

Resistance pattern of *Mycobacterium tuberculosis* to first-line antituberculosis drugs

Tjahjani Mirawati Sudiro, Amin Soebandrio, Prawoto, Pratiwi Sudarmono

Abstrak

Dalam laporan ini kami menganalisis pola resistensi *M. tuberculosis* yang diisolasi di laboratorium Mikrobiologi Fakultas Kedokteran Universitas Indonesia selama tahun 1996-1998 dan membandingkannya dengan data tahun 1995 dari laboratorium kami yang telah dipublikasi. Selama tahun 1996, 1997, dan 1998 telah diperiksa masing-masing 2360, 2468 dan 1849 spesimen. Dari spesimen tersebut, dengan menggunakan medium Löwenstein-Jensen berturut-turut ditemukan 164 (6,9%), 181 (7,3%), dan 214 (11,6%) biakan positif *M. tuberculosis* pada tahun 1996, 1997 dan 1998. Dibandingkan dengan laporan tahun sebelumnya dari laboratorium kami oleh Wahid dkk., terlihat adanya fluktuasi tingkat resistensi terhadap satu atau lebih obat antituberkulosis utama (streptomisin, INH, etambutol, dan rifampisin) dari 15,9% pada tahun 1995,¹ 7,9% pada tahun 1996, 12,7% pada tahun 1997 dan 8,4% pada tahun 1998. Juga terlihat pola resistensi yang berbeda selama 4 tahun terakhir ini. Pada tahun 1995-1997 resistensi yang tertinggi adalah terhadap rifampisin, yaitu berturut-turut 14,0%, 7,9%, dan 9,4% pada tahun 1995, 1996 dan 1997, sedangkan pada tahun 1998 resistensi terhadap INH adalah yang tertinggi (4,7%). Resistensi terhadap etambutol tidak ditemukan pada tahun 1996 dan 1997, tetapi ditemukan pada 2 isolat pada tahun 1998. Selama tahun 1996 dan 1997 tidak ditemukan isolat yang resisten terhadap tiga atau lebih obat antituberkulosis (OAT). Pada tahun 1998 ditemukan 1 isolat yang resisten terhadap streptomisin, etambutol dan INH. Selama tahun 1996-1998 tidak ditemukan isolat *M. tuberculosis* yang resisten terhadap keempat OAT yang diuji.

Abstract

In this report we analyzed the resistance patterns of *M. tuberculosis* isolated in our laboratory from 1996 to 1998 and compared them with published data of the year 1995 from our laboratory. In our laboratory, 2360, 2468 and 1849 specimens were examined in 1996, 1997 and 1998, respectively. From these specimens, using Löwenstein-Jensen media, 164 (6.9%), 181 (7.3%) and 214 (11.6%) were found positive for *M. tuberculosis* in 1996, 1997, 1998 respectively. Compared with the earlier published reports from our laboratory, we found a fluctuation of the resistance rate to one or more first line antituberculosis drugs (streptomycin, INH, ethambutol, and rifampicin) from 15.9% in 1995,¹ 7.9% in 1996, 12.7% in 1997 and 8.4% in 1998. We also found different patterns of resistance in the last 4 years. During 1995 to 1997 the highest rate of resistance was to rifampicin, i.e. 14.0%, 7.9%, and 9.4% in 1995, 1996 and 1997 respectively; while in 1998 the resistance to INH was the highest (4.7%). Resistance to ethambutol was not found in 1996 and 1997, but it was found in 2 isolates in 1998. Resistance to three or more drugs was not found in 1996 and 1997. Resistance to streptomycin, ethambutol and INH was found in one isolate in 1998. Resistance to four antituberculosis drugs was not found in 1996 to 1998.

