Rifampicin Antibiotic Resistance Level Positive TB Results with Molecular Rapid Test (MRT) in Mataram City Hospital

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Abstract. Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. Tuberculosis is the most dangerous infectious disease in the world. The purpose of this study was to determine the level of antibiotic resistance to rofampicin on positive TB results in the Mataram City Hospital. In this research, the research method used is analytic observational. The research data used is in the form of secondary data, which comes from the tuberculosis examination report book. In this study, the research sample was 290 samples during the January-December 2019 examination period at the Mataram City Hospital. The results indicated that at the Mataram City Hospital, there were 11 samples (4%) that were not resistant to the antibiotic rifampin and 275 samples (95%) were still sensitive and 4 other samples (1%) could not be determined to the antibiotic.

Keywords: Mycobacterium tuberculosis · Tuberculosis · Resistance · Rifampicin

1 Introduction

Mycobacterium tuberculosis (TBC) is defined as a type of infection caused by Mycobacterium tuberculosis. Tuberculosis is an infection that can cause paralysis and is the most common cause of death in the world. According to World Health Organization (WHO) data, 1.5 million people die as a result of tuberculosis (1.1 million HIV negatives and 0.4 million HIV positives) (WHO, 2015). According to the World Health Organization's Global Tuberculosis Report (2015), there are 58% of new cases of tuberculosis occurring in a few countries, including Thailand, India, and Indonesia, which are the countries with the highest number of cases of tuberculosis in the world as of today. Ini [1].

Tuberculosis treatment can be treated using antibiotics, in this case pyrazinamide (PZA), streptomycin, ethambutol (EMB), isoniazid (INH), and also rifampin (RIF) which have been used for several years to treat tuberculosis. However, many patients demonstrate resistance to these first-line drugs. Tuberculosis cases have increased worldwide in the 1980s, this is due to the presence of Multi Drug Resistant Tuberculosis (MDR-TB) [2]. The bacteria that cause MDR-TB are strains of M. tuberculosis that are resistant to

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first-line anti-TB drugs, such as rifampin and isoniazid [3]. One of the main drugs for tuberculosis is rifampin, which works by inhibiting bacterial growth by binding strongly to bacterial DNA-dependent RNA polymerase, thereby inhibiting bacterial RNA synthesis [4]. The emergence of drug resistance in M. tuberculosis is due to random mutations in the bacterial chromosome. This mutation process takes place spontaneously [5].

Based on the high incidence of TB in the city of Mataram as well as rifampin resistance, which can potentially become MDR, it becomes a health problem for people's lives related to M. tuberculosis infection. Starting from this information, the examination of M. tuberculosis with a fast and accurate method has High sensitivity and specificity really need to be done to determine the incidence of M. tuberculosis infection and determine the resistance of M. tuberculosis to OAT.

This study aims to determine the level of rifampin antibiotic resistance to positive results of TB with the Molecular Rapid Test (MRT) and to analyze the percentage level of rifampin antibiotic resistance to positive results of TB with the Molecular Rapid Test (MRT) at Mataram City Hospital.

2 Research Methods

2.1 Research Design

This study uses an analytical observational design because in this study only observes without treating the object to be studied. The data was taken from secondary data in the result report book. The data is patient data from the results of the examination at the Clinical Pathology Laboratory, the Microbiology Room at the Mataram City Hospital. The data collection is presented in tabular form. Analysis of the data used in this research is a descriptive qualitative analysis by collecting data from the results of initial observations and secondary data obtained from the Clinical Pathology Laboratory, Microbiology Room, Mataram City Hospital. The data obtained is entered into a table and then described.

3 Results and Discussion

Results, This research was carried out in the Clinical Pathology Laboratory of the Microbiology Room of the Mataram City Hospital in March 2020, with the number of samples in this study there were 290 positive TB samples that carried out the Molecular Rapid Test (MRT) examination in the Clinical Pathology Laboratory, Microbiology Room, Mataram City Hospital for To determine the level of rifampin antibiotic resistance against positive results of TB with the Molecular Rapid Test (MRT) at the Mataram City Hospital, the results in the form of research data are presented in the form of a table as follows:

Figure 1 aims to increase rifampisin resistance in response to positive results from rapid molecular testing at RSUD Mataram City. Data ranging from TBC Sensitif (approximately 275%) to TBC RIF Resistant (approximately 11%) and TBC Indeterminate (approximately 4%), indicating a significant difference between TBC Sensitif and TBC Resistant or Indeterminate.

