Tuberculosis Treatment History Influenced Multidrug-Resistant Tuberculosis (MDR-TB) Incidence Based on Gene-Xpert Examination

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Abstract. Multidrugs Resistant-Tuberculosis (MDR-TB) caused by drugs resistant at least Isoniazid and Rifampicin Mycobacterium tuberculosis affects tuberculosis cases eradication efforts in the world. In 2014, 153 countries had reported MDR TB cases. MDR-TB can be caused by irregularity in taking medication tuberculosis drugs and categorized as TB-relapse, TB-failure, and TB-drop out.

Purpose To determine Tuberculosis treatment history influenced the incidence of Multidrugs-Resistant Tuberculosis (MDR TB). *Methodology/Approach.* Cross sectional studies in 88 TB-patients at dr. Ario Wirawan Hospital of Lung Salatiga examined by Gene Xpert MTB/RIF at August 2018 until March 2019. TB treatment history data obtained from TB-patients medical record. *Findings.* Eighty-eight TB patients showed 43 (48.8%) were 26–45 years old, 50 (56.8%) were men. TB treatment history was 38 (43.2%) relapse, 13 (14.8%) failed and 11 (12.5%) drop out. Gene Xpert's examination results were 53 (60.2%) MDR TB Rifampicin resistant and 35 (39.7%) TB Rifampicin sensitive. Percentage of MDR TB Rifampicin resistant with history treatment TB Relaps were 25 (28.4%), Failed 9 (10.2%) and Drop out 11 (12.5%) and 8 (9.1%) for New-TB patient. TB treatment history influenced Multidrugs-Resistant Tuberculosis (MDR TB), p value 0.001, R value 0.228. Value/Implication – Regular awareness of taking medication tuberculosis drugs is important to avoid the incidence of MDR TB.

Keywords: MDR-Tuberculosis · TB-treatment history · Gene Xpert

1 Introduction

WHO estimates tuberculosis incidence in Indonesia will be 395 cases/100,000 population in 2015 with the death rate of 40/100,000 population. There are 330,729 cases of Tuberculosis in 2015 and 351,893 cases in 2016 [1]. Prevention and treatment of tuberculosis is a major concern throughout the world. DOTS (Directly Observed Treatment

I. Permana and E. Rochmawati (Eds.): ICOSI-HSN 2022, 55, pp. 21–27, 2022.
https://doi.org/10.2991/978-94-6463-070-1_5

Shortcourse) strategy is an effort to treat tuberculosis, which the treatment carried out for 6 months under the supervision of a Drug Swallowing Supervisor. Out of standard tuberculosis treatment or interrupting treatment period caused resistance Tuberculosis Drugs [2]. Multi drugs Resistant Tuberculosis (MDR TB) is a resistance to more than one first-line Tuberculosis Drugs. New cases MDR- TB reached 480,000 cases with deaths rate 190,000 cases [3].

Multi drugs Resistant Tuberculosis patients were transmitted by direct contact with resistant tuberculosis from an MDR TB patient or by tuberculosis drug resistance while tuberculosis treatment was previously undertaken. MDR TB can be caused by incomplete treatment history, living in a country with a high incidence of MDR TB, or failure to provide a clinical response to an adequate regimen. Tuberculosis drug resistance associated with tuberculosis treatment history. Taking medication tuberculosis drug irregularly caused tuberculosis drugs resistance, for example, the tuberculosis drugs are consumed for two weeks and then stopped for one month and then came for treatment again to get the drug again and have not yet implemented treatment with the DOTS strategy [4]. Tuberculosis patients who have already received treatment with tuberculosis drugs will have a fourfold chance to resistance, and ten times to Multidrug-Resistant Tuberculosis (MDR TB) [5].

Multidrug-Resistant Tuberculosis (MDR-TB) suspect patients are classified as 1. TB patients relapsed, 2. TB patients who failed category 1 treatment, 3. TB patients who fail category 2 treatment (chronic), 4. TB patients who return to treatment after default, 5. TB patients who were not converted to category 2 treatment, 6. MTB patients who did not convert after insertion treatment, 7. TB patients with a history treatment at Non-DOTS Healthcare facility, 8. TB patients who have a close contact history with MDR TB patients, 9. PLWHA (People with HIV/AIDS) with symptoms of TB/HIV [2]. The tuberculosis treatment process takes six months, often causes tuberculosis patients bored in undergoing regular treatment and it makes the cessation before complete treatment, intermittent, or non-routine treatment. Inadequate tuberculosis treatment will kill most of the Mycobacterium tuberculosis but small numbers of resistant organisms still grow and arise with spontaneous mutations. Single drug-resistant Mycobacterium tuberculosis emerges and inadequate treatment to mutated bacteria causes further drug resistance [6].