Keywords: Streptomycin, INH, ethambutol, rifampicin

Tuberculosis (TB) is still an important public health problem in Indonesia and all over the world. In 1996, 3.8 million cases of TB have been reported to WHO.² Recently the problem of tuberculosis have been re-increasing due to the increase of Human Immunodeficiency Virus (HIV) infections and multi-drug resistant TB (MDR-TB). Since the antituberculosis

drugs available are limited, routine monitoring of the MDR-TB is very important. Wahid et al have reported that *M. tuberculosis* isolated in our laboratory in 1995 showed overall resistance of 15.6%, and 5.1% showed resistance to the 4 first-line drugs.¹ Here we report an evaluation of routine susceptibility testing of *M. tuberculosis* isolated from clinical specimens sent to the laboratory of the Department of Microbiology, Faculty of Medicine, University of Indonesia in Jakarta from 1996 to 1998 and compared its results with the data published in 1995 from the same laboratory.

METHODS

Samples

Retrospective analysis was done on the data, dealing with the susceptibility of *M. tuberculosis* against anti-TB, obtained from various clinical specimens sent to our laboratory by clinicians throughout Jakarta. All specimens came from suspected tuberculosis patients, and mainly consisted of sputum, but there were also pleural effusion, bronchial washing, pus, urine, and body fluid/ascites. The sputum collected were the morning sputum taken in three consecutive days.

Isolation of *M. tuberculosis*

The samples were first decontaminated and homogenized using sodium hydroxide at a final concentration of 2%. Samples were inoculated onto Löwenstein-Jensen medium, incubated at 37°C and observed twice a week for 6 to 8 weeks for mycobacterial growth.

Drug susceptibility test

The proportional method by comparing the isolates with the international standard strain of *M. tuberculosis* H37Rv was used to detect drug resistance. The concentrations of the drugs tested were respectively as followed: streptomycin (1; 10; and 100 µg/ml), isoniazid (INH) (0.1; 1 and 10 µg/ml), ethambutol (1; 10 and 100 µg/ml), and rifampicin (2.5; 5 and 20 µg/ml).

RESULTS

We examined a number of 2360, 2468 and 1849 specimens collected from suspected TB patients in 1996, 1997, and 1998 respectively (Table 1). From those samples collected in 1996, 1997, and 1998 we found 164 (6.9%), 181 (7.3%), and 214 (11.6%) were culture-positive for *M. tuberculosis* respectively. Those positive clinical specimens were obtained from

sputum, pleural fluid, bronchial washing, pus, body fluid/ascites, cerebrospinal fluid and exudates.

Table 1. Specimens collected from suspected TB patients from 1996 to 1998

Specimen	1996	1997	1998
Sputum	1985	1985	1446
Pleural fluid	108	137	130
Bronchial washing	79	102	92
Pus	55	70	59
Others	133	174	122
Total	2360	2468	1849

In 1996, 13 out of 164 isolates (7.9%) were found to be resistant to rifampicin, and no MDR-TB was detected. In 1997, from 181 isolates we found 2 (1.1%) resistant to streptomycin, 4 (2.2%) resistant to INH, 13 (7.2%) resistant to rifampicin, 1 resistant to streptomycin and rifampicin, and 3 resistant to INH and rifampicin. In 1998 from 214 isolates, 196 (91.6%) were sensitive to the four first-line drugs. From 18 (8.4%) resistant isolates we found 2 isolates were resistant to streptomycin, 8 isolates were resistant to INH, 5 isolates were resistant to rifampicin, 1 isolate was resistant to streptomycin and INH, and 1 isolate was resistant to streptomycin and ethambutol. We found 1 isolate was resistant to 3 drugs, i.e. streptomycin, ethambutol, and INH. Isolates resistant to four drugs were not found (Table 2).

Regarding the resistance to each drug, in 1996 we found drug resistance of *M. tuberculosis* only to rifampicin, i.e. 13 (7.9%) isolates. In 1997, 3 (1.7%) isolates were found to be resistant to streptomycin, 7 (3.9%) isolates were resistant to isoniazid, and 17 (9.4%) isolates were resistant to rifampicin. In 1998, 10 isolates (4.7% of total isolates) were resistant to isoniazid, 5 (2.3%) isolates were resistant to streptomycin, 5 (2.3%) isolates were resistant to rifampicin, and 2 (0.9%) isolates were resistant to ethambutol (Table 3).

