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Original Article

Adverse Drug Reactions to Antituberculosis Drugs in Tuberculosis Patients Using the Naranjo Algorithm at a Regional Hospital in Mataram

Reaksi Obat yang Merugikan terhadap Obat Antituberkulosis pada Pasien Tuberkulosis Menggunakan Algoritma Naranjo di Rumah Sakit Regional di Mataram

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Abstract

Tuberculosis (TB) remains one of the major health problems in Indonesia. As of October 2023, 67,770 TB cases were reported in West Nusa Tenggara Province (NTB). TB treatment requires long-term therapy using combinations of antituberculosis drugs (ATBD), which have the potential to cause Adverse Drug Reactions (ADRs). ADRs that are not properly identified and managed can increase morbidity and mortality in TB patients and negatively affect treatment outcomes.This study aimed to determine the incidence of ADRs related to the use of ATBD in TB patients at Mataram City Regional General Hospital, NTB, from February to June 2023. This observational study employed a cross-sectional design. Data were collected through structured interviews, and the Naranjo Algorithm was used to assess the causality between reported symptoms and drug use. A total of 66 patients were included in the study. The most common definite ADRs was associated with rifampicin, characterized by reddish discoloration of urine (45.70%), followed by isoniazid-induced fatigue (34%). Probable ADRs were observed with streptomycin, isoniazid, rifampicin, and pyrazinamide, mainly presenting as itching or skin rash (11.10%). Possible ADRs included headache (4.90%) and pain (4.30%), predominantly related to rifampicin use. In conclusion, ADRs among TB patients receiving ATBD at Mataram City Regional General Hospital were diverse, with rifampicin-related urine discoloration being the most prevalent.

Abstrak

Tuberkulosis (TB) tetap menjadi salah satu masalah kesehatan utama di Indonesia. Hingga Oktober 2023, dilaporkan 67.770 kasus TB di Provinsi Nusa Tenggara Barat (NTB). Pengobatan TB membutuhkan terapi jangka panjang menggunakan kombinasi obat antituberkulosis (ATBD), yang berpotensi menyebabkan Reaksi Obat yang Merugikan (Adverse Drug Reactions/ADR). ADR yang tidak diidentifikasi dan dikelola dengan baik dapat meningkatkan morbiditas dan mortalitas pada pasien TB dan berdampak negatif pada hasil pengobatan. Penelitian ini bertujuan untuk mengetahui insiden ADR yang berkaitan dengan penggunaan ATBD pada pasien TB di Rumah Sakit Umum Daerah Kota Mataram, NTB, dari Februari hingga Juni 2023. Studi observasional ini menggunakan desain cross-sectional. Data dikumpulkan melalui wawancara terstruktur, dan Algoritma Naranjo digunakan untuk menilai kausalitas antara gejala yang dilaporkan dan penggunaan obat. Sebanyak 66 pasien dimasukkan dalam penelitian ini. Efek samping obat (ADR) yang paling umum dan pasti dikaitkan dengan rifampisin, ditandai dengan perubahan warna urin menjadi kemerahan (45,70%), diikuti oleh kelelahan akibat isoniazid (34%). ADR yang mungkin terjadi diamati dengan streptomisin, isoniazid, rifampisin, dan pirazinamid, terutama berupa gatal atau ruam kulit (11,10%). ADR yang mungkin terjadi meliputi sakit kepala (4,90%) dan nyeri (4,30%), terutama terkait dengan penggunaan rifampisin. Kesimpulannya, ADR di antara pasien TB yang menerima ATBD di Rumah Sakit Umum Daerah Kota Mataram beragam, dengan perubahan warna urin terkait rifampisin sebagai yang paling umum.

