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Original Article

Second-Line Anti-Tuberculosis Drugs Susceptibility Pattern in Multidrug-resistant Tuberculosis Patients at Dr. Hasan Sadikin General Hospital, Bandung, Indonesia

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Abstract

Background: Indonesia has the second-highest tuberculosis prevalence in the world. Moreover, Indonesia is among the 30 countries with the highest burden of multidrug-resistant tuberculosis (MDR-TB). This study aimed to determine the pattern of second-line anti-tuberculosis drug resistance in MDR-TB patients.

Methods: This study was a descriptive cross-sectional using data from MDR-TB patients aged 18 years and older, diagnosed with drug-resistant TB at Dr. Hasan Sadikin General Hospital from December 2021 to June 2022. Total sampling was used. Data on age, gender, history of previous antituberculosis drug treatment and second-line antituberculosis drug susceptibility test results were collected. Resistance distribution patterns were identified using the Line Probe Assay (LPA) and the Mycobacteria Growth Indicator Tube (MGIT) test.

Results: Of 134 data retrieved, only 82 data were complete. The median age of the patients was 42 years (range 27–51 years), predominantly female (53.7%), without a history of antituberculosis drug treatment (52.4%). The highest number of resistances was resistant to high dose isoniazid (43.9%), followed by low dose fluoroquinolone (14.6%). Among patients who were resistant to low dose moxifloxacin, 16.7% of patients were still sensitive to high dose moxifloxacin. There was no resistance to bedaquiline.

Conclusion: Almost half of the patients are resistant to high dose isoniazid, followed by resistance to low dose fluoroquinolone. These finding are expected to be taken into consideration by clinicians in making decisions on the diagnosis or management of MDR-TB patients and can further serve as input for the government in implementing MDR-TB control programs in Indonesia..

Keywords: Multidrug-resistant tuberculosis, multiple drug resistance, second- line anti tuberculosis

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Introduction

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis (Mtb) that is transmitted through droplets produced by coughing or sneezing of TB patients.[1] Data from the World Health Organization (WHO) shows an increase in new TB cases of about 10% from 2015 to 2019, however, there was a decrease in cases of around 18% in 2020.[2] This might be related to the COVID-19 pandemic that year, which made it more difficult to diagnose TB patients, leading to a decrease in the number of reported TB cases.[3] Indonesia (9.2%) is one of the countries with the largest contribution to the new TB cases in the world, which is in second position after India (28%).[4]

Data from WHO in 2020 showed that

there were 157,903 new cases reported, consisting of 132,222 cases of multidrug-resistant tuberculosis (MDR-TB)/rifampicin-resistant tuberculosis (RR-TB) and 25,681 cases of pre-extensively drug-resistant tuberculosis (XDR)/XDR-TB.[5] Indonesia was once again ranked fifth as the country with the highest number of MDR-TB cases in 2020, and is included in the 30 countries with the highest burden of MDR-TB in the world.[4,6] This high number of drug- resistant TB cases has prompted the government to issue TB treatment guidelines by referring to existing international recommendations. Drugs used in the treatment of drug resistant TB consist of second-line antituberculosis drugs.[7] Laboratory tests to measure drug susceptibility can be done to ensure the efficacy of treatment. This examination can be carried out using conventional examination methods or molecular rapid test. Conventional examinations in the TB Control Program are only carried out using the Mycobacterium Growth Indicator Tube (MGIT). For the molecular rapid test method, Xpert MTB/RIF or Line Probe Assay (LPA) has been used.[8]

Although the prevalence of TB in Indonesia is very high, however, data on the pattern of second-line antituberculosis drug susceptibility tests results in drug-resistant TB patients at Dr. Hasan Sadikin General Hospital in Bandung as a referral hospital for drug-resistant TB patients in West Java are still lacking. The second-line antituberculosis drug susceptibility tests include clofazimine, linezolid, and bedaquiline. Therefore, this study aimed to determine the pattern of second-line anti-tuberculosis drug resistance with LPA and MGIT in MDR-TB patients at Dr. Hasan Sadikin General Hospital, which can be a consideration for clinicians and government programs in treating MDR-TB patients.

Methods

This study used a cross-sectional descriptive study design. Secondary data were collected using the total sampling method, retrieved from the Tuberculosis Information System (Sistem Informasi Tuberkulosis,SITB) at the MDR clinic Dr. Hasan Sadikin General Hospital Bandung, West Java, Indonesia, from December 2021 to June 2022. The inclusion criteria were complete data of patients aged 18 years or older diagnosed with drug-resistant TB treated at the MDR clinic of Dr. Hasan Sadikin Bandung. Incomplete or missing data were excluded from this study.

