DRUG SUSCEPTIBILITY PATTERNS OF *MYCOBACTERIUM TUBERCULOSIS* AND CLINICAL OUTCOMES OF DRUG-RESISTANT TUBERCULOSIS AT SRINAGARIND HOSPITAL, A TERTIARY CARE CENTER IN NORTHEASTERN THAILAND

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Abstract. Drug-resistant tuberculosis is a major public health problem. The aim of this study was to assess the local susceptibility patterns of *Mycobacterium tuberculosis* and clinical outcomes of drug resistant tuberculosis (DR-TB) at Srinagarind Hospital, a tertiary care center in northeastern Thailand. Between January 2004 and December 2008, 1,052 patients had culture-proven *M. tuberculosis* infections at Srinagarind Hospital. *M. tuberculosis* was resistant to isoniazid (2.3%), rifampicin (2.8%), ethambutol (3.8%), streptomycin (2.1%), kanamycin (0.7%) and ofloxacin (1.9%). The occurrences of multi-drug resistant tuberculosis (MDR-TB) and extensively drug resistant tuberculosis (XDR-TB) were 1.2% and 0.38%, respectively. Of the 65 DR-TB patients, complete medical records were found for 55. The male to female ratio was 2.2:1. The mean age was 50 years. Thirteen patients had MDR-TB. The duration of symptoms in the MDR-TB group was longer than the non-MDR-TB group, 11.6 months *vs* 2.6 months, respectively. Half of MDR-TB and one-third of non-MDR-TB patients had a previous history of being treated for tuberculosis. Nearly 20% of cases were HIV positive. Mono-drug resistance was initially treated with standard first-line drugs (CAT 1). The clinical course was more likely to be worse during the maintenance phase if there was resistance to rifampicin. Whenever there was resistance to two, three or four drugs, the antituberculosis drugs were prescribed based on susceptibility patterns. Only 30% of patients with MDR-TB and XDR-TB responded to treatment. Culture and sensitivity testing for *M. tuberculosis* cases is recommended in patients at high risk for DR-TB, such as patients previously treated for tuberculosis and those HIV positive.

Keywords: *Mycobacterium tuberculosis*, drug susceptibility, clinical outcomes, Thailand

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INTRODUCTION

An estimated one-third of the world's population is infected with *M.tuberculosis*, and about 9.4 million persons developed the disease each year (WHO, 2010). In

2008, there were 1.82 million deaths from tuberculosis world-wide (WHO, 2009). The emergence of drug-resistant strains and co-infection with the HIV virus have turned tuberculosis into a global public health crisis (Donald and van Helden, 2009). Short-course chemotherapy regimens usually are not effective in patients with drug resistant strains. Drug-resistant tuberculosis (DR-TB), and multidrug-resistant tuberculosis (MDR-TB), pose an important challenge for tuberculosis treatment and control programs (Nuermberger *et al*, 2010).

In 1996, Thailand officially adopted the internationally recommended tuberculosis (TB) control strategy known as DOTS (directly observed treatment, short course), and declared in 2001 that DOTS had been implemented in all districts (Jittimanee *et al*, 2009). In 2009 World Health Organization (WHO, 2009) reported the global status of TB; Thailand had a TB incidence of 92,087 cases and a prevalence of 110,129 cases; sputum smears were positive in 44,475 cases and death due to TB occurred in 12,890 cases; 17% of TB patients had positive HIV serology. In the same report, MDR-TB was seen in 2,774 cases: problems in Thailand. In 2008, the case detection rate for TB in Thailand was 71% and the treatment success rate was 82.4% (Ministry of Public Health, 2009). The WHO targets are to detect 84% of infectious tuberculosis cases globally with a treatment success rate among smear-positive cases of 87% by the year 2015 (WHO, 2010).

A national TB drug-resistance survey conducted in Thailand between 2001 and 2005, found the MDR-TB rate in 2002 was 1% among 1,505 new TB patients and 20% among 172 previously treated patients. In new patients, resistance to at least isoniazid (INH) was found in 9.5% and to rifampicin (RIF) in 1.4%. A second drug-resistance survey carried out in 2006, the rate of MDR-TB had increased to 1.7% among 1,150 new TB patients and 34.5% among 194 previously treated patients. In the new patients, resistance to at least INH was found in 9.7%, and resistance to RIF had increased to 2.6% (Jittimanee *et al*, 2009; WHO/SEARO, 2009).

