Factors Predicting Sputum Smear Conversion and Treatment Outcomes in New Smear-Positive Pulmonary Tuberculosis

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Background: *Epidemiological studies indicated that the proportion of TB patients who remained smear-positive after two months of treatment could be greater than 20%. The lack of smear conversion in the second month of treatment was one of the predictors of treatment failure and relapse.*
Objective: *To determine factors associated with the persisting positive smear after two months of treatment and its value in predicting treatment failure.*
Material and Method: *A 3-year retrospective cohort study was conducted in a 1,200-bed government hospital in Thailand. New smear-positive tuberculosis patients who had pretreatment drug susceptibility test, the result of 2-month sputum smear, and treatment outcomes were selected. The pretreatment drug susceptibility pattern and statistically differences on variables between groups of patients were described.*
Results: *Three hundred fifty six patients were included in the present study. The level of pretreatment isoniazid resistance and multi-drug resistance were 13.8% and 3.1% respectively. Factors associated with the 2-month positive smear were male sex, high initial sputum acid-fast bacilli grades, and cavitary diseases. The presence of human immuno-deficiency virus infection, drug resistance and the 2-month positive smear were significantly associated with treatment failure.*
Conclusion: *Male sex, high initial sputum acid-fast bacilli grades, and cavitary diseases were factors associated with the 2-month positive smear and increasing risk of treatment failure.*

Keywords: *Sputum conversion, Treatment failure*

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More than thirty thousand new smear-positive tuberculosis (TB) patients were expected every year in Thailand[1]. These sputum-positive patients produced droplet nuclei through coughing, sneezing, talking and were responsible for the spread of the infection in the community. Early diagnosis and its treatment were essential in a control program to reduce the severity, mortality, and transmission of the disease.

Because resources were limited, the pre-treatment drug susceptibility test (DST) was not done in most new patients. The national DST data and during-treatment monitoring were vital in order to guide therapy and establish patients' treatment outcomes. Sputum smear examination for acid-fast bacilli (AFB) was faster, simpler, less expensive and thus had been used for diagnosis and monitoring during the course of treatment. At two months, the sputum AFB smears was necessary to decide on whether to prolong the intensive phase for a third month if the results were positive, or to move to the continuation phase if the results were negative[2]. Epidemiological studies indicated that the proportion of TB patients who remained smear-positive after two months of treatment could be greater than 20%[3,4]. Other evidence indicated that lack of smear conversion in the second month of treatment was one of the predictors of treatment failure and relapse[5,6]. Additionally, these patients might turn out to be harboring drug resistant cases. Thus, identification of the risk factors was very important for TB control policies and for allocation of public health resources.

The World Health Organization (WHO) recently revised its guidelines stating that the intensive phase extension was not further recommended regardless to the sputum-smear at two months of treatment[7]. The changing recommendation raised

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controversies among countries with high drug resistance including Thailand[8,9].

The present study was undertaken to determine factors associated with the persisting positive sputum-smear after two months of treatment, to evaluate its impact on treatment outcomes.

Material and Method

The study design was a retrospective cohort study of all pulmonary TB patients registered between October 2007 and September 2010 in Rajavithi Hospital, a 1,200-bed government hospital located in central Bangkok, Thailand. The trial protocol was approved by the hospital's ethic committee. Medical records were reviewed to obtain the following information: age, gender, chest x-ray (CXR), human immunodeficiency virus (HIV) status, the result of sputum AFB smear at the beginning, at the end of the second, fifth, and sixth month, pretreatment DST, and treatment outcomes. Patients selected in the cohort were newly diagnosed patients who were smear positive at the time of the diagnosis, having pretreatment DST, having sputum AFB smear at the end of the second month, and known treatment outcomes. Non-tuberculous mycobacterium cases and patients who had inadequate data were excluded.

Definition

1. AFB grades: sputum smears were examined for AFB by Kinyoun carbolfuchsin staining techniques and were graded according to the American Thoracic Society/Center for Disease Control and Prevention (ATS/CDC)[10]: 1-9 AFB/100 fields (+1), 1-9 AFB/10 fields (+2), 1-9 AFB/field (+3), and >9 AFB/field (+4). The highest grade among the consecutive samples was recorded.

2. Treatment outcomes:

2.1. Success: cure or complete

Cure: a patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion.

Complete: a patient who completed treatment but did not meet the criteria for cure or failure.

