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***Mycobacterium tuberculosis* resistance pattern against first-line drugs in patients from urban area**



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ABSTRACT

Objective/Background: Tuberculosis (TB) infection is still a major public health burden in Indonesia. TB cases in Indonesia constitute 35% of all the TB cases detected worldwide and the prevalence of TB drug resistance in this country is approximately 3%. The aim of this study was to evaluate the resistance of *Mycobacterium tuberculosis* to first-line TB drugs among isolates from clinical specimens from a hospital in an urban area.

Methods: This laboratory-based study was conducted in Tangerang District, Indonesia, from January 2011 to December 2014. Sputum and other clinical specimens were obtained from patients with pulmonary and extrapulmonary TB. The specimens were stained with Ziehl–Neelsen, inoculated on Löwenstein–Jensen media for 6–8 weeks, and tested for sensitivity against first-line TB drugs [isoniazid (INH), rifampicin (RIF), ethambutol (EMB), and streptomycin (SM)].

Results: All TB patients in this study lived in urban areas with male preponderance. Of the 127 *M. tuberculosis* isolates collected, 22% showed resistance to first-line TB drugs. Among these resistant isolates, 20.5% showed resistance to at least one of the first-line TB drugs and 0.8% showed multidrug resistance (MDR). Resistance to EMB, INH, RIF, and SM was seen in 6.3%, 6.3%, 4.7%, and 1.6% of isolates, respectively. Polyresistance to EMB and INH, EMB and RIF, and EMB, INH, and RIF was seen in 0.8% of the isolates, respectively.

Conclusion: Our study confirms that drug resistance, including MDR, observed against all first-line TB drugs was a real threat in the management of TB infection in Indonesia. The resistance pattern identified in this study could assist clinicians in providing appropriate treatment regimen to TB patients and improve their clinical outcome.

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Introduction

Tuberculosis (TB) is a disease caused by acid-fast bacilli *Mycobacterium tuberculosis*, which infects the lungs

(pulmonary TB) and other organs (extrapulmonary) such as the brain, spine, lymph nodes, abdomen, genitourinary system, skin, and joints [1]. Drug-resistant-TB (DR-TB), especially multidrug-resistant TB (MDR-TB) and extensive

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drug-resistant-TB, has become a major public health problem in many countries. According to the 2014 World Health Organization Global Report, of the estimated 9 million TB cases in the world, approximately 56% were from South-East Asia and Western Pacific regions. Of these TB cases, 3.5% of new cases and 20.5% of retreatment cases were attributed to MDR-TB [2]. Indonesia is one of the countries with the highest TB prevalence, with 430,000 new TB cases reported every year, and an estimated MDR-TB proportion of 1.9% among new cases and 12% among retreatment cases [2]. The directly observed treatment, short course (DOTS) strategy implemented since 1995 by the Indonesian National TB Program (NTP) has enabled Indonesia to reach the global target for new smear-positive TB case notification rate—73 cases/100,000 population in 2010 [3]. Routine monitoring of DR-TB is very important because of the limited availability of first-line TB drugs, the high price of second-line TB drugs, and lack of facilities in most health-care centers in Indonesia that could detect DR-TB or have access to second-line TB treatment [4]. Therefore, data on local TB drugs resistance are essential for patient management and selection of appropriate regimen for patients suspected to have the resistance strain, as this helps to prevent the spread of resistant TB [2,5]. Thus, the aim of this study was to evaluate the resistance of *M. tuberculosis* to first-line TB drugs among isolates from clinical specimens from a hospital in an urban area of Indonesia (Tangerang District).

Materials and methods

This study was conducted in Siloam General Hospital, Tangerang District, Indonesia. Tangerang is a city in Banten Province, located approximately 25 km from Jakarta. The study area is one of the largest cities in Indonesia with a population of approximately 2 million distributed over an area of 164.55 km². The Disease Control, Prevention and Health Environment Bureau reported that in 2012, Banten Province had 286.7 new TB cases/100,000 population, and the crude death rate in this region was 1.1% [6]. Patients in the participating hospital represented a wide range of socioeconomic strata.

