ORIGINAL ARTICLE

First-Line Anti-Tuberculosis Drug Resistance Pattern

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ABSTRACT

Introduction: An important concern regarding TB currently is the case of anti-TB drug resistance; hence research on resistance patterns and risk factors is essential. This study aimed to identify the pattern of first-line anti-TB drug resistance.
Methods: This descriptive retrospective study was conducted at MDR-TB polyclinic Dr. Soetomo General Hospital, Surabaya, in 2017-2019. Only complete medical records were included. The variables were first-line anti-TB drug resistance (isoniazid, rifampicin, ethambutol, streptomycin) and patients' characteristics (age, gender, treatment history, and comorbidities). The drug resistance test was performed using certified culture methods.
Results: Among 239 patients, the incidences of resistance to H, R, E, and S were 79.08%, 94.14%, 25.94%, and 20.08%, respectively. The most common patterns were HR (42.26%), R (18.83%), and HRE (12.55%). The largest age group was 45-54 years old (38%). The dominant gender was male (56.49%). The most treatment history category was relapsed patients (48%) and there were more patients with comorbidity (57%).
Conclusion: The highest incidence rate of resistance was rifampicin and the most common resistance pattern was HR. Most of the patients were of working age, male, relapse patients, and had comorbidities. An appropriate TB therapy treatment plays an important role in preventing resistance.

INTRODUCTION

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis* (MTB) which usually attacks the lungs.[1] Indonesia is in third place with the most TB cases worldwide. In 2017, it was estimated that the total TB cases in Indonesia reached 842,000, then increased in 2018 to 845,000.[2,3] An important concern regarding TB disease today is the case of multi-drug resistance TB (MDR-TB). In 2017, MDR/RR-TB cases in Indonesia reached 23,000 cases.[2] Meanwhile, in 2018, multi-drug resistance (MDR) or rifampicin resistance TB (RR-TB) cases in Indonesia reached 24,000 cases.[3]

MDR-TB is one of the main challenges in global TB control. Treatment of MDR-TB takes longer and is more complex, requiring many drugs, including second-line injectable drugs. Second-line drugs have more significant side effects, thus making medication adherence more difficult.[4] MDR-TB can be caused by two main reasons, inappropriate TB treatment and person-to-person transmission. Inappropriate use of antimicrobials, such as single-drug consumption, poor-quality drugs, and early treatment discontinuation, can lead to drug resistance, which can then be transmitted.[5,6]

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Several studies have been performed in various countries. One of which is an observational study in India which found that 71.1% patients experienced resistance to at least one type of anti-TB drug. The highest prevalence of resistance pattern was isoniazid as much as 61.7%, followed by rifampicin (57.0%), streptomycin (50.6%), ethambutol (40.8%), and 52.8% of them were MDR-TB.[7] Study on the pattern of first-line anti-TB drug resistance was also performed in Germany by in the period of 2008-2017. From this study, there were four dominant patterns, namely streptomycin (3.1%), isoniazid (2.9%), isoniazid and streptomycin (2.1%), and pyrazinamide (1.6%).[8]

In addition, study on risk factors is important to look at the populations which have the risk of developing anti-TB drug resistance. Age is an important factor. People aged 10-25 years old can be at risk related to medication adherence.[9] History of previous TB treatment such as failed category 1 TB cases, relapsed TB cases, and dropped out of treatment are groups at high risk of developing resistance.[10] Comorbidity can also be a risk factor for anti-TB drug resistance associated with decreased immunity.[11]

Based on the differences in first-line anti-TB drug resistance patterns in various places and the previously mentioned facts, there are several opportunities in the development of studies on first-line anti-TB drug resistance patterns in Indonesia. In addition, this study is important because the incidence of MDR-TB is still high due to various factors as previously described. Therefore, this study discussed the pattern of first-line anti-TB drug resistance at Dr. Soetomo General Hospital, Surabaya. This study also considered risk factors by identifying the patients' age, gender, treatment history, and comorbidities.