We previously analyzed data regarding *M. tuberculosis* infections between 1995 and 2000 at Srinagarind Hospital, a tertiary level hospital situated in northeastern Thailand and found MDR-TB in 2.4% of tuberculosis patients, the most frequent resistance being to RIF (8.2%) (Reechaipichitkul, 2002). The resistance rates to the other drugs were 4.2% for INH, 4.3% for ethambutol (EMB), 3.7% for streptomycin (SM), 3.0% for kanamycine and 2.3% for ofloxacin. In order to improve the TB management strategy at our hospital, we undertook the current study to analyze the drug susceptibility patterns of *M. tuberculosis* from 2004 to 2008. The results were compared with our previous study to determine the trend of drug-resistant TB at our hospital. In DR-TB cases the outcomes of treatment were analyzed according to the treatment regimens. These data should help develop treatment strategies fro DR-TB and MDR-TB.

MATERIALS AND METHODS

This cross-sectional study was conducted between January 2004 and December 2008, at Srinagarind Hospital in northeastern Thailand.

Specimens were added to an equal volume of N-acetyl-L-cysteine (NALC) and 4% sodium hydroxide (final concentration, 2%) for 15 minutes at room temperature to decontaminate them. After decontamination, the specimens

were neutralized with phosphate buffer solution at a pH of 6.8 and centrifuged at 3,000 cycles/minute for 20 minutes. The pellet was re-suspended in water to obtain a final volume of 1.5 ml, and 0.5 ml was placed in liquid culture MGIT™. The media was incubated until growth was seen or up to 42 days of no growth.

M. tuberculosis was identified by staining, growth rate and biochemical tests (nitrate, niacin, PNB, catalase and urease). Susceptibility testing was carried out using the absolute concentration method for isoniazid, rifampicin, streptomycin, ethambutol, kanamycin and ofloxacin at 1, 40, 16, 20, 40 and 4 g/ml, respectively.

The drug susceptibility patterns of *M. tuberculosis* during the 5 years were analyzed. All patients included in the study were over 15 years old. MDR-TB was defined as *M. tuberculosis* resistant to at least isoniazid and rifampicin. Extensively drug-resistant tuberculosis (XDR-TB) was defined as MDR-TB also resistant to most effective second-line therapeutic drugs commonly used to treat MDR-TB: the fluoroquinolones and at least one of three injectable second-line drugs (amikacin, kanamycin, or capreomycin).

Patients infected with *M.tuberculosis* resistant to at least one drug were analyzed. We categorized patients into two groups: DR-TB and MDR-TB.

Demographic data were recorded, including age, sex, duration of symptoms, previous history of TB treatment, underlying disease, and site of infection. Treatment outcomes were analyzed by the number of drugs the TB was found to be resistant to: one, two, three, four and MDR-TB. The outcome was defined as improvement if the patient was cured or completed treatment and their clinical status improved. The case was defined as failure or death if the patient did not improve or died, respectively. The outcome was considered inconclusive if the patient defaulted or transferred out.

Category 1 (CAT 1) was a six-month regimen of anti-TB drugs, the standard short-course chemotherapy for TB using a 4-drug regimen for 2 months using INH, RIF, pyrazinamide (PZA) and ethambutol (EMB) followed by a 2-drug regimen for 4 months using INH and RIF. Other regimens included second-line anti-TB drugs.

The study was approved by the ethics committee of the Faculty of Medicine, Khon Kaen University, Khon Kaen, Thailand.

Statistical analysis

Descriptive statistics were used to describe the data. Means and SD were used for continuous data and numbers and percentages for categorical data.

RESULTS

One thousand fifty-two adult patients with culture-proven *M.tuberculosis* were included in the study. The susceptibility patterns were shown in Table 1. The *M. tuberculosis* isolates were resistant to isoniazid (2.3%), rifampicin (2.8%), ethambutol (3.8%), streptomycin (2.1%), kanamycin (0.7%) and ofloxacin (1.9%). The incidences of MDR-TB and XDR-TB were 1.2% and 0.38%, respectively.

There were 65 patients infected with DR-TB. Thirteen patients were infected with MDR-TB in whom we were able to review all their charts. Fifty-two patients were infected with TB resistant to at least one drug; but did not meet criteria for MDR-TB. In this group, we were able to review the charts of 42 patients (80.8%). Overall, 55 patients (13 with MDR-TB and 42 with DR-TB) were analyzed (Table 2).