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INTRODUCTION

Tuberculosis (TB) is a group of chronic infectious diseases caused by the bacterium *Mycobacterium tuberculosis*, which causes infection in the lungs and leads to pulmonary TB. In addition, *Mycobacterium tuberculosis* bacteria can also infect other parts of the body, such as the pleura, lymph nodes, bones, and other extrapulmonary organs, which is often referred to as extrapulmonary TB [1]. According to 2021 data from the World Health Organization (WHO), TB causes two million deaths each year, and it is estimated that around one billion people are infected with pulmonary tuberculosis [2]. Highest incidence of tuberculosis occurs in Southeast Asia (11%), Africa (47%), the Western Pasific (34%) and Europe (40%) [3]. Based on data from the Indonesian Ministry of Health in 2022, the estimated incidence of TB in Indonesia is 969.000 or 354 per 100.000 population, with estimated 144.000 deaths from Tb or 52 per 100.000 population[4]. According to the West Nusa Tenggara Health Office, the number of TB cases in West Nusa Tenggara as of October 2023 was 67.770 cases (67.86%) According to the NTB Health Office, the number of TB cases in West Nusa Tenggara (NTB) as of October 2023 was 67,770 cases (67.86%) [5].

The TB treatment procedure consists of two stages: an intensive satges phase lasting two months and a continuation phase lasting four to seven months [6]. The TB trearment therapy used is combination therapy with vatious types of drugs in sufficient quantities and appropriate doses according to each treatment group, such as the first line drug group, which includes Isoniazide (H), Ethambutol (E), Pyrazinamide (Z), Rifamppicin (R), and Streptomycin (S). While for TB-Drug Resistant (DR) treatment, it consists of Kanamicyn (Km), Ethionamide (Eto) or Prothionamide (Pto), High-dose Isoniazide (HD-H), Moxifloxacyn (Mfx), Clofazimine (Cfz), Ethambutol (E), Pyrazinamide (Z) [7]. The administration of this combination therapy must be considered carefully, taking into account the organ function of TB patients, as it will affect the pharmacodynamic and pharmacokinetic effects of the drugs, especially in geriatric TB patients or TB patients with comorbidities such as diabetes or HIV. Failure in TB treatment can be caused by Adverse Drug Reactions (ADRs) or pharmacological side effects of drugs, leading to treatment non complience by patient [8]. Other studies also explain that some TB patients experience mild to severe ADRs or side effects during TB treatment [9]. Side effects include anorexia, nausea, vomiting, abdominal pain, vertigo, cephalalgia, pruritus, visuak disturbances, ototoxicuty, hematuria, etc [10]. Therefore, the occurrence of ADRs from the use of TB drugs will increase morbidity and mortality [9]. It is very impotrtant to accurately identify ADRs from antituberculosis drugs so that appropriate treatment can be given and patient complience can be improved during the treatment period. Therefore, it is necessary to adequately identify and addres potential ADRs[11 12].

The Naranjo Algorithm is used to support the monitoring of potential ADRs. This method is supported by the Ministry of Health to identify drug side effects. The Naranjo questionnaire is intended to determine whether the observed side effects are caused by antituberculosis drugs or whether are other variables that contribute to the side effects[13]. Indonesia has commited to achieving the goal of eliminating tuberculosis by 2030 with a target incidence 0f 65 per 100.000 population and a mortality rate 6 per 100.000 population[4]. To support government's program, it is very important to conduct pharmacovigilance studies, especially on adverse drug reactions. The consequences of adverse drug reactions include treatment failure, the development of *Mycobacterium tuberculosis* resistance, ande reduced treatment effectiveness. Other studies also explain that ADRs incidents cause a 3%-12% increase the number of patients and a 5%-10% increase in treatment costs in Western countries[14]. The main reason TB patients discontinue their treatment is the of ADRs. 38% of patients discontinue treatment due to unwanted side effects[15]. Therefore the purpose of this study is to determine the incidence of antituberculosis Adverse Drug Reactions in TB patients.

METHODS

Research Design

This study is an obeservational study with across-sectional design, conducted from February This study is an observational study with a*cross-sectional* design conducted from February toJune 2023 at the outpatient facility of the Mataram City Regional General Hospital. This study has obtained research permission from Mataram City Regional General Hospital (NO: 445/0463.2/RSUD/II/2023).