METHODS

This was a retrospective descriptive study of first-line anti-TB drug resistance pattern at Dr. Soetomo General Hospital, Surabaya in the period of 2017-2019. The data were obtained from the patients' medical record. Ethical licensing was submitted to and approved by the Research Ethics Commission of Dr. Soetomo General Hospital (No.0189/LOE/301.4.2/XI/2020).

The sample of this study was taken by total sampling technique and were all TB patients with first-line anti-TB drug resistance which were registered at MDR-TB Polyclinic based on inclusion and exclusion criteria. The inclusion criteria were pulmonary TB patients with first-line drug resistance based on the antibiotic sensitivity tests in medical records and were registered in the period of 2017-2019. The exclusion criteria were patients with incomplete medical record data.

The variables used in this study were first-line anti-TB drug resistance (isoniazid, rifampicin, ethambutol, streptomycin) and patients' characteristics (age, gender, treatment history, and comorbidity). The resistance test was performed using certified culture methods with Lowenstein Jensen and BACTEC MGIT. Category of treatment history was based on the guidelines of the Ministry of Health.[12] Comorbidities were other diseases suffered by patients, namely diabetes mellitus, hypertension, and human immunodeficiency virus (HIV). Data analysis was performed descriptively.

RESULTS

Patients' Characteristics

Patients' characteristics consisting of age, gender, treatment history, and comorbidities can be seen in Table 1. Among 239 patients, it was found that the most age group was 45-54 years old (38%), most dominant gender were male (56.49%), dominated by relapse cases (48%), and more patients had comorbidity (57%).

Table 1. Patients' characteristics

Variable	N (n = 239)	%
Age		
<15 years old	2	1%
15-24 years old	11	5%
25-44 years old	70	29%
45-54 years old	92	38%
55-64 years old	52	22%
>64 years old	12	5%
Gender		
Male	135	56.49%
Female	104	43.51%
Treatment History		
New case	48	20%
Relapse	115	48%
Failed treatment	4	2%
Loss to follow up	37	15%
Others	10	4%
Unknown	3	1%
Comorbidities		
Yes	137	57%
No	102	43%

The Incidence of First-Line Anti-Tuberculosis Drug Resistance

Total patients with first-line anti-TB drug resistance were 346 patients. However, the samples that met the inclusion criteria were 239 patients. The following is the incidence of resistance to first-line anti-TB drugs (Table 2).

Of the four first-line anti-TB drugs, the highest incidence of resistance was rifampicin. Based on the trend, the drug which experienced an increase from 2017 to 2019 was isoniazid and the other three drugs had fluctuating trends.

First-Line Anti-Tuberculosis Drug Resistance Pattern

The following table shows the drug resistance pattern consisting of monoresistance, a combination of two drugs, three drugs, and four drugs (Table 3).

Table 2. Incidence of first-line anti-tuberculosis drug resistance

Drug	2017 (n = 79)	2018 (n = 63)	2019 (n = 97)	Total (n = 239)
Isoniazid				
n	60	49	80	189
%	75.95%	77.78%	82.47%	79.08%
Rifampicin				
n	74	60	91	225
%	93.67%	95.24%	93.81%	94.14%
Ethambutol				
n	20	17	25	62
%	25.32%	26.98%	25.77%	25.94%
Streptomycin				
n	17	14	17	48
%	21.52%	22.22%	17.52%	20.08%

Table 3. First-line anti-tuberculosis drug resistance pattern

Number of Drug	Drug				Total patients (n = 239)	%
	H	R	E	S		
1	+				9	3.77%
		+			45	18.83%
			+		1	0.42%
				+	0	0.00%
2	+	+			101	42.26%
	+		+		2	0.84%
	+			+	1	0.42%
		+	+		3	1.26%
		+		+	1	0.42%
			+	+	0	0.00%
3	+	+	+		30	12.55%
	+	+		+	20	8.37%
	+		+	+	1	0.42%
		+	+	+	0	0.00%
4	+	+	+	+	25	10.46%

H: isoniazid, R: rifampicin, E: ethambutol, S: streptomycin

The most common pattern in the period of 2017 to 2019 was isoniazid, rifampicin (HR), which was 101 patients (42.26%), followed by R monoresistance (18.83%), and isoniazid, rifampicin, ethambutol (HRE) (12.55%). Meanwhile, based on the number of drugs, the highest incidence was resistance to two types of drugs.

