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Resistance Patterns in Drug-Resistant Pulmonary Tuberculosis Patients at Dr. Mohammad Hoesin Palembang Hospital

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ABSTRACT

Tuberculosis (TB) is a contagious infectious disease caused by acid-resistant bacteria, Mycobacterium Tuberculosis (MTb). Based on immunity, there are two types of pulmonary TB infection: drug-sensitive and drug-resistant. Based on ATD sensitization tests, MTb resistance types consist of TB that is monoresistant, polyresistant, multidrug resistance (MDR), pre-extensively drug resistant (Pre-XDR), extensively drug-resistant (XDR). Globally, in 2022, there will be an estimated 450,000 cases of DR-TB, but only 161,000 treated. In Indonesia, in 2022, there were an estimated 24,000 cases of DR-TB; only 8,268 were notified and 5,082 cases had started therapy. In this study, conducted with a retrospective descriptive method, during the period 2022 at RSMH Palembang, 92 patients with DR-TB were obtained who received treatment at RSMH Palembang. Of the 92 subjects, the mean age of diagnosis of DR-TB was 44.47 ± 16.5. The most common gender was male 62 subjects (67.4%) and 30 subjects were female (32.6%). Of the 92 rifampicin-resistant patients, there were a total of 39 patients (42.4%) with isoniazid resistance. Among these 39 patients, 21 patients (54%) were primary resistance cases and 18 patients (46%) were secondary resistance cases. The most common type of therapy regimen used was a long-term regimen as many as 68 subjects (74%) and short-term as many as 24 subjects (26%) Primary resistance patterns were obtained in 43 subjects (46.8%) and secondary resistance in 49 subjects (53.2%). Of the 49 secondary resistance subjects, 52 subjects (56.5%) had TB-RR, 33 subjects (35.8%) had MDR-TB, 6 subjects (6.5%) had pre-XDR TB, and 1 subject (1.2%) had XDR-TB. The researcher concluded that the dominant resistance pattern of pulmonary TB cases was secondary resistance, with the results of the drug sensitivity test being TB-RR. However, it should be noted that DR-TB with a primary resistance pattern also has a higher percentage.

1. Introduction

Tuberculosis (TB) is a contagious infectious disease caused by the acid-fast bacterium: Mycobacterium tuberculosis (MTb), that often infects the lungs. Pulmonary tuberculosis is the fourth leading cause of death after ischemic heart disease, cerebrovascular disease, and diabetes mellitus (DM) in Indonesia. In general, resistance to antituberculosis drugs (ATD) is divided into (1) primary resistance, if the patient has not previously received TB treatment, (2) secondary resistance, if the patient has a history of the TB treatment. The MTb resistance to drugs is divided into five different categories: mono-resistant, poly-resistant, multi-drug resistant (MDR), pre-extensive drug-resistant (Pre-XDR), and extensive drug-resistant (XDR).[1,2]

Mycobacterium tuberculosis (MTb) is an aerobic bacterium which the multiplication rate is strongly influenced by the oxygen concentration. Higher oxygen concentration, such as what is found in the

cavities of the lung parenchyma, rapid multiplication of MTb is possible. The MTb resistance to ATD is caused by spontaneous genetic mutations. Although the ATD resistance in the wild M.Tb population is commonly relatively small, treatments with ATD puts selective pressure on the MTb population, killing ATD-susceptible bacilli but allows the ATD-resistant mutant population to reproduce, causing the emergence of the drug resistance. Mutations causing resistance to ATD is commonly affecting only one of the drugs or drug groups. Resistance to two or more drugs is caused by sequential mutations in multiple different MTb genes. Inappropriate regimens, inappropriate use of recommended doses, poor drug quality, and poor adherence to treatment are also associated with the emergence of drug resistance.[3]

According to the Global Tuberculosis Report for 2022, there are an estimated 450,000 cases of DR-TB while only 161,000 cases of them were receiving treatments. In Indonesia, in 2022, there were an estimated 24,000 cases of DR-TB, while only 8,268 cases of them were notified and 5,082 cases had started therapy. In Palembang, there is no published research that discusses the resistance pattern of drug-resistant pulmonary TB. This study aims to elucidate the pattern of drug-resistance of pulmonary TB infection in Dr. Mohammad Hoesin General Hospital (RSMH), Palembang.