WHO has suggested an examination with a high enough validity for the diagnosis of Multidrug-Resistant Tuberculosis (MDR TB), namely Gene Xpert MTB/RIF. The examination is a molecular level examination that can automatically detect Mycobacterium tuberculosis as well as to determine resistance to Rifampicin. Rifampicin resistance Tuberculosis patient is also resistant to Isoniazid automatically, it means that Rifampicin resistance is suspicion of Multidrug-Resistant Tuberculosis (MDR TB) [7]. The aims study to determine Tuberculosis treatment history influenced the incidence of Multidrugs-Resistant Tuberculosis (MDR TB).

2 Methods

Eighty-eight active Tuberculosis patients according to the doctor's diagnosis at the Lung Hospital dr. Ario Wirawan Salatiga from August 2018 until March 2019 were enrolled. Gene Xpert MTB/RIF examination results as MTB not detected, detected MTB (+) RIF

Table 1. Tuberculosis diagnosis criteria based on tuberculosis treatment history and Gen-xpert examination results

TB diagnosis criteria	Frequency (n)	Percentage (%)
Relapse	38	43.2
Failed	13	14.8
Drop Out	11	12.5
New case	26	29.5
Gen Xpert examination result		
MTB- RIF Resistant	53	60.2
MTB- RIF Sensitive	35	39.8

Table 2. Correlation between Gen xpert examnation result with Tuberculosis diagnosis criteria

Gen xpert Examination Result (MDR-TB)	Tuberculosis Diagnosis Criteria				**P
	Rellaps	Fail	Drop Out	New Case	
RIF Resistant	25 (28.4%)	9 (10.2%)	11 (12.5%)	8 (9.1%)	0.033
RIF Sensitive	13 (14.8%)	4 (4.5%)	0 (0%)	18 (20.5%)	r = 0.228
Total (N = 88)	38 (43.2%)	13 (14.8%)	11 (12.5%)	26 (29.5%)	

Sen and detected MTB (+) RIF Res and Tuberculosis treatment history were categorized as Recurrent TB, Default TB, Drop Out TB, and New TB Cases. Tuberculosis treatment history influenced the incidence of Multidrugs-Resistant Tuberculosis (MDR TB) was analysis uses the chi-square test and the Spearman test.

3 Results

Eighty-eight active Tuberculosis patients were 56.8% male and 48.8% were 26–45 years old. TB diagnosis criteria determine based on history of tuberculosis treatment. Relaps TB was the most frequent as much as 43.2%. New cases TB, Failed TB and Drop Out TB were 29.5%, 14.8% and 12.5% respectively. Gen-xpert examination results were MTB RIF- Resistant and 40% MTB RIF Sensitive (Table 1).

TB-relaps patient with MTB detected - RIF Resistant are 25 (28.4%) patients, there is a significant relationship between the Gen-xpert examination results MDR-TB detected RIF Resistant with tuberculosis diagnosis criteria (p value = 0.033) and r value = 0.228 indicates poor correlation strength with a positive correlation (Table 2.). TB-Rellaps were associated with MDR-TB incidence based on Gen-xpert examination result as MTB-detected Rif-resistance.

Eighty-eight active Tuberculosis patients were 56.8% male and 48.8% were 26–45 years old. The adult is a productive age that can be a risk factor to tuberculosis transmission, whom men have a heavier workload, a smoker, alcohol consumer, and

another unhealthy lifestyle that leads to decreasing the immune system. Adult men with 15–54 years old are vulnerable to pulmonary tuberculosis [8] and gender-related to pulmonary tuberculosis [9].

Tuberculosis diagnosis criteria based on tuberculosis treatment history there are 38 (43,2%) patients with TB relapse. TB relapse is defined as a patient that has received TB treatment, stated recovered or complete treatment, but then came back with AFB test positive (+). Taking medication tuberculosis drug irregularly caused TB relapse. Tuberculosis medicine consumption related to TB relaps and increases 43 times higher if patients do not take medicine regularly. Tuberculosis needs long term treatment, must discipline on taking its medicine. Some patients who think that their symptoms are getting better, often do not take medicine regularly [10]. Pulmonary TB patient that do not take medicine regularly assume that their treatment is succeeded. Pulmonary TB patient that does not discipline taking medicine will have longer treatment because they must repeat from the beginning. TB relaps is still haunting even when the patient is stated to fully recover or complete treatment. This is due to bacteria mutation in a range when the patient does not take the medicine regularly [2].

MTB detected Rif-Resistant is patients who resistant to Rifampicin also Isoniazid was as MDR TB patients. The incidence of MDR-TB can be divided into primary resistance and secondary resistance. Primary resistance occurs in MDR-TB patients without prior tuberculosis drug treatment and is usually due to direct transmission from MDR-TB patients. Resistant Mycobacterium tuberculosis enters the body directly to the patient who never gets diagnosed with tuberculosis. This resistant strain bacteria-infected easily the immunocompromised patient such as the patient with diabetes mellitus and/or HIV/AIDS. MDR TB secondary resistance occurs in a patient who had received TB treatment before. This occurs due to indiscipline in taking the medicine. Secondary resistance results in relapse, fail or drop outpatient [5].

