The Relationship between Previous Tuberculosis Treatment and HIV Status with Multidrug-Resistant Tuberculosis

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Abstract

Multidrug-resistant tuberculosis (MDR-TB) is becoming major public health issues in the world. Among the causes are history of previous TB treatment and increased co-infection of TB-HIV (Human Immunodeficiency Virus). This study aimed to identify the relationship between history of previous TB treatment and HIV status with MDR-TB. This is a case control study. The sample case was patients with MDR-TB, while sample control was patient who have drug-sensitive TB. Secondary data was obtained from patient medical records and laboratory results at Rotinsulu Pulmonary Hospital Bandung. Data were analyzed using chi-square. Multiple logistic regression was used to identify the dominant factor that influence the occurrence of MDR-TB. This study showed that the history of previous TB treatment was statistically significant with MDR-TB (p value= 0.001; OR= 18.889; 95% CI= 4.093-87.172) and it is the dominant factor that influence MDR-TB (p value= 0.0001; OR= 56.84; 95% CI= 6.9- 468.87). HIV infection at control group (who contracted drug-sensitive TB) was 26.1% (p value= 0.022). This finding suggested that HIV testing should be performed to each TB and MDR-TB patients and increased collaboration TB-HIV program between the other health care facilities should ensue. Drug sensitivity testing should be conducted at the start of TB treatment for patients with previous TB treatment and TB-HIV co-infection.
incarceration and HIV infection (Dean et al., 2017). Previous tuberculosis treatment is associated with 10 times or greater risk of MDR-TB compared with patients who have not been previously treated with tuberculosis drugs (Burhan, 2010). Main causes of MDR-TB are poor implementation of DOTS program (Directly Observed Treatment Short-course) in hospitals and health care facilities, inadequate supply of quality drugs, inadequate patient compliance and other factors, such as HIV infection (Hanf et al., 2012).

Inadequate treatment of tuberculosis induces gene mutation in the bacteria and cause resistance to anti-tuberculosis drugs such as isoniazid and rifampicin. In the Mycobacteria, the influx of toxic compounds is significantly restricted by the complex cell wall, and the lipid bilayer presents a significant barrier to the influx of antibiotics. Decreased intracellular concentrations of more than one antibiotic may lead to increased resistance to multiple anti-TB drugs (Louw et al., 2009).

MDR-TB can either be primary or secondary resistance. Primary resistance occurs in patients who have never received prior treatment. Primary resistance is usually found in patients with HIV infection. Secondary resistance is obtained during therapy in people who is previously sensitive to drug (Sharma & Mohan, 2004). Increased TB-HIV co-infection affects the progression of the disease, prolong the period of infection, and increase risk of MDR-TB (Soepandi, 2012) due to weaker immune system in people with HIV (Sharma & Mohan, 2004).

Rotinsulu Pulmonary Hospital Bandung in 2005 found that 28.2% were resistant to rifampicin-isoniazid; 17.8% resistant to rifampicin-isoniazid-ethambutol; and 13.8% resistant to rifampicin-isoniazid-ethambutol-pyrazinamide-streptomycin. A study in 2010 found 80.8% were categorized as MDR-TB and the remaining 19.2% as Extensively Drug-resistant TB (XDR-TB) (Nugrahaeni & Malik, 2013). This study aimed to understand the relationship between history of previous TB treatment and HIV status with MDR-TB at Rotinsulu Pulmonary Hospital Bandung.

**Method**

This is a case control study that compares cases with controls, and looks back retrospectively to compare the exposure in each group to determine the relationship between the risk factor and disease. Data was collected from medical records of patient with multidrug-resistant tuberculosis and drugs-sensitive tuberculosis from January to December 2014 in Rotinsulu Pulmonary Hospital Bandung.

Sample cases in this study were defined as person with MDR-TB (person infected with an isolate resistant to at least isoniazid and rifampicin) based on clinical diagnosis, bacterial culture and anti-TB susceptibility testing. We identified 23 person. Sample controls are defined as people with drug-sensitive tuberculosis based on acid fast bacilli and chest X-ray test. We identified 23 person. Sample control was age and gender-matched to the sample case. Patients with pregnancy, diabetes mellitus, and cancer were excluded from this study.

The variables used in this study are the following: patient characteristic (level of education and employment jobs), type of resistant anti-TB drug, type of tuberculosis, history of previous TB treatment, and HIV status. Univariate analysis was conducted to obtain frequency distribution variable, while bivariate analysis was conducted using chi-square test. Multivariate analysis using multiple logistic regression was used to determine the final multivariate model and to identify the dominant factor that influences the occurrence of MDR-TB.

This study used medical record register of patient with multidrug-resistant tuberculosis and drugs sensitive tuberculosis. This study have been carried out according to ethical, legal, social implications and other applicable regulation. This study passed Ethical clearance and has been approved by Health Research Ethics Committee, Faculty of Medicine, Universitas Padjadjaran Bandung (approval No. 418/UN6.C1.3.2/KEPK/PN/2015, 25 June 2015).