Data Collection

Respondents for this study were sampled using purposive sampling based on the inclusion and exclusion criteria. Inclusion criteria for this study were patients, both male and female, diagnosed with tuberculosis and receiving antituberculosis therapy, patients with complete medical records, willing to participate in the study, and able to communicate effetivelly. Exclusion criteria for this study were pregnant or breastfeeding women. Data on antituberculosis therapy was obtained from secondary data, namely patient medical records, while primary data was obtained from Naranjo Algorithm questionaire, which was administered concurrently through interviews with patients drint routine check-up which was administered concurrently through interviews with patients during routine check-ups or while waiting to collect their medication. TB patients who were willing to be respondents filled out the Naranjo Algorithm questionnaire provided. The data collection periode was five months.

Research Instrument

The instrument used in this study was the Naranjo Algorithm, a validated causality assesment tool widely used to evaluated the likelihood of adverse drug reactions (ADRs). The algorithm consists of a structured questionnaire with a specific scoring system that categorizes ADRs probability into definite, probable, possible, or doubtful. This instrument was selected because it enables qualitative and semi quantitative assessment of ADRs occurrences.

Research Sample

The sample size in this study was calculated based on the Slovin formula, namely:

$$n = \frac{N}{1+N\,(d)^2} \quad \text{..... (1)}$$

N= required sample size; N = total population size ; d = precision level of 10% (0.1)

Substituting the values:

$$n = \frac{188}{1 + 188\,(0{,}1)^2}$$

$$n = 65{,}28 \sim 66$$

Therefore, the minimum required sample size was 66 patients

Data Analysis

The analysis was conducted to determine the demographic and clinical characteristics of the patients. Furthermore, data were collected based on patients complaints. The collected data were assessed for causality using the Naranjo Algorithm, and the ADRs probability scores were calculated. The scoring categories were as follows: 1-3 (possible ADRs); 4-8 (probable ADRs); ≥ 9 (definite ADRs).

RESULT AND DISCUSSION

Based on the data presented in Table 1, the majority of patients in this study were aged <60 years (77%), indicating that TB cases were predominatly found in the productive group. This finding is consistent with previous study by Putri (20220 and Oktaviani (2022), which reported that TB is more commonly observed among adolescents and young adults. Individuals in this group may be more vulnerable to immunological and hormonal changes occuring during adolescnce and early adulthood. In addition, several known risk factors may contribute to TB development, including malnutrition, immunosuppression, diabetes mellitus, obesity, smoking, and alcohol consumption. Behavioral and environmental factors may also play an important role. Adolescents and young adults tend to spend considerable time in school or workplace settings, were prolonged close contact in enclosed spaces with inadequate ventilation can facilitate TB transmission. Moreover, pulmonary TB patients in this age group often have realtively high transmission potential [16 17].

Several studies have reported that nutritional satus is significantly associated with the incidence of pulmonary TB. Individuals with poor nutritional status are at a higher risk of developing TB infection. Nutritional status plays a crucial role in maintaining immune function, as adequate nutrient intake is essential for optimal immune response. An imbalance between nutrient intake and the body's requirements may impair immune competence, particularly in the formation and fuction of antibodies and lymphocytes. Proteins and carbohydrates are essential for the development of these immune components, which serve as key defense macanisme against infectious agents, including *Mycobacterium tuberculosis,* the causative agent of pulmonary TB [18].

Table 1. Demographic and Clinical Characteristics of Tuberculosis (TB) Patients (n= 75)

No.	Variable	Category	n (%)
1	Age	< 60 years	58 (77%)
		≥60 years	17 (23%)
2.	Gender	Male	37 (49%)
		Female	38 (51%)
3.	Treatment Phase	Intensive Stage	63 (84%)
		Follow-up Phase	12 (16%)
4	Comorbidity Status	With comorbidities	46 (61%)
		Without Comorbidities	29 (39%)

In this study, the proportion of TB cases among females (51%) and males (49%) was nearly equal, indicating no substantial sex disparity in the study population. This finding noteworthy, as TB is often reported to be more prevalent among males in many epidemiological studies. However, Osman in 2022 reported that the risk of TB among females may peak during mid-adolescence compared to males. This pattern has been associated with higher TB-HIV co-infection rates and increased TB related mortality among adolescent girls. In addition, several biological and physiological factors may cntribute to increased susceptibility among females including hormonal changes during menarche, pregnancy-related immunological alterations, and the interaction between TB and HIV infection [19].