Data on age, gender, history of previous antituberculosis drug treatment, and pattern of second-line antituberculosis drug susceptibility test results were collected. The history of previous antituberculosis drug treatment was classified as new cases, TB patients who failed 2nd category treatment, TB patients with 2nd category treatment which not converted in 3 months of treatment, TB patients who failed 1st category treatment, TB patients with 1st category treatment who remained positive after 3 months of treatment, relapsed TB patient, categories 1 and 2, returning TB patients after lost to follow-up, suspected TB patients with a history of close contact with MDR-TB patients, TB-HIV co-infection patients who did not respond to anti-TB drug administration, and TB patient who had a non-standard TB treatment history using quinolone and 2nd line anti-TB drug injection for at least 1 month. The pattern of of second-line antituberculosis drugs susceptibility test results was divided into using LPA and MGIT. Meanwhile for LPA, it was classified into resistant to low-dose moxifloxacin, high-dose moxifloxacin, and low-dose levofloxacin. Furthermore, MGIT was classified into resistant to high dose moxifloxacin, low-dose levofloxacin, clofazimine, linezolid, high- dose of isoniazid, and bedaquiline. Data were then collected using Microsoft Excel.

Ethical approval for this study was given by the Ethics Committee of Universitas Padjadjaran no. 834/UN6.KEP/EC/2022 and Dr. Hasan Sadikin General Hospital Bandung no. LB.02.01/X.2.2.1/19254/2022.

Results

In the study period, there were 134 data of drug-resistant tuberculosis patient; however, 7 patients came 2 times and were re-registered into the database, 45 data were excluded due to incomplete data and age criteria, thus, only 82 were analysed further.

Most of the patients in this study were of productive age (median age 42 years old, ranging from 27–51 years), predominantly female. According to the history of previous antituberculosis drug treatment, primary or new MDR dominated the cases in this study (52.4%), followed by relapse cases (29.3%).

Among 82 TB patients examined using LPA, low-dose moxifloxacin resistance gave the same number of resistances with low- dose levofloxacin (14.6%). Among 12 patients who were resistant to low dose moxifloxacin, 16.7% were still sensitive to high-dose moxifloxacin.

Table 1 Distribution of Drug Resistant TB Based on Patient Characteristics

Characteristic	Drug-Resistant TB patients (n=82)	
	n	%
Age (years) – Median (IQR)	42 (27-51)	-
Gender		
Male	38	46.3
Female	44	53.7
History of previous antituberculosis drug treatment		
New cases	43	52.4
Cases with history of previous TB treatments:	39	47.6
- Failed from 2nd category TB regiment	1	1.2
- No conversion after 3 months of 2nd category TB regiment	-	-
- Failed from 1st category TB regiment	6	7.4
- Remain positive after 3 months of 1st category TB regiment	1	1.2
- Relapse TB patient, categories 1 and 2	24	29.3
- Returning TB patients after loss to follow-up	5	6.1
- Suspected TB patients with a history of close contact with MDR-TB patients	-	-
- TB-HIV co-infection patients who do not respond to anti-TB drug administration	1	1.2
- TB patient who have a non-standard TB treatment history using quinolone and 2nd line anti-TB drug injection for at least 1 month	1	1.2

Table 2 Patterns of Second-line Antituberculosis Drug Susceptibility Test Results in Drug resistant TB patients using LPA Method

Patterns of Second-line Antituberculosis Drug Susceptibility Test	Sensitive		Resistant	
	n	%	n	%
Low-dose Moxifloxacin	70	85.4	12	14.6
High-dose Moxifloxacin	72	87.8	10	12.2
Low-dose Levofloxacin	70	85.4	12	14.6

The results of second-line antituberculosis drug susceptibility test with liquid media (MGIT) showed that almost half of the patients in this study were resistant to high-dose isoniazid (43.9%), followed by low-dose levofloxacin resistance (9.8%). None of them were resistant to bedaquiline.

Discussion

Drug-resistant tuberculosis mostly occurs in productive age patients. The median age of this study was 42 years (range of 26–51 years), which is similar to previous study in West Java, in that the majority of patients were in the 35–44 year age group.6 Another study conducted in India also showed similar result.[9] High mobility in productive age might increase the risk of exposure to Mycobacterium tuberculosis (Mtb).[10]

In our study, females (53.7%) were found to be more common among drug-resistant tuberculosis patients, similar to a study in Peru (52%).[11] In developing countries, most females in poor families are exposed to a lot of smoke from firewood burned as fuel in poorly ventilated room during the cooking process. Chronic smoke exposure impairs the normal

Table 3 Patterns of Second-line Antituberculosis Drug Susceptibility Test Results in Drug Resistant TB Patients using MGIT