2. Methods

This study was conducted as a retrospective, descriptive study. This study was conducted at the Borang Clinic, Dr. Mohammad Hoesin General Hospital (RSMH) Palembang. This population involved in this study was all medical records of the patients with DR-TB in the TB Information System (SI-TB) of RSMH Palembang. The sample of this study was all medical records of all patients diagnosed with the drug-resistant pulmonary TB at RSMH, Palembang in year 2022. The inclusion criteria in this study were drug-resistant pulmonary TB patients who were confirmed based on bacteriological examination, TCM, or Xpert MTB/RIF; aged between 18-65 years with complete medical records. This study involved all records fulfilling the inclusion criteria. The resistance was divided into primary resistance (patients who have never received ATD) and secondary resistance (patients who have received prior ATD treatments). The TB resistance was further subdivided into mono-resistant, poly-resistant, MDR, pre-XDR, and XDR. The data were analyzed through the SPSS 25 for Windows and presented as tables and figures.

3. Results

Figure 1 shows an almost even distribution of resistance in each sub-district of Palembang. Highest number of the resistance was observed in Sukarami sub-district, with 11 cases in 2022 alone. For the whole 2022, there were 92 subjects who met the inclusion criteria of this study. Of the 92 subjects, the mean age of diagnosis of DR-TB was 44.47 ± 16.5 years old.

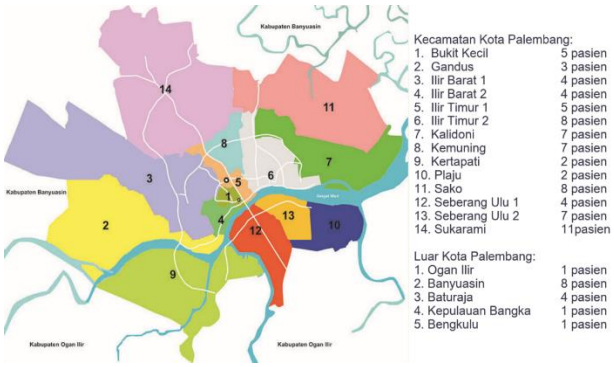

Figure 1. Map of patient distribution based on sub-districts in Palembang city

Our study found that cases of resistance were more common in male subjects, involving 62 cases (67.4%) while the rest 30 (32.6%) of the subjects were female. The most common type of the ADT regimen utilized was a long-term regimen, with 68 subjects (74%) receiving this type of the regimen. The short-term regimen was provided to 24 subjects (26%). The distribution of the resistance pattern is provided in the Table 1.

Table 1. Resistance pattern distribution

Characteristic	Patient Distribution	
	n=92	%
Age	44,47 ± 16,5	
Gender		
Male	62	67,4%
Female	30	32,6%
Primary Resistance	43	46,8%
Secondary Resistance	49	53,2%
-Fail ATD Category 1 or 2	7	7,6%
-Fail second line ATD	5	5,4%
-Unstandardized ATD	1	1,1%
-Lost to follow up	5	5,4%
-Relaps	31	33,7%
ATD Regiment		
Shorter Treatment Regiment	24	26%
Longer Treatment Regiment	68	74%
Resistance Type		
TB, mono-resistant (RR)	51	55,4%
TB, poly-resistant (RR+Z)	1	1,2%
TB MDR		
(R+INH)	21	22,8%
(R+INH+Z)	12	13%
TB Pre XDR (R+INH+Flq)	6	6,5%
TB XDR (R+INH+Flq+Bdq)	1	1,2%

