberculosis medications

Adverse drug reaction	Frequency	Percentage	Cumulative incidence
Gastrointestinal intolerance	3	6.5%	0.5
Mild or localised skin reactions	16	34.8%	3.05
Orange-coloured urine	0	0%	0
Burning sensation in the feet due to peripheral neuropathy	1	2.2%	0.19
Arthralgia due to hyperuricemia	1	2.2%	0.19
Flu-like symptoms (fever, muscle pains, inflammation of the respiratory tract)	0	0%	0
Severe skin rash due to hypersensitivity	15	32.6%	2.86
Jaundice due to hepatitis	10	21.7%	1.91
Impairment of visual acuity and colour vision due to optic neuritis	0	0%	0
Oliguria or albuminuria due to renal disorder	0	0%	0
Psychosis and convulsion	0	0%	0
Thrombocytopaenia, anaemia, shock	0	0%	0

extrapulmonary TB have about 2.231 higher odds of having ADR than those that have pulmonary TB. Patients under retreatment have about 0.280 lower odds of having ADR than those treated as new cases. The TB history of a patient was also associated with the presence of ADR and vice-versa.

DISCUSSION

Key Results

- Patients with extrapulmonary TB had about 2.23 times higher odds of developing adverse drug reactions (ADRs) compared to those with pulmonary TB.[8]
- Patients on retreatment had about 0.28 times lower odds of ADRs compared to new cases.
- TB history was also significantly linked with the occurrence of ADRs.[9]

Study Details

- Total patients: 524 on first-line anti-TB drugs
- ADR prevalence: 8.78%
- Median age of patients with ADRs: 42.5 years (younger than expected risk group >60 years)

Common ADRs Found

- Most frequent ADRs were skin-related **reactions**, not gastrointestinal problems as seen in other studies:
  - Mild/local skin reactions: 34.8%
  - Severe skin rash (hypersensitivity): 32.6%
  - Jaundice due to hepatitis: 21.7%

☞ This differs from other studies where nausea, vomiting, and stomach pain are most common.

Other Finding

- About 20% of patients experienced tingling or burning in hands and feet
- Mainly linked to isoniazid, and less commonly ethambutol.

A study in Shenzhen, China reported that linezolid used for MDR-TB was associated with neurotoxicity, including peripheral and optic neuritis. One patient reported tingling symptoms, but the exact drug cause was unclear due to use of a fixed-dose combination therapy. Monitoring tools such as the Michigan Neuropathy Screening Instrument (MNSI) and serum trough levels were used to assess toxicity.[10,11]

The study found that patients with extrapulmonary TB had about 2.23 times higher odds of developing adverse drug reactions (ADRs) compared to those with pulmonary TB. However, other studies showed mixed results, with some reporting higher ADRs in pulmonary TB or no difference between groups.[12,13]

Patients under retreatment had lower odds (0.28 times) of ADRs compared to new cases. TB history was also linked with ADR occurrence.[14,15]

Comorbidities such as HIV and diabetes were important risk factors for ADRs due to immune suppression, oxidative stress, and polypharmacy.[16,17]

The study's findings differed from several international studies, showing variation in ADR patterns across regions.[18,19]

The average time to develop ADRs was 35 days (range 6–90 days), which was longer than reported in some other studies.[20,21]

Most patients who developed ADRs still completed treatment, although this was not statistically significant. Other studies have shown both favorable and unfavorable outcomes linked with ADRs.[22,23]

Overall, ADRs were common and influenced by factors such as TB type, treatment history, and comorbidities.[24-25] Skin reactions were the most common ADRs, differing from other studies where gastrointestinal or liver effects were more common.

The study had limitations including small sample size and single-hospital data, limiting generalizability.[26-29]

CONCLUSION

ADRs are an important challenge in TB treatment and may affect patient adherence. Early detection and monitoring can improve safety and treatment success. More large, multi-center studies are needed to better understand risk factors, especially in extrapulmonary TB and patients with diabetes or HIV.

Ethical Note

The study used retrospective hospital records with ethics approval and waived patient consent. Data were stored securely following privacy regulations and national research guidelines.

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