Patterns of Second-line Antituberculosis Drug Susceptibility Test	Sensitive		Resistant	
	n	%	n	%
Low-dose levofloxacin	74	90.2	8	9.8
High-dose moxifloxacin	77	93.9	5	6.1
Clofazimine	79	96.3	3	3.7
Linezolid	81	98.8	1	1.2
High dose isoniazid	46	56.1	36	43.9
Bedaquiline	82	100	-	-

clearance of tracheobronchial mucosal surface secretion and alveolar macrophage function, allowing Mtb to escape host defenses and cause TB.[12] Moreover, social roles that lead female to spend more time in poorly lit and ventilated homes , which tend to be dark and humid, increase the survival rate of Mtb and the risk of tuberculosis infection.[13] However, it seems unusual that males patients are more commo than female, as in previous studies in West Java and China.[14,15] Differences in social role mean that adult males spend more time outside the home working, thus increasing the risk of exposure to TB. In addition, men smoke more than women, as smoking is one of the predisposing factors for TB.[14,15]

The majority of patients in this study were primary MDR-TB patients (52.4%), similar to a study in Netherlands (69%).[16] Interestingly, this finding differs from the majority of the studies. Inadequate treatment will lead to spontaneous mutation that allow the growth of resistant bacteria.[17] A study in West Java showed the majority (77%) of drug-resistant TB cases were patients with a history of antituberculosis drug treatment.[15] Different results can be caused by underreported cases of previous drug use by patients. This information bias can lead to increase in new cases of drug resistant TB.[16] Enhance TB surveillance work is recommended to overcome this bias.[18] A history of contact with MDR-TB patients can also increase the risk of primary MDR-TB.[19]

Most of the patients who had a history of drug use were relapse cases (29.3%), followed by treatment failure cases (8.6%), which is in accordance with a study in Ethiopia.[20] The high rate of relapse cases indicates that follow-up of patients after recovery is not effective enough. Most MDR-TB programs recommend regular follow-up within 2 years after complete treatment. Therefore, prolonged follow-up is recommended. Additionally, patients should be made aware of the long-term risk, as well as the warning signs and symptoms of recurrence.[21]

In this study, similar result has been obtained for low-dose levofloxacin resistance and low dose moxifloxacin detected by LPA. This finding is similar to a study in China.[22] Interestingly, low-dose levofloxacin resistance detected by LPA examination showed a higher number of resistance than MGIT examination in the same patients. The same result was obtained for high dose moxifloxacin resistance detected by LPA showed a higher number of resistance than MGIT examination. This is due to the ability of the LPA test to detect silent mutation, while MGIT is unable to. Silent mutation has been defined as when the gene's protein-coding region experiences a single DNA nucleotide alteration that has no impact on the amino acid sequence that makes up the gene's protein. MGIT also fails to detect low-level resistance mutation below the drug breakpoint, which may have contributed to the lower number of resistance detected by MGIT.[23]

The World Health Organization recommends the use of high-dose moxifloxacin in cases of resistance to low-dose moxifloxacin and low-dose levofloxacin.[24] In this study, among 12 patients who were resistant to low-dose moxifloxacin, 16.7% were still sensitive to high-dose moxifloxacin, suggesting that high-dose moxifloxacin can still be used for patients who are resistant to low dose moxifloxacin and levofloxacin.

Furthermore, almost half of the patients (43.9%) in this study were resistant to high dose isoniazid and most of them had

secondary MDR-TB. Resistance to isoniazid most commonly found because this drug is most effective against Mtb, so it is often used for therapy.[25] The high number of isoniazid resistance can be as high as over 60% as stated by another study.[26] Interestingly, none of the patients in this study were resistant to bedaquiline, similar to previous studies in Taiwan, France, Russia, and China with only a few patients being resistant to bedaquiline (<5%). Resistance to bedaquiline may have developed naturally, throughout treatment with further anti-TB drug or prior use of antifungal drug. Nevertheless, the exact reason for pre-existing bedaquiline resistance is still unknown.[27]

This study has limitation. This study was done in one hospital with a short period of time, so it might not represent the actual condition. Therefore, future studies are suggested to have more complete data with multicenter studies with a longer period of time, so that more precise result can be obtained.

In conclusion, most of the drug-resistant tuberculosis patients are of productive age, female , and without previous antituberculosis drug treatment. Almost half of the drug-resistant tuberculosis patients are resistant to high-dose isoniazid, followed by low-dose fluoroquinolone and high-dose of moxifloxacin. Among the patients who are resistant to low-dose moxifloxacin, 16.7% are still sensitive to high dose moxifloxacin. Nevertheless, none of the patients in this study are resistant to bedaquiline.

The results of this study are expected to be used as consideration by clinicians in making decisions on diagnosis or management of MDR-TB patients and can further serve as an input for the government in implementing the MDR-TB control programs in Indonesia.

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