Table 1
M. tuberculosis drug susceptibility patterns between 2004 and 2008.

Resistant to	2004 $N = 216$	2005 $N = 215$	2006 $N = 217$	2007 $N = 204$	2008 $N = 200$	Total $N = 1,052$
Isoniazid (*n*,%)	2 (0.9)	13 (6.0)	5 (2.3)	2 (1.0)	2 (1.0)	24 (2.3)
Rifampicin (*n*,%)	4 (1.8)	8 (3.7)	6 (2.8)	4 (2.0)	8 (4.0)	30 (2.8)
Ethambutol (*n*,%)	6 (2.8)	20 (9.3)	3 (1.4)	9 (4.4)	2 (1.0)	40 (3.8)
Streptomycin (*n*,%)	7 (3.2)	10 (4.6)	2 (0.9)	1 (0.5)	2 (1.0)	22 (2.1)
Kanamycin (*n*,%)	1 (0.5)	2 (0.9)	0 (0)	0 (0)	4 (2.0)	7 (0.7)
Ofloxacin (*n*,%)	2 (0.9)	13 (6.0)	0 (0)	3 (1.5)	2 (1.0)	20 (1.9)
MDR-TB (*n*,%)	1 (0.5)	4 (1.9)	5 (2.3)	2 (1.0)	1 (0.5)	13 (1.2)[a]

n, number of patients resistant to each drug; *N*, number of patients with culture-proven *M. tuberculosis*
MDR-TB, multi-drug resistant tuberculosis
[a](the 13 MDR-TB cases included 2 cases with XDR-TB)

Table 2
Demographic data regarding 55 patients with drug-resistant tuberculosis.

Patient characteristics	Non-MDR-TB $N = 42$	MDR-TB $N = 13$	Total $N = 55$
Age in years, mean (SD)	51.4 (16.2)	45.8 (13.4)	50.0 (16.3)
Sex, males : females	2.5:1	1.6:1	2.2:1
Duration of symptoms in months, mean (SD)	2.6 (3.6)	11.6 (20.2)	4.9 (12.5)
Previously treated tuberculosis, *n* (%)	13 (30.9)	7 (53.8)	20 (36.4)
Underlying diseases, *n* (%)			
Diabetes mellitus	6 (14.3)	2 (15.4)	8 (14.3)
HIV	8 (19.0)	2 (15.4)	10 (17.8)
Site of infection, *n* (%)			
Lungs	34 (81)	11 (84.6)	45 (81.8)
Lymph nodes	7 (16.7)	0 (0)	7 (12.7)
Skin and soft tissue	4 (9.5)	1 (7.7)	5 (9.1)
Gastrointestinal tract	0 (0)	1 (7.7)	1 (1.8)
Disseminated	3 (7.1)	0 (0)	3 (5.4)

The mean age was 50 years, the male to female ratio was 2.2:1. Patients infected with MDR-TB had a longer duration of symptoms than non-MDR-TB, (11.6 *vs* 2.6 months). Half of MDR-TB patients and one-third of non-MDR-TB patients had a previous history of tuberculosis treatment. Fourteen percent of patients had underlying diabetes, 17% were HIV positive. The lungs were the most common site of drug-resistant tuberculosis, occurring in 80% of affected patients. Other sites included the lymph nodes (12.7%), skin and soft tissue (9.1%), gastrointestinal tract

Table 3
Types of drug resistant tuberculosis and outcomes of treatment.

