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PROFILE OF DRUG-RESISTANT TUBERCULOSIS PATIENTS AT RUMAH SAKIT UNIVERSITAS INDONESIA DEPOK PERIOD OCTOBER 2024

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ABSTRACT

Indonesia has been one of the three countries in Asia that contributes to the highest case of Tuberculosis (TB) in the world. Tuberculosis itself counted as the top ten cause of death globally. Two of the challenges in controlling TB cases are the occurrence of drug-resistance strain and patients' adherence. Drug-resistant TB has to be treated with the second line drugs of TB with higher risk of adverse events. Linezolid as one of the suggested drugs by WHO in the treatment may increase patients' risk of cytopenia events. This study was conducted to represent the profile of drug-resistant TB obtained from Rumah Sakit Universitas Indonesia (RSUI) Depok period October 2024. Design of this study is a quantitative-descriptive where the data of patients obtained from the patients' medical records in the period of October 2024. The findings of this study showed the total number of drug-resistant TB was 104 with 3 cases of HIV and 70 patients having Linezolid in their regimen. Most of the patients are male with mean of age 41.3 years. New cases and RR/MDR TB level are dominated while on the other hand there's 9 cases of After Failure and 4 others are After Loss to Follow-up. Median values obtained for patients' leukocytes, hemoglobin, and platelets are 7818.0, 11.9, 279.5 respectively.

KEYWORDS *Drug-resistant, Linezolid, Tuberculosis*

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INTRODUCTION

Tuberculosis (TB) is one of the top 10 diseases leading to death in the world. *The World Health Organization* (WHO) through the (2021) *Global Tuberculosis Report* reported that the prevalence of TB in 2021 reached 10 million patients worldwide with an estimated mortality rate of 1.4 million people. Geographically, Southeast Asia is the region with the highest number of TB patients (45%) in 2021 and Indonesia is one of the countries contributing two-thirds of the global TB patients (9.2%). West Java is the province with the highest TB burden in Indonesia by contributing 101,272 cases in 2021.

One of the challenges in TB control efforts is the existence of TB cases that are resistant to first-line anti-TB drugs (OAT) such as Isoniazid and Rifampicin. There was a surge in the total global incidence of TB-RO (TB Resistant OAT) in 2021 to 450,000 cases and Indonesia experienced an increase of 17% compared to the previous year with an estimated total of 24,666 cases. A total of 1,551 cases came from West Java Province (; WHO, 2022 The First Day of the World, 2022)

The number of TB-RO cases starting treatment is increasing year by year. However, the treatment success rate is still around 45-50%, far below the national target (80%). The high rate of drug withdrawal and mortality are factors that cause the lack of therapy success (Ministry of Health, 2022). TB-RO requires patients to use a combination of second-line drugs and treatment for a longer period of time, which affects the safety risk and adherence to the patient's treatment. Linezolid is one of the drugs used in the combination of TB-RO treatment therapy and has been known to cause neuropathy and cytopenia in long-term use (Graciaa et al., 2022).

The success of TB treatment can be influenced by several factors such as age, gender, weight, and comorbidities such as HIV and Diabetes Mellitus type II. Patients with older age have a tendency to face complications and have more comorbidities. The study conducted by (Chilyabanyama et al., 2024) showed patients with >55 years of age were less likely to achieve therapy success than younger age groups (Hase et al., 2021).

Men have been commonly known as a group that has a high risk of TB. This is commonly associated with social and behavioural factors, such as smoking habits and delays in seeking treatment Data shows a high mortality rate from TB among women in Southeast Asia and Africa with a rate of up to 90% in Africa. This is also shown by the results of studies conducted where women are more at risk of facing TB and TB complications with severe HIV co-infection compared to men. (Humayun et al., 2022)

Low nutrition to malnutrition is considered one of the determining factors for TB incidence and can also affect therapy outcomes. It also impacts TB-RO patients where sputum culture conversion tends to take longer and increases the rate of therapy failure. Studies conducted by found a strong association between weight change and therapeutic outcomes where weight gain may also increase therapy success. However, a study conducted in Indonesia by showed that BMI is not included as a predictor of therapy success in TB patients (Andriyanto et al., 2022; Bade et al., 2021; Wagnew et al., 2023, 2024).