Table 2. Comparison of the resistance rate of *M.tuberculosis* isolated from 1995 to 1998

	1995*		1996		1997		1998	
	n	%†	n	%	n	%	n	%
Sensitive	132	84.1	151	92.1	158	87.3	196	91.6
Resistant to S					2	1.1	2	0.9
Resistant to H	3	1.91			4	2.2	8	3.7
Resistant to E								
Resistant to R	6	3.82	13	7.9	13	7.2	5	2.3
Resistant to S+H							1	0.5
Resistant to S+E							1	0.5
Resistant to S+R					1	0.5		
Resistant to H+E								
Resistant to H+R					3	1.7		
Resistant to E+R	2	1.27						
Resistant to S+H+E							1	0.5
Resistant to S+H+R	5	3.18						
Resistant to S+E+R								
Resistant to H+E+R	1	0.64						
Resistant to S+H+E+R	8	5.10						

* From Wahid et al (1997)

† : percentage of total isolates

S : Streptomycin; H: Isoniazid; E: Ethambutol; R: Rifampicin.

Table 3. Percentage of *M.tuberculosis* resistance to each drug

	S	H	E	R
1995*	13 (8.3%)	17 (10.8%)	11 (7.0%)	22 (14.0%)
1996	0	0	0	13 (7.9%)
1997	3 (1.7%)	7 (3.9%)	0	17 (9.4%)
1998	5 (2.3%)	10 (4.7%)	2 (0.9%)	5 (2.3%)

S: Streptomycin; H: Isoniazid; E: Ethambutol; R: Rifampicin.

*From Wahid et al (1997)

DISCUSSION

Resistance of *M. tuberculosis* to antituberculosis drugs has been reported worldwide. Comparing our report here with the earlier published report from our laboratory, we found a fluctuation of the resistance rate to 1 or more drugs (streptomycin, isoniazid, rifampicin, and ethambutol), which was 15.9% in 1995,¹ 7.9% in 1996, 12.7% in 1997 and 8.4% in 1998 respectively (Table 2). The susceptibility to pyrazinamide was not tested. We also found different patterns of resistance in the last 4 years. While in 1995, 1996, and 1997 the highest rate of resistance was to rifampicin, i.e. 14.0%, 7.9%, and 9.4% respectively; in 1998, resistance to INH was the highest (4.7%) (Table 3). Resistance to ethambutol,

which was not found in 1996 and 1997, was found in 1998 in 2 isolates. Resistance to three or more drugs was not found in 1996 and 1997, but found in one isolate in 1998. In 1995, the presence of 8 isolates resistant to 4 drugs had been reported, but we could not find it in 1996 to 1998.

Compared to reports from other investigators, the resistance rate of *M. tuberculosis* reported here is considered to be relatively low. For example, Aditama et al reported a resistance rate of 29.63% in cases obtained from Jakarta in 1994,³ and a resistance rate of 33% had been reported in New York city in 1991.⁴ The low rate of resistance showed here might reflect the pattern of new or primary cases, but unfortunately we could not obtain the complete history of the cases

with positive *M. tuberculosis* culture. It has been reported that cases with secondary tuberculosis have a higher rate of resistance compared to primary cases.^{3,4} Our laboratory does not attach directly to a particular hospital, and most of the specimens came from outpatient cases. Thus, the data on MDR-TB collected in our laboratory may not reflect the real MDR-TB in the population. Treatment failure of TB patients reported by clinicians is relatively high, although the reason of failure may not necessarily caused by MDR-TB, but mainly due to the compliance of patients in taking drugs.

CONCLUSION

Here we reported our data on the resistance pattern of *M. tuberculosis* isolated in our laboratory in 1995-1998 to isoniazid, ethambutol, streptomycin, and rifampicin. Although the resistance rate of *M. tuberculosis* in our report is relatively low, it shows that there is indeed, a change of resistance pattern from year to year. Resistance to ethambutol, as well as resistance to more than two drugs that we could not find in 1996 and 1997, could be found in 1998. These results shows the importance of MDR-TB monitoring,

and also suggests that multidrug therapy is still considered to be the method of choice in the management of tuberculosis.

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