2.2. Failure: a patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment.

Data analysis and statistics

The analyses focused on risk factors associated with the persisting positive smear after 2 months of treatment and factors increasing risk to treatment failure. Estimating that the rate of the persisting positive smear after 2 months of treatment was 20%[3], the minimum sample size for 95% confidence level calculated by Lwanga and Lemeshow 1991 formula[11] was 246 cases. Statistical analysis was performed using the SPSS 17.0 software and p-values of less than 0.05 were regarded as significant. The continuous variables were presented as mean ± standard deviation (SD), min-max, and compared using the Student t-test. The categorical variables were presented as numbers (n) and percentages (%) and were analyzed using either the Pearson Chi-square test or the Fisher's exact test depending on which was more appropriate. Variables that were statistically significant in univariate analysis were entered into the Binary Logistic Regression model in order to identify the factors independently. The odds ratios (OR) and 95% confidence intervals (CI) were determined.

Table 1. Baseline clinical characteristics (n = 356)

Characteristics	Number	%
Gender		
Female	141	39.6
Male	215	60.4
Age: years		
Mean ± SD	38.07±14.47	
Min-max	15-83	
Initial AFB grades		
+1	12	3.4
+2	67	18.8
+3	59	16.6
+4	218	61.2
HIV status		
Negative	292	82.0
Positive	38	10.7
Unknown	26	7.3
Chest x-ray		
No cavity	243	68.3
Cavity	84	23.6
Unknown	29	8.1
Drug susceptibility test		
Fully susceptible	278	78.1
Resistance	78	21.9
Any H resistance	49	13.8
Any R resistance	11	3.1
Any E resistance	8	2.2
Any S resistance	41	11.5
MDR	11	3.1

H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug resistance

Results

Between October 1, 2007 and September 30, 2010, 856 new sputum-positive pulmonary TB patients were registered at the hospital. Of these patients, 356 (41%) fulfilled all the inclusion and exclusion criteria and were the basis of the present study. There were more male than female patients in this cohort population whose mean age was 38 years. HIV status was tested in 330 patients (92.7%) and found to be positive in 38 cases (11.5%). Overall, 21.9% of the studied population was resistant to at least one anti-TB drug. Pretreatment isoniazid (INH) resistance and multi-drug resistance (MDR) levels were 13.8% and 3.1% respectively. Other clinical characteristics were shown in Table 1.

Factors associated with persisting positive smear after two months of treatment

The sputum-smear after two months of treatment remained positive in 123 patients (34.6%). The univariate analysis indicated that the risk of a persistent positive smear was greater in patients who were male (p = 0.047), cavitary disease (p = 0.001), and had a higher (+3, +4) bacillary load (p<0.001). There were no statistically significant differences in other evaluated variables such as age (p = 0.163), HIV seropositivity (p = 0.418), pretreatment DST (p = 0.989), and medications during the intensive phase (p = 0.780) (Table 2).

Factors influenced to treatment outcomes

Twenty-eight patients (7.9%) were treatment failure. The risk factors associated with treatment failure included the HIV-infected patients (OR 7.03, 95% CI 2.96-16.67), drug resistant TB (OR 6.77, 95% CI 3.02-15.17), and the persisting positive sputum-smear after 2 months of treatment (OR 2.35, 95% CI 1.08-5.12). Any rifampicin resistance and MDR carried the highest risk (OR 109.23, 95% CI 21.05-566.79) (Table 3). The multivariate analysis

Table 2. Variables associated with persisting positive AFB smear after 2 months (n = 356)