Table 1. Positive Rifampicin Resistant Tuberculosis Results in 2019.

No	Sample	Month	Criteria	Result
1	A1	January	TBC RIF Resistant	1
2	B1	February	TBC RIF Resistant	1
3	C1	March	TBC RIF Resistant	1
4	D1	April	TBC RIF Resistant	1
5	E1	May	TBC RIF Resistant	0
6	F1	June	TBC RIF Resistant	1
7	G1	July	TBC RIF Resistant	1
8	H1	August	TBC RIF Resistant	1
9	I1	September	TBC RIF Resistant	0
10	J1	October	TBC RIF Resistant	2
11	K1	November	TBC RIF Resistant	1
12	L1	December	TBC RIF Resistant	1
Total				11

Source: secondary data 2019

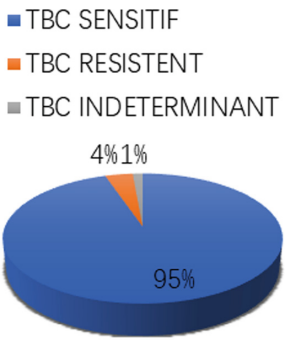

Fig. 1. Data TBC Positive Sensitive, Resistant, and Indeterminant.

This research was carried out in the clinical pathology laboratory of the microbiology room of the Mataram City Hospital in March 2020 with a total of 290 samples of positive TB samples, where samples were obtained which were samples from the examination from January to December 2019. The samples in this study were obtained through examination results. The Molecular Rapid Test (MRT) has been examined, and the data obtained from the examination is obtained through the TB examination result notebook in the microbiology room of the Mataram City Hospital.

Based on the results of the study in Table 1, data were obtained in the form of positive TB results with the criteria for sensitive TB, resistant TB, and indeterminate tuberculosis, data obtained through the results of molecular rapid tests carried out in the laboratory,

this study obtained results in the form of sensitive TB as many as 275 samples (95%), 11 samples of resistant TB (4%), and 4 samples of indeterminate tuberculosis (1%). The percentage of rifampin-resistant TB obtained was due to the ability of this drug to suppress and inhibit the growth of M. tuberculosis bacteria, with rifampin antibiotic resistance of 4% indicating a low level of resistance, rifampin resistance can be an early marker of MDR (Multi Drug Resistant) cases, so that Rifampicin antibiotics are used as an initial screening for TB case detection to determine the potential for MDR TB cases to arise through rifampin antibiotic resistance. With the value of rifampin antibiotic resistance, the possibility of cases of Low MDR TB of all 290 samples were confirmed to be resistant to rifampin in 11 samples (4%). Data on TB in the city of Mataram, NTB had previously been reported by Salim, et al. using pleural fluid on 17 samples using the PCR technique, it was found that resistance to rifampin was 23.53% [6]. Furthermore, different results were reported by Kurniawan, et al. using positive AFB sputum with samples from East Lombok, the results showed that there was no resistance/sensitivity to the anti-tuberculosis drug regimen, namely Rifampicin, Ethambutol, Isoniazid using the PCR technique [7]. This research is in line with the research of Alifia Rimadhani Yuwono "Profile of Drug Resistant Tuberculosis Cases at Dr. RSUP. Soeradji Tirtonegoro Klaten Period 2012–2017" with a resistance rate of 5% to rifampin and 2% isoniazid [8]. This is in line with the results of a study conducted by Sihombing in 2012 at H. Adam Malik Hospital Medan, with the results of study that the level of resistance to rifampin was (1.18%) [9]. According to Rinstiswati and Wijayanti there is a difference in the percentage of total resistance from each region. The factors that cause the difference in the percentage data are, among others, test isolates of different strains, social and economic conditions of patients, as well as doses and methods used in treating tuberculosis cases, such as the PCR method, which is more complex in detecting antibiotic resistance other than rifampin [10].

This study, it was found that there were 11 samples (4%) experiencing resistance to the antibiotic rifampin, 275 samples (95%) sensitive to the antibiotic rifampin, with the difference in the percentage of rifampin resistance was 4% and rifampin sensitivity was 95%. The rifampin antibiotic resistance in the Mataram City Hospital has a low level of resistance to rifampin antibiotics, and has a high sensitivity to rifampin antibiotics. This means that the use of rifampin antibiotics is still effective against TB cases in the Mataram City Hospital along with other antibiotics.