R; rifampicin; INH: isoniazid; Z: pyrazinamide; Flq: fluoroquinolones; Bdq: bedaquiline; RR: rifampicin-resistant

Table 2. Resistance pattern distribution and sensitivity of ATD

Resistance pattern	ATD Sensibility									
	Isoniazid		Levofloxacin		Moxifloxacin		Bedaquiline		Pyrazinamide	
	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive	Resistant	Sensitive
Primary Resistance	21	22	3	40	1	42	0	43	9	34
Secondary resistance	0	7	0	7	0	7	0	7	0	7
Failed second line ATD	4	1	0	5	0	5	0	5	1	4
Lost to follow up	2	3	1	4	0	5	0	5	0	5
Relapse	12	19	1	30	2	29	1	31	4	27
Non-standard ATD	0	1	0	1	0	1	0	1	0	1

As shown in the Table 2, the isoniazid resistance was observed in 39 (42.4%) patients with rifampicin resistance (92 cases). Among these 39 patients, 21 patients (54%) were primary resistance cases while the 18 patients (46%) were secondary resistance cases.

Table 3. Odds Ratio of ATD History on the Incidence of INH Resistance

Predictor	Odds Ratio	*p*-value
Secondary Resistance & INH Resistance	0,6	0,02

In the Table 3, we present the risk of secondary resistance to isoniazid. The risk of secondary isoniazid resistance was 0.6 (p = 0.02) in patients that has previously taken ATD.

4. Discussion

The secondary resistance was observed in 53.2% of the resistance cases in this study. Unpublished study by Hadi et al. (1999) in Palembang showed that the secondary resistance was observed in 67.9% of the DR-TB cases. The gradual increase of primary resistance is observed through the years, up to the point of 47.8% of the DR-TB cases in 2022 were primary resistance. The increase of primary resistance shows the increase of DR-MTb population in the wild. A study in Soetomo Hospital Surabaya in 2014 showed the secondary resistance was observed in 42.7% of the DR-TB cases.[4]

As can be observed in Table 1, The mean age in this study was 44.47 years old. This study is in contrast with the study from Wibowo et al., who reported that 80% of DR-TB cases belongs to the 18-40 years age group.[5] Other studies discovered that the incidence of DR-TB is three times higher in men, although the global prevalence data did not find the gender as one of the risk factors of DR-TB infections.[6] In our study, the secondary resistance were observed in 53.2% of the subjects, which is in line with the research report by Wu et al. showing higher incidence of DR-TB in patients previously receiving ATD.[7]

The history of previous ADT administration becomes a risk factor for the development of DR-TB. A study by Eshetie et al. reported 8.1 times higher risk of DR-TB in patients previously receiving ADT.[8] Interestingly, we found 40% reduction of the risk to develop isoniazid resistance after previous ADT treatment (Table 3). In the integrated management of drug-resistant tuberculosis (MTPTRO), WHO is set to prioritize the DR-TB epidemic through several means. The first means of DR-TB prevention is through the provision of quality treatment for patients with drug-sensitive tuberculosis (DS-TB).[1,2] The secondary resistance was observed in 53.2% of the cases in this study. The high number of the secondary resistance that the existence of the gaps in providing quality treatments to patients with DR-TB. Further evaluation on the implementation of the TB eradication program at the primary care facilities are necessary to better clarify the existence of the quality gap. Community education and tracing, screening and diagnosis, in conjunction with treatment efforts and post-treatment monitoring are essential to prevent the rise of DR-TB.

The limitation of this study includes the inability to illustrate the pattern of resistance pattern of TB in Palembang city as a whole due to single-center nature of this study. Future studies should be focused on tackling the lack of data to allow for citywide description of DR-TB resistance pattern.

5. Conclusion

Secondary resistance is the most common form of the drug resistance in the patients of this study. The most common probable cause of resistance was the relapse of the TB. Rifampicin resistance was the most common type of the drug resistance observed in this study.

6. References

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