DISCUSSION

The Incidence of First-Line Anti-Tuberculosis Drug Resistance

The highest incidence of resistance among the first-line anti-TB drug was rifampicin. Meanwhile, based on the trend, the drug which experienced an increase from 2017 to 2019 was isoniazid. Another study conducted in Ethiopia in 2015-2016 found the incidence of rifampicin resistance was 89 out of 226 patients (39.4%) which still had lower prevalence than isoniazid.[13]

In this study, rifampicin resistance was found to have the highest incidence when compared to the other drugs. History of previous TB treatment is a strong risk factor for MDR-TB. This can be caused by poor drug quality, repetition, or even taking the wrong medication. The likelihood of developing RR-TB was three times higher in previously treated patients than in new patients. In addition, the development of better diagnostic tools, especially the use of GeneXpert, can also increase the discovery of rifampicin resistance.[14]

This study shows the incidence of isoniazid resistance experienced an increase from 2017 to 2019. This is slightly different from a study in China, which showed a significant decrease in isoniazid resistance from 128 patients (45.6%) to 89 patients (29.1%). This decrease may be due to improvements in TB treatment in Hangzhou through the directly observed therapy short course (DOTS) Plus.[15] Meanwhile, the increase of cases in Indonesia can be influenced by many factors, ranging from patient factors, environment, and diseases.[16]

The numbers of ethambutol resistance in 2017-2019 were 62 patients (25.94%). Compared to other drugs, the incidence of ethambutol resistance was not too high. This is also supported by a study in Germany which obtained results from 3,324 patients with anti-TB drug resistance, only 13 patients (0.4%) of whom experienced ethambutol resistance.[8]

Meanwhile, the total numbers of streptomycin resistance in 2017-2019 were 48 patients (20.08%). In previous studies, streptomycin resistance is the second highest incidence after isoniazid.[13,17] A study in Ethiopia found the incidence of streptomycin resistance was 94 out of 226 patients (41.6%).[13] A study in China obtained results from 2,678 resistant cases, in which 1,811 patients experienced streptomycin resistance (67.6%).[17] This can be caused by prolonged and frequent use of streptomycin.[8]

First-Line Anti-Tuberculosis Drug Resistance Pattern

In this study, the most common pattern in the period of 2017 to 2019 was HR with 101 patients (42.26%), followed by R and HRE. Based on the number of drugs, the highest incidence was resistances to two types of drugs. The results of this study are supported by previous study conducted at Dr. Soetomo General Hospital, Surabaya for the period of August 2009-April 2018. The study was conducted on a population of MDR-TB patients and showed that the highest first-line drug resistance pattern was HR as many as 204 of 433 patients (47%), followed by HRE (26%), and HRES (16%).[18]

In addition, another study in Riau, Indonesia showed the same results, in which the most common pattern was HR with as many as 9 out of 18 patients (50%), followed by HRE and isoniazid, rifampicin, ethambutol, streptomycin (HRES).[19] Another study in Balikpapan, Indonesia also showed that the dominant pattern was HR in 5 of 15 patients (33.3%) and followed by isoniazid, rifampicin, pyrazinamide, ethambutol (HRZE) in 2 patients (13.3%).[10]

Based on several studies in Indonesia, the dominant pattern of first-line anti-TB drug resistance in Indonesia is HR. [10,18,19] This may be due to the fact that isoniazid and rifampicin are the first-line active drugs in TB therapy. Therefore, the possibility of isoniazid and rifampicin used as monotherapy or in combination with other antibiotics is higher.[19] Isoniazid resistance is often related to its use as an essential drug in TB therapy and TB prophylaxis in certain populations.[13]