Additionally, behavioral factors such as smoking and alcohol consumtion, which are more prevelant among men may contribute to increased susceptibility to pulmonary TB [20]. Both behaviors are known to impair immune function and compromise respiratory defense mecanisms. Cigarette smoke contains harmful substances that can damage the structure and function of the respiratory epithelium, including impairment of ciliary activity in the airway. This disruption reduces the effectiveness of mucociliary clearance, thereby facilitating the entry and persistence of *Mycobacterium tuberculosis* in the respiratory tract. Furthermore, smoking has been reported to alter both innate and adaptive immune responses, particularly affecting macrophage and leukocyte function, which play essential role in host defense againts TB infection [18].

In a study conducted by Kumarjit Sinha involving 102 patients, the majority of ADRs cases were observed in the 30-40 year age group (27.45%). However, the highest proportion of ADRs was reported in patients aged <20 years, while the lowest incidence was found in the 51-60 yeqr qge group. The differences in ADRs occurrence across age groups were statistically significant ($p < 0.001$). Furthermore, femate TB patients experienced ADRs more frequently than males (91.67% vs. 62.82%), and this difference was also statically significant ($p < 0.001$) [21]. In the present study, most TB patients (84%) were undergoing treatment in the intensive phase. This finding is consistent with previous research reporting that greater proportion of TB patients were in intensive treatment phase (57.70%) compared to the continuation phase (42.30%) [22]. The intensive phase of TB treatment is administered for the first two months with daily dosing and requires close monitoring to ensure treatment adherence and prevent drug resistance. This is followed by the continuation phase , which is typically administered for four months to achieve sustained bacterial eradication and prevent relapse [7].

Table 1 shows that the majority of patients in this study had comorbidities (61%). The most common comorbidity was diabetes mellitus (34 cases), followed by diabetes with pneumonia (4 cases), HIV with diabetes (3 cases), Chronic Obstructive Pulmonary Disease (COPD) (3 cases), and diabetes with COPD (2 cases) (Figure 1). These findings are consistent with the study by Wang (2024), which reported that 849 (19,91%) individuals in the case group and 1.141 (6.69%) in the control group experienced multimorbidity. Patients with one, two, or ≥3 comorbidities had an increased risk of developing pulmonary TB, with adjusted Odds Ratio (aOR) ranging from 2.85 to 5.16. This suggests that the presence and number of comorbid conditions may significantly increase susceptibility to pulmonary TB. Comorbidities frequently associated with increased TB risk include diabetes, chronic lower respiratory tract diseases (such as COPD, emphysema, and bronchitis) hypertension and cerebrovascular disease [23].

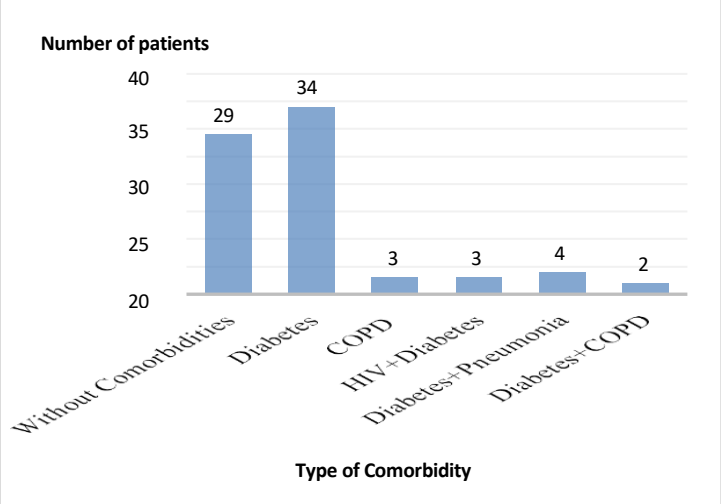


Figure 1. Distribution of Comorbidities Among Tuberculosis (TB) Patients

Diabetes mellitus is defined as a condition characterized by elevated blood glucose level (≥126 mg/dL). Although the exact impact of diabetes on TB severity remains under investigation, diabetes has been shown to negatively affect antituberculosis treatment outcomes. One propoesed mecanisms involves altered pharmacokinetics af anti-TB drugs. Studies have reported difference in plasma rifampicin concentrations between TB patients with and without diabetes. Rifampicin is potent inducer of hepatic enzymes, particularly cytochrope P450 (CYP) 3A4 and CYP2C, leading to reduce plasma concentrations of several co-administered drugs. This include (S)-warfarin and first and second generation sulfonyurea antidiabetic agents such as tolbutamide, glibenclamide (glyburide), glimepiride and glipizide [24] [25].