Variables	n	Negative smear n = 233 (%)	Positive smear n = 123 (%)	Crude OR (95% CI)	p-value
Gender					
Female	141	101 (71.6)	40 (28.4)	1.00	
Male	215	132 (61.4)	83 (38.6)	1.59 (1.01-2.51)	0.047*
Age: years	356	37.29±14.58	39.54±14.21	1.01 (0.99-1.03)	0.163
Initial AFB grades					
+1, +2	79	68 (86.1)	11 (13.9)	1.00	
+3, +4	277	165 (59.6)	112 (40.4)	4.20 (2.12-8.29)	<0.001*
HIV status					
Negative	292	188 (64.4)	104 (35.6)	1.00	
Positive	38	27 (71.1)	11 (28.9)	0.74 (0.35-1.55)	0.418
Unknown	26	18 (69.2)	8 (30.8)	0.80 (0.34-1.91)	0.621
CXR: cavity					
Negative	243	170 (70.0)	73 (30.0)	1.00	
Positive	84	41 (48.8)	43 (51.2)	2.44 (1.47-4.06)	0.001*
Unknown	29	22 (75.9)	7 (24.1)	0.74 (0.30-1.81)	0.511
Drug susceptibility test					
Full susceptible	278	182 (65.5)	96 (34.5)	1.00	
Resist any drugs	78	51 (65.4)	27 (34.6)	1.004 (0.59-1.70)	0.989
Resist any H	49	32 (65.3)	17 (34.7)	1.007 (0.53-1.91)	0.983
Resist any R	11	7 (63.6)	4 (36.4)	1.08 (0.31-3.79)	0.900
Resist any E	8	3 (37.5)	5 (62.5)	3.16 (0.74-13.51)	0.103
Resist any S	41	28 (68.3)	13 (31.7)	0.88 (0.44-1.78)	0.722
MDR	11	7 (63.6)	4 (36.4)	1.08 (0.31-3.79)	0.900
Intensive phase medication					
HRZE	337	220 (65.3)	117 (34.7)	1.00	
Not HRZE	19	13 (68.4)	6 (31.6)	1.15 (0.43-3.11)	0.780

H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug resistance

Table 3. Variables influenced to treatment outcomes (n = 356)

Variables	n	Success, n = 328 (%)	Fail, n = 28 (%)	Crude OR (95% CI)	p-value
Initial AFB grades					
+1, +2	79	74 (93.7)	5 (6.3)	1.00	
+3, +4	277	254 (91.7)	23 (8.3)	1.34 (0.49-3.65)	0.565
HIV status					
Negative	292	276 (94.5)	16 (5.5)	1.00	
Positive	38	27 (71.1)	11 (28.9)	7.03 (2.96-16.67)	<0.001*
Unknown	26	25 (96.2)	1 (3.8)	0.69 (0.09-5.42)	0.724
CXR: cavity					
Negative	243	223 (91.8)	20 (8.2)	1.00	
Positive	84	78 (92.9)	6 (7.1)	0.86 (0.33-2.21)	0.751
Unknown	29	27 (93.1)	2 (6.9)	0.83 (0.18-3.73)	0.804
Drug susceptibility test					
Full susceptible	278	267 (96.0)	11 (4.0)	1.00	
Resist any drugs	78	61 (78.2)	17 (21.8)	6.77 (3.02-15.17)	<0.001*
Resist any H	49	34 (69.4)	15 (30.6)	10.71 (4.55-25.20)	<0.001*
Resist any R	11	2 (18.2)	9 (81.8)	109.23 (21.05-566.79)	<0.001*
Resist any E	8	4 (50.0)	4 (50.0)	24.27 (5.36-110.03)	<0.001*
Resist any S	41	34 (82.9)	7 (17.1)	5.00 (1.82-13.76)	0.004*
MDR	11	2 (18.2)	9 (81.8)	109.23 (21.05-566.79)	<0.001*
AFB after 2 months					
Negative	233	220 (94.4)	13 (5.6)	1.00	
Positive	123	108 (87.8)	15 (12.2)	2.35 (1.08-5.12)	0.027*

H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug resistance

Table 4. Multivariate analysis on variables influenced to treatment outcomes (n = 356)

Variables	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
HIV status				
Negative	1.00	1.00		
Positive	7.03 (2.96-16.67)	<0.001*	10.22 (3.71-28.15)	<0.001*
Drug susceptibility test				
Full susceptible	1.00	1.00		
Resistance	6.77 (3.02-15.17)	<0.001*	7.86 (3.14-19.64)	<0.001*
AFB after 2 months				
Negative	1.00	1.00		
Positive	2.35 (1.08-5.12)	0.027*	3.30 (1.34-8.13)	0.010*

indicated that all three significant variables from the univariate analysis were independently associated with treatment failure (Table 4).

Discussion

Without the pretreatment DST, assessment or prediction of treatment response is especially important in patients at high drug resistant TB. The present study showed that the chance of persisting positive smears after two months of treatment was high and associated with male gender, high initial AFB grades, and cavitary diseases. High AFB grades and cavitary diseases reflected high bacillary loads and were well-recognized risk factors. The delayed or no conversion in male patients could be due to greater disease extent, better quality of sputum specimens, and less medication adherence. Drug resistance, HIV status, and medications in the intensive phase had no effect on sputum-smear conversion. Similar findings had been reported earlier[12-14].