Resistance to RIF is due to mutations that occur in the rpoB gene fragment that encodes the RNA polymerase subunit, especially in the 81 base pair (pb) long region, which is the element that determines the nature of RIF resistance (codon 507–533), which where the highest frequency is with codons 526 and 531. RNA polymerase composed of 4 unequal or different subunits (α, , ' and) and is encoded with the rpoA, rpoB, rpoC and rpoD genes. Many of these rifampin-resistant clinical isolates mutated to the rpoB gene, this resulted in decreased affinity for the drug, thus resistance would develop. About 96% of M. tuberculosis isolates were resistant to rifampin. The cause is a mutation that occurs in the "hot-spot region" of the 81-bp core region (rifampicin resistance-determining region or RRDR) with a codon range of 507–533 for the rpoB gene. This mutation will in turn change the primary structure of rpoB. Missense mutations contained in codons 513, 526 and 531 are mutations that have a relationship with rifampin resistance.

Mutations occurring in this codon can confer a high degree of resistance to rifampin [11]. Mutations that can cause MTB resistance are caused by inadequate treatment factors, for example, the use of a single drug for the treatment of tuberculosis, the use of inappropriate treatment regimens, for example, giving only INH and RIF which are at high levels of resistance for both types. The drug, irregular drug administration and also irregular drug supply (sometimes drug delivery to certain areas stops for several months) [12].

The antibiotic rifampin has bactericidal properties that can inhibit the growth of tuberculosis bacteria. Rifampin is one of the most effective anti-tuberculosis antibiotics, and isoniazid is the basis for multi-drug TB treatment regimens. The target of rifampin in M. tuberculosis is the subunit of RNA polymerase, which can inhibit and then bind to the elongation process of the messenger RNA. The most important characteristic of this rifampin is that it can work or operate against bacteria that are actively growing or not [11].

The resistance to this antibiotic can also be caused by two things, namely the patient experiences resistance to anti-tuberculosis drugs that occur primarily when the patient has never received treatment but has experienced drug resistance due to infection by bacterial strains that have developed resistance. In addition, the process of drug resistance can also be caused by patients who have received treatment but whose bacterial strain has changed. Apart from these two things, there are many other causes of TB patients experiencing resistance to the antibiotic drug rifampin. According to the European Regional Congress of the Union, it concluded that rifampin resistance could be an early marker of MDR (Multi Drug Resistant) cases in areas with a high prevalence of TB. As many as 95–98% of clinical isolates that are resistant to RIF have mutations in RRDR. RIF resistance is said to be a surrogate marker for the incidence of MDR-TB because 90% of rifampin-resistant clinical isolates are also known to be resistant to isoniazid [13]. Indonesia is an area with a high prevalence of TB, which is ranked 2nd with an estimated one million cases per year in Indonesia [1]. There are several kinds of resistance to rifampin antibiotics, namely, primary resistance, secondary resistance, and resistance mutants [14].

The molecular rapid test examination in this study is an initial diagnosis carried out on patients who have never received antibiotic drug therapy before because this molecular rapid test can detect resistance to rifampin antibiotics, meaning that there have been cases of tuberculosis that have changed in bacterial strains that are resistant to rifampin., so that there are known cases of rifampin-resistant TB strains.

Although the resistance rate is small, namely 4%, it can be a high case if you are not careful in areas with a high incidence of tuberculosis, including in the city of Mataram, with the number of suspected tuberculosis receiving services according to standards according to the health profile data of the province of NTB in Mataram city in 2018, i.e. as many as 1,532 [9].

The level of rifampin antibiotic resistance in this study showed a picture of the pattern of tuberculosis resistance in the Mataram City Hospital. The results of this study stated that rifampin antibiotics with a low resistance level of 4%, which indicates that rifampin antibiotics have high sensitivity and are good enough to treat TB cases. This knowledge is intended to provide basic information for health workers, especially in terms of handling TB cases, which includes diagnosis and also determining appropriate

and fast therapy for patients. This molecular rapid test examination is an effective and efficient initial diagnosis for a person who is confirmed to be positive for TB and is resistant to the antibiotic rifampin.

4 Conclusion

The research that has been carried out is safe that from 290 positive TB samples, 11 samples were resistant to rifampin antibiotics, 275 other samples were sensitive to rifampin antibiotics and 4 other samples could not be determined to be rifampin antibiotics. This proves that the level of rifampin antibiotic resistance in the Mataram City Hospital is still relatively low with a percentage of 4%, while the sensitivity level of rifampin antibiotics is 95%.

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