The six-month treatment of tuberculosis is a long journey, sometimes make the patient get bored. Once the patients do not take the medicine, they need to repeat the treatment from the start of a minimum of 6 months. Inadequate treatment leads to bacteria resistance because the bacteria are not killed and allow them to do spontaneous mutation. When the treatment is repeated with the same medicine, the drug affinity decreased and the resistance bacteria will multiply more. The percentage of MDR-TB incidence in new cases TB is in the range of 0–32.3% [11]. Similar range this study 15.1% new cases TB. Another study in Jakarta, the most cases MDR TB were developed from relapse TB cases 15 (83.3%), dropped out TB 2 (11.1%) and failed TB 1 (5.6%) [6, 12].

TB relapse cases became the largest cause of MDR TB, followed by drop out TB cases 12.5%, failed TB cases 10.25%, and new TB cases 9.1%. Many relapse TB cases are caused by the lack of understanding of the rules of tuberculosis treatment and the lack of patient taking medicine compliance. Patients who do not obey the rules of taking medication must restart treatment starting from the first month, for a minimum of six months. Re-treatment needs a longer time and the treatment not on time. Inadequate treatment may be related to decreased immunity or infection with the same strain, which has experienced resistance to tuberculosis drugs. Patients who completed their treatment, not on time (less/more than 6 months) had a 5% difference in risk of relapse tuberculosis compared to patients who completed treatment exactly 6 months [13]. Rellaps TB is

caused by reinfection due to closed contact with tuberculosis patients. The more often patients come into contact with other active pulmonary TB patients, the more likely they are to be re-exposed by Mycobacterium tuberculosis. Mycobacterium tuberculosis transmitted through droplets while sneezing, coughing, and even talking. Relapse pulmonary tuberculosis will occur while Pulmonary TB patients who live at home or close to other pulmonary TB patients. In addition, concomitant diseases such as Diabetes Mellitus and HIV/AIDS have been known can cause reactivation of pulmonary TB as well [14]. TB relapsed cases will require drugs with greater toxic effects so it is assumed to be MDR TB. MTB detected Rif-resistant patients were found in tuberculosis drop out patients as many as 11 (12.5%). Drop out is a patient who has been on medication for at least one month and has stopped treatment for 2 weeks or more with positive smear. A lot of MDR TB in tuberculosis drop out cases are the patients usually feel that they have recovered from their illness after following intensive treatment for two months and the lack of knowledge about the rules of tuberculosis treatment for six months routinely and regularly. Incomplete/interrupted treatment will present a new problem, namely the emergence of drug-resistant strains in the treatment phase [15]. Interrupted treatment or not following DOTS treatment standards will lead to cases of MDR TB [13].

MTB detected Rif-resistant patients were found in fail tuberculosis cases patients as many as 9 (10,2%). Fail TB patients defined as tuberculosis patients with positive (+) AFB examination or recurrence to positive in the last fifth month or a month before the end of treatment. AFB examination that does not convert after stage two intensive treatment (2 months) is suspected to MDR TB patient. Pulmonary tuberculosis with positive (+) AFB examination generally will convert to negative (−) after 2 months of treatment. In the other case, some patient needs a longer time, so they need insertion medicine for four months after the intensive stage if the AFB examination has not to convert yet. If there is no sign of AFB examination conversion, it is highly suspected as an MDR TB case. Research in central java found 60% of MDR TB patients undergo failure in treatment. The bacteria which have resistance to tuberculosis drugs would require a longer timed of treatment. The physician should give a higher category of medicine that will cause a worse side effect and it will affect their compliance with treatment. MTB detected Rif-resistant patients were present in 8 new cases TB (9.1%). The expectation of MDR-TB in new cases TB is not much, because if MDR-TB cases are dominated by new cases TB it will be dangerous, meaning that more and more TB resistant bacteria are present. Resistant TB bacteria that have a higher risk of transmission will be a problem because it can cause much increase in the incidence of MDR TB. The mortality and morbidity rates of pulmonary TB patients are increased compared to non-MDR-TB. TB patients need to understand and make efforts to prevent the transmission of TB to others. MTB detected Rif-resistance is found in tuberculosis new cases as much as 9,1%. We hope the MDR TB in the new case is not much because if it is dominating will be dangerous as we will found much TB bacteria resistance. The resistance TB bacteria will gain a spreading risk will be a bigger problem causing more TB MDR occurrence, mortalituy and morbidity rate of pulmonary TB will be increased than non MDR-TB. TB patient should understand and prevent the spread of TB to others.

4 Conclusion

There is a significant relationship between the Gen-xpert examination results MDR-TB detected RIF Resistant with Relaps tuberculosis. Regular awareness of taking medication tuberculosis drugs is important to avoid the incidence of MDR TB.

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