**Result and Discussion**

Multidrug-resistant tuberculosis (MDR-TB) patients determined on the basis of clinical diagnosis, bacterial culture from sputum and anti-TB drug susceptibility test was defined as sample cases. Whereas sample control are
patients with drug-sensitive TB based on acid fast bacilli and chest X-ray test.

This study found that of all MDR-TB patients who have received previous treatment with anti-TB drug, 39.1% was considered treatment relapse (bacteriologically positive tuberculosis following previously cured TB), and 34.8% was considered treatment default (interruption of treatment for ≥ 2 consecutive months) (figure 1).

MDR-TB patients resistant to four (4) potentially anti-TB drugs (rifampicin, isoniazid, Ethambutol, and Streptomycin) were 39% (figure 2). The occurrence of resistance to the combination of four (4) anti-TB drugs in this study has increased compared to previous studies at Rotinsulu Pulmonary Hospital 2010 which amounted to 15.4% (Nugrahaeni & Malik, 2013).

Characteristic distribution of MDR-TB patients were as follows: 39.1% is a housewife and 65.2% have elementary education level. Up to 87% of patients with prior TB treatment were diagnosed with MDR-TB (Table 1). History of previous TB treatment was statistically significant with the occurrence of MDR-TB (p value= 0.001), Odds Ratio (OR= 18.889; 95% CI= 4.093-87.172). This study was consistent
with a study in Belarus, Russia (2010-2011) in which the majority (75.6%) of MDR-TB patients have a history of previous TB treatment. History of previous treatment for TB was the strongest independent risk factor for MDR-TB (OR= 6.5; 95% CI= 5.2 – 8.2) (Skrahina, 2012).

HIV infection in sample control (respondents with drug-sensitive TB) was 26.1%. The present study found an association between HIV infection and MDR-TB (p value= 0.022). In Europe, Faustini, Hall, and Perucci (2005) found that HIV status was significantly associated with the occurrence of MDR-TB (OR= 3.52; 95% CI= 2.48-5.01). A study in Belarus, Russia, found that HIV co-infection with TB is a risk factor for MDR-TB (p value= 0.0001; OR= 2.6, 95% CI= 1.7-4.1).

In the final multivariate model, independent variables that influences the occurrence of MDR-TB are occupation, level of education and history of past TB treatment. History of previous TB treatment is the dominant factor that influences the occurrence of MDR-TB (p value= 0.0001; OR= 56.84; 95% CI= 6.9-468.87) (Table 2).

Tuberculosis control and eradication strategies are constrain by MDR-TB as it increase complexities in diagnosis and treatment failure of tuberculosis, leading to higher mortality rate in MDR-TB (Suchindran et al., 2009). Multidrug-resistant tuberculosis is tuberculosis infection caused by *Mycobacterium tuberculosis* that are resistant to at least two of the first-line anti-TB drugs, such as isoniazid and rifampicin. In this study, we founded 26.1% of patients was resistant to isoniazid and rifampicin.

MDR-TB was caused by inadequate TB treatment such as, monotherapy drugs, noncompliance with treatment, extreme poverty, intolerance to medication and shortage of medication. These conditions allow development of resistance to anti-TB drugs (acquired MDR-TB or direct transmission of

### Table 1. The Relationship History of Previous TB Treatment and HIV Status with the Occurrence of MDR-TB

<table>
<thead>
<tr>
<th>Variable</th>
<th>Case</th>
<th>Control</th>
<th>Total</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Level of Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elementary education</td>
<td>15 (65.2%)</td>
<td>14 (60.8%)</td>
<td>29 (63.0%)</td>
<td>0.76</td>
<td>1.2 (0.36 – 3.99)</td>
</tr>
<tr>
<td>Higher education</td>
<td>8 (34.8%)</td>
<td>9 (39.1%)</td>
<td>17 (37.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment Jobs</td>
<td></td>
<td></td>
<td></td>
<td>0.625</td>
<td></td>
</tr>
<tr>
<td>Government employees</td>
<td>2 (8.70%)</td>
<td>1 (4.3%)</td>
<td>3 (6.50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private sector</td>
<td>11 (47.8%)</td>
<td>14 (60.9%)</td>
<td>25 (54.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Housewife</td>
<td>9 (39.1%)</td>
<td>8 (34.8%)</td>
<td>17 (37.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Student</td>
<td>1 (4.3%)</td>
<td>0 (0%)</td>
<td>1 (2.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of Previous TB Treatment</td>
<td></td>
<td></td>
<td></td>
<td>0.001</td>
<td>18.9 (4.093-87.172)</td>
</tr>
<tr>
<td>Previously treated case (1-5 times)</td>
<td>20 (87)</td>
<td>6 (26.1%)</td>
<td>26 (56.5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New case</td>
<td>3 (13%)</td>
<td>17 (73.9%)</td>
<td>20 (43.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV Status</td>
<td></td>
<td></td>
<td></td>
<td>0.022</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>0 (0%)</td>
<td>6 (26.1%)</td>
<td>6 (13.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>23 (100%)</td>
<td>17 (73.9%)</td>
<td>40 (87.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>23 (100%)</td>
<td>23 (100%)</td>
<td>46 (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Sourch: Medical Record Rotinsulu Pulmonary Hospital Bandung, 2014