Type of drug resistance	Number	Outcome		
		Improved	Not improved	Inconclusive
One drug resistance	18	9 (50%)	5 (27.8%)	4 (22.2%)
Isoniazid (I)	2	0 (0%)	1 (50%)	1 (50%)
Rifampicin (R)	6	2 (33.3%)	1 (16.7%)	3 (50%)
Ethambutol (E)	7	4 (57.1%)	3 (42.3%)	0 (0%)
Ofloxacin (O)	3	3 (100%)	0 (0%)	0 (0%)
Two drug resistance	15	11 (73.3%)	1 (6.7%)	3 (20%)
Isoniazid + Streptomycin	3	3 (100%)	0 (0%)	0 (0%)
Rifampicin + Ethambutol	1	1 (100%)	0 (0%)	0 (0%)
Rifampicin + Streptomycin	1	1 (100%)	0 (0%)	0 (0%)
Rifampicin + Kanamycin	3	2 (66.7%)	0 (0%)	1 (33.3%)
Ethambutol + Kanamycin	1	0 (0%)	0 (0%)	1 (100%)
Ethambutol + Ofloxacin	6	4 (66.7%)	1 (33.3%)	1 (33.3%)
Three drug resistance	7	4 (57.1%)	2 (28.6%)	1 (14.3%)
R+E+O	1	1 (100%)	0 (0%)	0 (0%)
R+O+S	1	1 (100%)	0 (0%)	0 (0%)
E+O+S	5	2 (40%)	2 (40%)	1 (20%)
Four drug resistance	2	2 (100%)	0 (0%)	0 (0%)
R+E+O+S	1	1 (100%)	0 (0%)	0 (0%)
I+E+O+S	1	1 (100%)	0 (0%)	0 (0%)
Multi-drug resistance	13	4 (30.8%)	6 (46.2%)	2 (23.1%)

Table 4
Outcomes of treatment by regimen.

Type of drug resistance	Regimen of treatment	Outcome of treatment (*n*,%)		
		Improved	Not improved	Inconclusive
One drug resistance	Category 1 (*n* =13)	9 (69.2)	3 (23.1)	1 (7.7)
(*N* = 18)	Other regimens (*n* =1)	0 (0)	0 (0)	1 (100)
	Refered (*n* =4)	0 (0)	2 (50)	2 (50)
Two drug resistance	Category 1 (*n* =7)	6 (85.7)	0 (0)	1 (14.3)
(*N* = 15)	Other regimens (*n* =6)	5 (83.3)	1 (16.7)	0 (0)
	Refered (*n* =2)	0 (0)	0 (0)	2 (100)
Three drug resistance	Category 1 (*n* =1)	1 (100)	0 (0)	0 (0)
(*N* = 7)	Other regimens (*n* =5)	3 (60)	2 (40)	0 (0)
	Refered (*n* =1)	0 (0)	0 (0)	1 (100)
Four drug resistance	Category 1 (*n* =0)	0 (0)	0 (0)	0 (0)
(*N* = 2)	Other regimens (*n* =2)	2 (100)	0 (0)	0 (0)
	Refered (*n* =0)	0 (0)	0 (0)	0 (0)
Multi-drug resistance	Category 1 (*n* =0)	0 (0)	0 (0)	0 (0)
(MDR-TB)	Other regimens (*n* =9)	4 (44.4)	5 (55.5)	0 (0)
(*N* = 13)	Refered (*n* =4)	0 (0)	1 (25)	3 (75)

(1.8%) and disseminated infection (5.4%).

Tables 3 and 4 presented the outcomes of treatment characterized by type of drug resistance and treatment regimen. For the 55 patients with DR-TB or MDR-TB, 18 had resistance to one drug, 15 had resistance to two drugs, 7 had resistance to three drugs, 2 had resistance to four drugs, and 13 had MDR-TB. Nine of the 18 patients (50%) with resistance to one drug had clinical improvement, 5 patients (27.8%) had no improvement, and 4 patients (22.2%) had an inconclusive response. Most of those with resistance to one drug were resistant to ethambutol (7) or rifampicin (6). Thirteen patients were treated with the Category 1 regimen and 9 patients had clinical improvement; 1 patient was treated with another regimen and 4 patients were referred.

Fifteen patients had two drug resistance, 6 to ethambutol and ofloxacin, 3 to isoniazid and streptomycin, and 3 to rifampicin and kanamycin. Only 1 patient each had two drug resistant TB to: (a) rifampicin and ethambutol, (b) rifampicin and streptomycin, and (c) ethambutol and kanamycin. Eleven of the 15 patients (73.3%) with two drug resistant TB had clinical improvement, 1 (6.7%) did not improve, and 3 were inconclusive. Six of 7 patients were treated with the Category 1 regimen and 5 of the 6 patients treated with other regimens had clinical improvement. Two patients were referred and their outcomes were inconclusive.

Seven patients had three drug resistant TB. Five patients were resistant to ethambutol + ofloxacin + streptomycin; one patient each was resistant to rifampicin + ethambutol + ofloxacin and rifampicin + ofloxacin + streptomycin. One patient was treated with the Category 1 regimen and had clinical improvement. Five patients were treated with other regimens, of these 3 improved and 2 did not. One patient was referred and the outcome was inconclusive.