Epidemiological data of TB patients and microbiological data of *M. tuberculosis* from various clinical specimens and its resistance to first-line TB drugs were retrospectively collected from January 2011 to December 2014. Sputum was collected early morning on 3 consecutive days. Other specimens were collected from bronchial fluid, cerebrospinal fluid, urine, and pus from abscess. The diagnosis of pulmonary and extrapulmonary TB was made by clinicians based on history, physical examination, chest radiography, and positive acid-fast bacilli smear, and/or culture [7,8].

Drug-susceptibility testing

All specimens underwent decontamination and homogenization using sodium hydroxide at a final concentration of 2% followed by Ziehl–Neelsen staining [9,10]. The drug-susceptibility testing against first-line TB drugs was carried out using the proportional method after inoculating the specimens on Löwenstein–Jensen (LJ) medium and incubating them at 37 °C. The

LJ medium was observed two times a week, for 6–8 weeks, to check for growth of the pathogen. The growth was compared with the international standard strain of *M. tuberculosis* H37Rv, which is used to detect resistance [10,11]. The drug susceptibility was determined as the percentage of colonies that grew on the following concentration of four first-line TB drugs: isoniazid (INH), 0.1 µg/mL, 1 µg/mL, and 10 µg/mL; rifampicin (RIF), 2.5 µg/mL, 5 µg/mL, and 20 µg/mL; ethambutol (EMB), 1 µg/mL, 10 µg/mL, and 100 µg/mL; and streptomycin (SM), 1 µg/mL, 10 µg/mL, 100 µg/mL, respectively [10].

Definition

Any drug resistance was defined as resistance to one or more first-line TB drugs (INH, RIF, EMB, and SM). Monoresistance was defined as resistance to only one first-line TB drug, and polyresistance was defined as resistance to at least two or more first-line TB drugs except the INH and RIF combination [8,12]. MDR-TB was defined as resistance to the two key first-line TB drugs, namely, INH and RIF [2,5].

Results

The total number of positive culture for *M. tuberculosis* was 127 (15, 37, 45, and 30 cultures collected consecutively in 2011, 2012, 2013, and 2014, respectively). All patients in this study lived in urban areas (55.1% male and 44.9% female patients). Other profiles of TB patients are presented in Table 1.

The proportion of resistance to first-line TB drugs during 4-year observation period is presented in Table 2. Most of the *M. tuberculosis* isolates were collected from sputum specimens (87.4%). Isolates collected from the cerebrospinal fluid of patients with brain infection caused by *M. tuberculosis* constituted 2.4% of the total specimen. The highest prevalence of any drug resistance was noted in 2012 and 2014. Twenty eight (22%) of the 127 *M. tuberculosis* isolates collected showed resistance; among these, 24 (18.9%) were monoresistant and two (1.6%) were polyresistant. There was only one isolate of MDR-TB, which was found in 2014. The overall resistance to single drugs was noted in eight isolates (6.8%; against EMB and INH); six (94.7%) isolates were resistant to RIF and two isolates (1.6%) were resistant to SM. Polyresistance to EMB and INH and EMB and RIF was noted in 0.8% of the isolates, respectively ($n = 1$ each).

Discussion

In last decades, Indonesia has been identified as one of the countries with the highest TB prevalence in the world. The incidence of TB has decreased as reported by the NTP report. However, the emergence and spread of DR-TB threatens TB control and has become a major public health problem in Indonesia. Development of DR-TB, including MDR, is attributed to poor patients' compliance, inappropriate TB drug regimen, inadequate laboratory facilities for drug-susceptibility testing, and acceleration of human immunodeficiency virus epidemic [3,5,13,14].

In this study, 18.9% of *M. tuberculosis* isolates were resistant to at least one first-line TB drug. This number was lower than

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