Pulmonary TB itself may also lead to structural lung damage, affecting the pulmonary vasculature, Damage to the lung parenchyma can result in vasculitis and endarteritis, potentially reducing the cross-sectional area of pulmonary blood vessels and contributing to pulmonary hypertension [26]. Furthermore, previous studies have demonstrated that patients with diabetes, HIV infection, alcoholism, substance abuse, immunosuppressive therapy, or malignancy tend to have lower treatment success rates and higher mortality compared to TB patients without these conditions ($p < 0.001$) [27]. Globally, the prevalence of ADRs among TB patients ranges from 8% to 85%. The occurrence of ADRs may be influenced by several factors, including diabetes, HIV co-infection, variations in anti-TB dosing, and pharmacological interations with antiretroviral and oral antidiabetis medications [28].

The Naranjo Algorithm is used to evaluate the likehood of ADRs associated with medication use. This method employs a structured questionnair to systematically assess the probability of drug-related adverse events. In this study, causality assesment using the Naranjo Algorithm was performed foe each patient to determine the likelihood that the reported adverse events were related to antituberculosis therapy [10]. Causality assessment is essential in clinical practice and pharmacovigilance, as it supports appropriate therapeutic decision making and drug safety monitoring. The results of ADRs analysis among TB patients, as presented in Table 2 and Figure 2, indicated that red coloredurine (45.70%), headache (4.90%), and pain (4.30%) were most frequently associated with rifampicin use. Fatigue or drowsiness (34%) was predominantly observed in patients receiving isoniazid. Meanwhile, itchung or skin rash (11.10%) was reported in patients receiving combination anti-TB therapy, including streptomycin, isoniazid, rifampicin and pyrazinamide.

Tabel 2. Naranjo-Based Causality Assessment of ADRs

Drug Name	Number of ESO Events (n=162)	Manifestation	Naranjo Scale	(%)
Rifampicin	74	Red- colored urine	definite	45.7
	8	Headache	possible	4.9
	7	Pain	possible	4.3
Isoniazid	55	Fatigue /drowsiness	definite	34
Streptomycin,isoniazid, Rifampicin, pyrazinamide	18	Itching/ skin rash	probable	11.10