Research conducted by shows that HIV infection can be considered a risk factor for TB-RO disease where immune status and drug-related factors play a role in this.

Immunosuppression allows for latent TB reactivation, an increased risk of reinfection due to new Mycobacteri TB (Mtb.) infection and accelerates progression to active TB. Problems related to drug interactions and toxicity, higher drug counts, drug malabsorption and immune recovery inflammatory syndrome (IRIS) have the potential to lead to the development of drug resistance and therapy failure in co-infected TB-HIV patients (Pradipta, 2020).

TB patients with Diabetes Mellitus type II (DM type II) have a hyper-reactive immune response that can increase lung tissue damage. This condition of hyperglycemia impairs immunity by affecting cytokine responses and interfering with the defense of alveolar macrophages. This leads to individuals who are susceptible to TB infection with a higher bacterial load. This also makes TB patients with type II DM more at risk of developing TB-RO. The success of therapy from TB-RO treatment itself is also influenced by the condition of hyperglycemia in type II DM patients, so it is important to know the comorbidities of type II DM in TB and TB-RO patients (Krishna & Jacob, 2021; Xu et al., 2023).

Laboratory tests such as leukocyte, hemoglobin, and platelet values to be able to monitor the impact of using Linezolid along with other antibiotics that can interfere with the kidneys and formation. Leukocyte, hemoglobin, and platelet values are recommended to be monitored. Abnormal leukocyte values may reflect the presence of an active infection or an ongoing inflammatory reaction. Leukocytosis is often found in active TB patients, while leukopenia can indicate bone marrow suppression due to drug side effects. Anemia is common in TB patients and can be caused by chronic infections, malnutrition, or drug side effects. Low hemoglobin levels are associated with poor treatment outcomes. Thrombocytosis or thrombocytopenia can occur in TB patients. Reactive thrombocytosis usually reflects systemic inflammation, while thrombocytopenia can be caused by drug toxicity or other complications (Adewole et al., 2024; Pratama et al., 2021)

RSUI is one of the references for TB-RO in the West Java region since 2022. As a teaching hospital as well as a TB TB service in Depok City, RSUI plays a role in contributing to the development of services related to therapy monitoring, especially in the treatment of TB-RO. The existence of the right steps in ensuring that TB-RO patients receive standard and quality treatment to achieve the success of therapy is part of the recommended TB-RO treatment strategy (; ; RSUI, 2022) (3, 2020) Depok City Health Profile, 2023.

RESEARCH METHOD

The design carried out in this study is a quantitative descriptive that describes the characteristics and number of patients at the Eucalyptus Poly of the University of Indonesia Hospital Depok. The population in this study is patients diagnosed with Drug-Resistant Tuberculosis. The sample inclusion criteria in this study were patients > 15 years old, had been receiving treatment for more than 2 weeks, and were still doing monthly control in October. Patients who have been declared complete treatment before October 2024 are excluded from this study sample. The data in this study was obtained through access to electronic medical records.

RESULT AND DISCUSSION

The description of the characteristics of TB-RO patients included in this study includes: Total number of patients, total number of patients using Linezolid, Age, Male gender, Weight, HIV infection, type II DM, Case definition, Drug resistance level, Resistance to Linezolid, Laboratory value, Positive sputum review, and Positive sputum culture.

Table 1. Characteristics and Demographic of Drug-Resistant Tuberculosis Patient

Total number of patients, n	104
Total number of patients given Linezolid as regiment therapy, n	70
Age (years), mean (±SD)	41.7 ± (14.3)
Sex, male, n (%)	57 (54.8)
Body-weight (kg), mean (±SD)	51.7 ± (12.4)
HIV infection, n (%)	3 (2.9)
Diabetes Melitus, n (%)	21 (20.4)
Case definitions, n (%)	
New	86 (83.5)
Relapse	0 (0)
After loss to follow-up	4 (3.9)
After failure	9 (8.7)
Other	5 (4.9)
Drug resistance level, n (%)	
RR/MDR TB	100 (97.1)
Pre-XDR TB	4 (3.9)
XDR TB	0 (0)
LNZ Resistance, n	0
Laboratory values, median (IQR)	
White blood cells (x 103/µL)	7818.0 (6252.5 – 8670.0)
Hemoglobin (g/dL)	11.9 (10.3 – 12.9)
Platelets (x 103/µL)	279.5 (229.0 – 361.3)
Sputum smear positivea, n	38
Sputum culture positivea, n	45

Abbreviation; IQR= Interquartile Range, LNZ= Linezolid, Pre-XDR= Pre-Extensive Drug Resistant, RR/MDR= Rifampicin-resistant/Multidrug Resistant, TB= Tuberculosis, XDR= Extensive Drug-Resistant [a= At treatment start].