Among the no-conversion patients, the sputum culture was done in 44 cases and found to be positive culture in only three cases (data not shown). Although this observation was based on low number

of patients, the low level of positive culture and the non-significant association to drug resistance made the persisting positive-smear at the end of the intensive phase less meaningful and may indicate non-viable bacilli[15].

The present study showed that HIV-infected patients, drug resistance, and the lack of sputum-smear conversion increased the risk for treatment failure. These findings addressed that drug regimen in the intensive phase was capable in sputum conversion even in drug resistant cases, but was not effective enough to cure the disease. Thus, the pretreatment DST should be scaled up in Thailand and detection of a positive smear at the end of the intensive phase remained important as a trigger for patient assessment.

The main limitations of the present study were the retrospective design, and the uncertainty about drug regimen adherence. Association of factors could be better understood through a prospective study with a larger sample.

Conclusion

Male patients, high initial sputum AFB grades and cavitary diseases were more likely to undergo delayed or non-conversion. Drug resistance, HIV status, and medications in the intensive phase had no effect on the conversion. In addition to drug resistance, HIV infection and the persisting positive smear at two months of treatment increased the risk of failure.

Potential conflicts of interest

None.

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ปัจจัยที่มีผลต่อการมีเสมหะบวกหลังการรักษาระยะเข้มข้นและผลการรักษาในผู้ป่วยวัณโรคปอดเสมหะบวกรายใหม่

สมคิด อุ่นเสมาธรรม, ไพรัช เกตุรัตนกุล

ภูมิหลัง: *จากการศึกษาที่ผ่านมาพบว่า ผู้ป่วยวัณโรคปอดเสมหะบวกรายใหม่มีผลตรวจเสมหะหลังสิ้นสุดการรักษาระยะเข้มข้นที่ระยะ 2 เดือน ยังเป็นบวกมากกว่าร้อยละ 20 การที่เสมหะยังเป็นบวกหลังสิ้นสุดการรักษาระยะเข้มข้นเป็นปัจจัยที่ทำนายผลการรักษาล้มเหลว*

วัตถุประสงค์: *ศึกษาปัจจัยที่มีผลต่อการมีผลเสมหะบวกหลังสิ้นสุดการรักษาระยะเข้มข้น และผลการรักษาในผู้ป่วยวัณโรคปอดที่มีผลการตรวจเสมหะเป็นบวกรายใหม่*

วัสดุและวิธีการ: *การศึกษาเชิงวิเคราะห์แบบย้อนหลัง 3 ปี ในโรงพยาบาลของรัฐบาลขนาด 1,200 เตียง ในประเทศไทย โดยคัดเลือกผู้ป่วยวัณโรคปอดรายใหม่ที่มีผลเสมหะเป็นบวก และได้ส่งเสมหะเพาะเชื้อวัณโรคทดสอบความไวของเชื้อวัณโรคต่อยาต้านวัณโรคก่อนการรักษา เพื่อหาปัจจัยที่สัมพันธ์กับผลเสมหะของผู้ป่วยวัณโรคปอดที่ยังเป็นบวกหลังจากการรักษาเป็นเวลา 2 เดือน และผลการรักษาวัณโรคในผู้ป่วยวัณโรคปอดรายใหม่ที่มีผลเสมหะเป็นบวก*

ผลการศึกษา: *ผู้ป่วยวัณโรคปอดจำนวน 356 ราย พบว่าเชื้อวัณโรคดื้อยาก่อนการรักษาต่อยา isoniazid 13.8% และดื้อต่อยาหลายขนาน 3.1% ปัจจัยที่สัมพันธ์กับการที่เสมหะไม่เปลี่ยนผลจากบวกเป็นลบภายหลังการรักษา 2 เดือน ได้แก่ เพศชาย พบเชื้อในเสมหะมากและมีรอยโรคปอดลักษณะเป็นโพรง ส่วนผู้ป่วยที่มีการติดเชื้อเอดส์ หรือ ผู้ป่วยที่ผลเสมหะย้อมยังเป็นบวกภายหลังการรักษา 2 เดือน จะมีความเสี่ยงต่อการรักษาล้มเหลว*

สรุป: *การพบเชื้อในเสมหะมากและมีรอยโรคปอดลักษณะเป็นโพรงในผู้ป่วยวัณโรคปอด เป็นปัจจัยที่สัมพันธ์กับการที่เสมหะไม่เปลี่ยนจากบวกเป็นลบภายหลังการรักษา 2 เดือน และมีความเสี่ยงต่อการรักษาล้มเหลว*