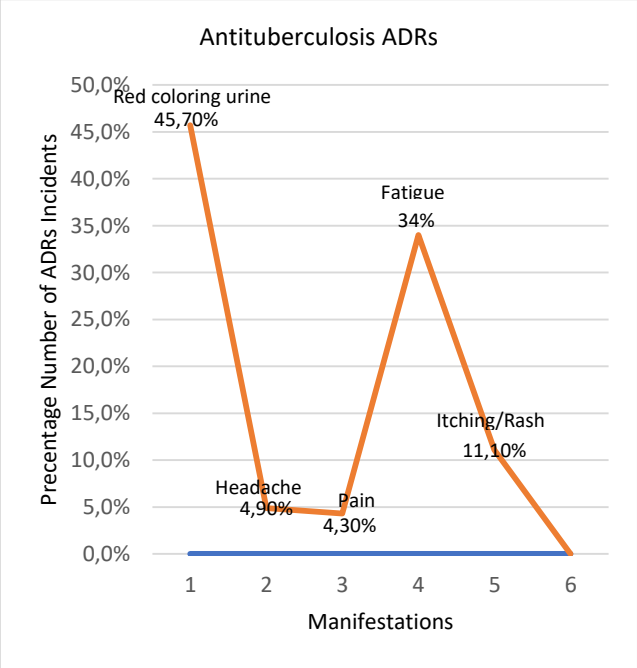


Figure 2. Frequency Distribution of ADRs Among Tuberculosis (TB) Patients

In line with the findings of this study, the Ministry of Health Guidelines for Tuberculosis Mangement (2020) acknowledge that anti-TB drugs are associated with various adverse effects. Skin rash has been reported with the use of streptomycin, isoniazid, rifampicin and pyrazinamide. Therefore, clinicians should carefully monitor patients who develop severe adverse reactions. Rifampicin, in particular is known to cause red-colored urine due to its pharmacological properties. Patients should be informed of this effect prior to treatment initiation, as it is considered a harmless andexpected reaction [7]. Previous dtudies have also reported that adverse effects frequently occur during TB treatment. During the first month of therapy, headache was among the most commonly reported symptoms (54,5%). In the second month, itching (72.7%), headache (72.7%), and nausea (72.7%) were frequently observed [10]. Drug induced hepatotoxicity is recognized as a serious adverse effect of isoniazid. According to Kim (2021), the incidence of isoniazid related hepatotoxicity in combination anti-TB regimens ranges from 1.6% to 2.7%. Rifampicin and pyrazinamide have also been implicated in hepatotoxic reactions. In addition, pyrazinamide and ethambutol have been reported to cause hyperuricemia in patients without prior gout, which may result in arthralgia [29]. Furthermore, anpther study involving 511 TB patients reported that 93 patients (18.20%) experienced adverse drug reactions during anti-TB therapy, most commonly gastrointestinal distrubences, skin hypersensitivity reactions, and hepatotoxicity [21].

Based on data from Korea Adverse Event Reporting System (KIDS-KAERS) between 2009 and 2018, a total of 17.843 Adverse Drug Reaction (ADR) cases were reported for first line anti-TB drugs (1.14%). The highest proportion of ADRs was associated with rifampicin (28%), followed by isoniazid (24.0%), pyrazinamide (23.9%) and ethambutol (23.4%). The most commonly affected organ system were gastrointestinal tract (32%), skin and appebdages (25.9%), and the liver and biliary system (14.2%). Nausea was the most frequently reported ADRs (14.6%), followed by elevated liver enzymes (14.2%), rash (11.7%), pruriyus (9.1%), vomiting (8.9%), and urticari (4,2%). Most ADRs occurred within the first month of treatment initiation. However, certain reactions such a neuropathy, paresthesia, hemtological abnormalities, renal function impairment, and liver enzyme abnormalities were also frequently reported after two months of therapy [30].

Limitation

This study has several limitations that should be consudered when interpreting the findings. First, the cross sectional design limits the ability to establish temporal relationship and causal inferences between anti-TB drugs and ADRs. Second, the study was conducted in a single hospital with relatively small sample sized (n=66), which may limit the generalizability of the results to broader TB populations in other region. Third the data were collected through patient interviews and medical records, which may introduce recall bias and information bias. Additionally, laboratory confirmation for certain ADRs, such as hepatotoxicity or renal impairment, was not comprehensively evaluated, and causality assessment relied solely on the Naranjo Algorithm without comparison to other validated causality tools. Future studies with larger multicenter cohort, prospective design and comprehensive clinical and laboratory monitoring are recommended tp strengthen the evidance regarding ADRs patterns in TB patients.

CONCLUSION

Adverse Drug Reactions (ADRs) were commonly identified among tuberculosis patients receiving first line anti-TB therapy, with rifampicin associated red colored urine being the most frequent reaction (45,70%), followed by headache (4.90%) and pain (4.30%). Isoniazid was primarily associated with fatigue or drowsiness (34%), while itching or skin rash (11.10%) was observed in patients receiving combination therapy with streptomycin, isoniazid, rifampicin, and pyrazinamide. These findings emphasize the importance of systematic ADRs monitoring snd early detection using structured causality assessment tools to support patient safety, maintain treatment adherence, and optimize therapeutic outcomes in tuberculosis management.

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AUTHOR CONTRIBUTION STATEMENT

FA contributed to conceptualization, data collection, data analysis, and drafting of the manuscript. **ROU** contributed to study design, supervision, data interpretation, critical revision of the manuscript, and served as the corresponding author. **PMDR** contributed to methodology development and data validation. **AM** contributed to data analysis and manuscript review.

CONFLICT OF INTEREST DECLARATION

The authors declare no conflict of interest

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