The total number of samples obtained was 104 patients. A total of 70 patients received Linezolid in their therapy regimen, either continued in therapy or discontinued. Linezolid has been classified in Drug A for TB-RO therapy regimens by the WHO and is also included in the BPaL/BpaLM regimen, so it is in line with the findings of the large number of patients taking Linezolid in their therapy regimens. WHO (2018) and Humayun et al. (2022) corroborate the results in this

study where men have a higher risk of being infected with TB and TB-RO disease. WHO (2018) also states that mothers infected with TB during pregnancy tend to transmit infection to their babies with the risk of deficiencies to malnutrition.

There were 57 male patients undergoing treatment, a higher number than female patients. The average age of patients undergoing TB-RO treatment was 41.7 ± 14.3 years with the youngest being 16 years and the oldest being 71 years. This does not include babies who are 7 months old who have been excluded from this study sample even though the mother of the child is still included in the study sample.

The average body weight (BB) of TB-RO patients undergoing treatment is 51.7 ± 12.4 kg. The lowest BB value was 24.5 kg and the highest value was 85.4 kg. There were 3 cases with a BB value ranging from 24.5-26.3 kg and received malnutrition status. According to TB-RO patients, they generally often experience a decrease in appetite so that it can cause weight loss and malnutrition. (Sayem et al., 2020)

TB-RO with HIV coinfection was found in 3 cases. Patients with HIV coinfection were found to have problems in mobilizing movement. Studies conducted by show that concomitant treatment of antriretrovirals (ARVs) with antituberculosis (Anti-TB) provides promising therapeutic outcomes, so there is no need to delay the administration of ARVs. However, this combination of therapies is common in increasing the risk of side effects (Smith et al., 2020).

There are 21 cases of comorbidities with type II diabetes. According to Xu et al. (2023), it is important to know the comorbidity of type 2 DM in patients undergoing TB-RO treatment so that the success of therapy is achieved and the risk of therapy failure due to hyperglycemia conditions can reduce the patient's immunity.

The definition of cases in this study is divided into new, relapsed, after *loss to follow-up*, after treatment failure, and others. The highest number of new cases was 86 cases, while starting treatment after failing was 9 cases, and after *loss to follow-up* as many as 4 cases. The rate of drug resistance cases is dominated by the *Rifampicin-Resistant/Multidrug-resistant* TB category, which is 100 cases. While the other 4 are pre-XDR TB cases that occur with patients having a case definition "after treatment failure". However, none of the patients had the results of a resistance sensitivity test to Linezolid.

The blood laboratory values included in this study were white blood cell (leukocytes), hemoglobin, and platelets with median values of 7818.0 x 103/µL, 11.9 g/dL, and 279.5 x 103/µL, respectively. The median value of hemoglobin shows a number below normal in both women and men. Meanwhile, the results of microbiological examination in the form of positive sputum review at the beginning of treatment only occurred in 38 cases, and positive sputum culture results at the

beginning of treatment only occurred in 45 cases. Another examination carried out at the beginning of diagnosis is TCM rif-res.

CONCLUSION

Based on the research that has been carried out, it was obtained that the description of the characteristics of TB-RO patients at RSUI during October 2024 is a total of 104 patients with 70 patients receiving Linezolid, average age 41.3 years, males as many as 54.8%, average body weight of 51.2kg, HIV coinfection 2.9%, type II DM 20.4%, new cases 83.5%, RR/MDR TB 97.1%, Linezolid resistance 0%, leukocyte value 7818, hemoglobin 11.9, platelets 279.5, number of positive sputum reviews 38 and positive sputum cultures 45.

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