Another study in Germany showed that from 3,324 patients, there were four dominant patterns, S (24.5%), H (23.1%), HS (16.6%), and Z (12.4%). High proportions of streptomycin and isoniazid resistance have been found in the German population and some other populations, especially those born in Eastern Europe. Monoresistance to streptomycin was the most common pattern of drug resistance in cases born in Germany and outside Germany. This is most likely due to a long history of streptomycin use.[8]

In this study, the highest incidence of resistance was found to be the resistance to two types of first-line anti-TB drugs, which was 45.2% and dominated by the HR pattern. The high incidence of isoniazid resistance may be due to the widespread use of the drug in the first-line treatment of TB patients.[13] This result is slightly different from the previous study which showed the highest incidence of resistance was four types of first-line anti-TB drugs, HRES, with the prevalence of 66%. Poly-resistance to anti-TB drugs may be associated with the history of previous treatment.[20]

Patients' Characteristics

The most dominant age group in patients with first-line anti-TB drug resistance was 45-54 years old consisting 92 patients (38%). This was supported by a study in China which showed the most dominant age group was 35-55 years old (39%).[21] Based on the study, it can be seen that the most common age group was the working age group, which is a population aged 15 to 64 years old.[22] This age group is mostly exposed to TB cases. It may be the reason this age group is more vulnerable.[7] In addition, high-risk behavior and the tendency to stop TB treatment can also affect the occurrence of resistance.[9]

This study found the number of male patients was 135 patients (56.49%). This is supported by previous study which found that there were more male patients as many as 56 patients (59%).[7] Another study in Germany also found more male patients as many as 1,617 patients (61%).[8] This can be influenced by several factors such as difficulty in accessing and utilizing health facilities in the study area, social contact, exposure to dust, smoking habits, and alcohol consumption.[23]

Based on the history of treatment, most patients were relapse patients as many as 115 patients (48%). Another study on MDR-TB patient in Riau also showed that the most common treatment history was relapse cases with 15 patients (83.3%).[19] Previous study conducted at Dr. Soetomo General Hospital, Surabaya in the period of August 2009 to April 2018 showed the same results in MDR-TB patients which found the most common treatment history was relapse patients as many as 160 patients (37%).[18] Relapse patient means a patient who had previously been treated and declared cured, fell ill again either due to relapse or reinfection. Relapse is often associated with poor treatment outcomes and a higher mortality rate compared to primary TB infection.[24]

In this study, it was found that among 239 patients, 137 patients (37%) had comorbidity. The comorbidities referred to in this study include diabetes mellitus, hypertension, and HIV. This study is supported by previous study conducted in Nigeria in the period of 1 August 2014 to 31 March 2017. The results showed that from 565 patients with drug resistance, more patients had comorbidities as many as 397 patients (70.3%). Comorbidities in this study include anemia, hypokalemia, hypothyroidism, and HIV.[14] In pulmonary TB patients with diabetes mellitus, higher numbers of bacteria were found at the start of therapy, thus there was a higher possibility of mutations and the occurrence of MDR-TB with large numbers of bacteria. Therefore, in these patients, longer therapy is needed.[25] HIV is one of the risk factors for TB associated with dysregulation of the immune system. It has been said that HIV infection may lead to malabsorption of anti-TB drugs and is associated with acquired rifampicin resistance.[20]

CONCLUSION

The highest incidence rate of resistance was rifampicin and the most common resistance pattern was HR. Most of the patients were of working age, male, relapse patients, and had comorbidity. An appropriate TB therapy treatment plays an important role in preventing resistance. Furthermore, it is necessary to improve education and support efforts for TB and drug resistance TB patients to improve patient compliance and achieve treatment success. Further research using analytical methods to identify and analyze risk factors which influence drug resistance TB cases may be needed.

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Conflict of Interest

The author declared there is no conflict of interest.

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Authors' Contributions

Designing the study, estimating & analyzing the issues: AZH. Reshaping the discussion: RJS. Reshaping the methods: RYM. All the authors contributed and approved the final version of the manuscript.

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