### Table 2. Multivariate Analysis of the Occurrence of MDR-TB

<table>
<thead>
<tr>
<th>Variable</th>
<th>B</th>
<th>P Value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occupation</td>
<td>-1.167</td>
<td>0.099</td>
<td>0.31 (0.078 -1.25)</td>
</tr>
<tr>
<td>Level of Education</td>
<td>1.449</td>
<td>0.124</td>
<td>4.2 (0.67 – 27.04)</td>
</tr>
<tr>
<td>History of previous TB treatment</td>
<td>4.04</td>
<td>0.0001</td>
<td>56.84 (6.9 – 468.87)</td>
</tr>
</tbody>
</table>

Sourch: Medical Record Rotinsulu Pulmonary Hospital Bandung, 2014
of patients suffering from MDR as a primary MDR-TB (Suchindran et al., 2009). Based on basic health research 2010, as many as 38.11% and 21.95% of pulmonary tuberculosis patients in private health care facilities and public health facilities, respectively, do not adhere to treatment. (OR= 2.19; 95% CI: 1.61 -2.97) (Fadila & Riono, 2014).

Past TB treatment can cause multidrug-resistant tuberculosis. Most MDR-TB patients have treatment relapse and default. Relapse and defaulted in tuberculosis treatment could cause inadequate treatment, allowing the Mycobacterium tuberculosis to acquire resistance against anti-TB drugs (Soepandi, 2010). Tuberculosis patient who receive irregular treatment of tuberculosis drug had a 2.3 times greater risk of developing MDR-TB than those taking regular treatment (P Value= 0.01, OR=2.3, 95% CI= 1.38-10.28) (Sarwani et al., 2012).

In this study, MDR-TB patient with no history of previous TB treatment (new tuberculosis case) was 13.0%. It is unknown whether or not the patients ever had a history of contact with MDR TB, referred to as primary MDR-TB. People with new MDR-TB case indicates transmission of resistant strains of M. tuberculosis in the community (Skrahina, 2012). The high number of people with MDR-TB among new TB cases indicates transmission of resistant strains of M. tuberculosis in the community (Skrahina, 2012). In this study, the extent of transmission of resistant strains could not be assessed and further studies based on genotyping should be conducted. The prevalence of MDR-TB was estimated to be up to 10 times higher in unsuccessful treatment (Faustini, 2006). We found that patients with previous tuberculosis treatment are at 18.9 times higher risk of MDR-TB. The dominant variable attributed to MDR-TB are past TB treatment and it can be predicted as the causes of MDR-TB (OR= 56.84; 95% CI= 6.9 – 468.87).

The association between HIV infection and TB infection or MDR-TB can be caused by multiple factors. The first factor is association with time window, where in HIV infected patients, the progression of the disease are rapid and can lead to co-infection of HIV-TB through community or institutional transmission (Suchindran et al., 2009). The association between HIV infection and MDR-TB may be confounded by risk factors, such as injection drug use, socioeconomic status, and hospitalization.

The incidence and mortality rates for new AIDS-defining opportunistic infections have been shown to be higher if individuals with HIV are co-infected with TB. HIV patients should avoid risk factors of contracting TB or MDR-TB disease. Therefore, there is a need for collaboration between HIV and TB prevention programs, through screening tests for TB and HIV patients. Infection control measures need to become a key element of global TB control.

**Conclusion**

Previous anti-TB treatment must be identified in each tuberculosis patients at all level of health facilities because they are at increased risk of drug resistance, including MDR-TB. Although some characteristics of TB treatment such as defaulting from treatment and relapsing are well known predictors of multidrug-resistant tuberculosis, other aspects of treatment such as the drugs used and the length of treatment need to be studied as they may contribute to improving control program.

Determining and recording the patient's HIV status is critical for treatment decisions as well as for monitoring trends and assessing program performance. Collaboration of TB and HIV/AIDS program between hospitals and that health care facilities that implement DOTS is required to reduce the burden of HIV in people diagnosed with TB and people living with HIV. Drugs sensitivity testing should be performed at the start of TB treatment in patients previously treated with anti-TB drugs and HIV-positive TB patients to avoid mortality due to unrecognized drug-resistant TB. The use of rapid DST (Drug Sensitivity Testing) in sputum smear-positive persons living with HIV is strongly encouraged.

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Reference