Two patients had four drug resistant TB: one patient was resistant to rifampicin + ethambutol + ofloxacin + streptomycin, and the other was resistant to isoniazid + ethambutol + ofloxacin + streptomycin. These 2 patients were treated with other regimens and both of them showed clinical improvement.

Thirteen patients were infected with MDR-TB, none were treated with the Category 1 regimen; 9 were treated with other regimens, 4 of whom had clinical improvement, while the other 5 did not. Four patients were referred, one become worse clinically before being referred and the outcomes of the other 3 were inconclusive.

DISCUSSION

The MDR-TB rate at our hospital was 1.2% in this study, lower than a previous report of the 2.4% (Reechaipichitkul, 2002). The trend by year decreased between 2004 and 2008. During that period, resistance to rifampicin decreased from 8.2% to 2.8% and the average rates of drug resistance to isoniazid, ethambutol, streptomycin, kanamycin and ofloxacin also decreased compared to a previous report (Reechaipichitkul, 2002). This decrease is similar to reports from Hong Kong and the USA (Wright *et al*, 2009). In contrast, some countries, such as South Korea and Russia, had a substantial increase in prevalence (Wright *et al*, 2009). Our findings may be due to adherence to appropriate strategies for the treatment of tuberculosis in Thailand. If DR-TB were not a problem, Thailand would be able to achieve the WHO treatment success rate

target among smear-positive tuberculosis patients by the year 2015 (WHO, 2010).

When we explored the patterns of drug resistance of *M. tuberculosis*, the drug to which TB was most commonly resistant was ethambutol (3.8%). Among injectable aminoglycosides, *M.tuberculosis* was more resistant to streptomycin (2.1%) than kanamycin (0.7%). Kanamycin should therefore be used in patients who fail to respond to standard short-course regimens before the results of the culture are known (Ministry of Public Health, 2008). If the culture shows susceptibility to streptomycin, the drug can be changed to streptomycin. Fluoroquinolones were the most effective second-line anti-TB drugs; the resistance rate to ofloxacin was low (1.9%) in our study. Fluoroquinolones are commonly combined with other second-line anti-TB drugs to treat multidrug-resistant tuberculosis (Prammananan *et al*, 2005; Ministry of Public Health, 2008; WHO, 2008; Chiang and Schaaf, 2010).

The common characteristics of patients infected with DR-TB were long duration of symptoms and previous treatment of TB. Other studies reported the strongest clinical predictors for DR-TB were a previous history of TB (failed or relapsed after the standard regimen) and contact with a patient or family member having MDR-TB (Martinez *et al*, 2010). Patients infected with MDR-TB had an average duration of symptoms of about one year; half had a history of previously treated TB. Patients infected with DR-TB, that were not MDR-TB, had a duration of symptoms of about 3 months; one-third of whom had previously treated TB. Nearly 20% of cases in our study were HIV positive; this is important because HIV infection is associated with drug resistance in some studies, mainly in industrialized countries (Faustini *et al*, 2006). The possibility of DR-TB should be considered in patients with a history of previously treatment of TB or in HIV positive patients. In these two settings specimens for culture and susceptibility should be obtained before starting treatment. An increased risk for drug-resistant tuberculosis among HIV patients has not been confirmed by other studies, especially from Africa, where the prevalence of HIV is high (Suchindran *et al*, 2009).

The lungs were the most common site of TB infection in our study, occurring in 80% of DR-TB patients. Effective regimens and cough etiquette may decrease the spread of TB. The most common feature of DR-TB in our study was resistance to only one anti-TB drug. Consequently, physicians can successfully treat patients using standard first-line anti-TB drugs. If there was resistance to rifampicin, the treatment success rate was lower than with resistance to other drugs. The second most common type of resistance was to two anti-TB drugs. Most isolates were resistant to ethambutol and ofloxacin. More than half of patients were successfully treated with standard first-line anti-TB drugs, while the other half were treated successfully with second-line anti-TB drugs. Ethambutol, ofloxacin and streptomycin were the most common drugs with resistance with three drug resistant cases. Some of the affected patients were successfully treated with standard first-line drugs; however, more than half were treated with second-line anti-TB drugs. All patients with four drug resistant TB responded to second-line anti-TB drugs. MDR-TB was found in 13 patients (1.2%), a rate which has not risen since last reported. However, the treatment success rate in this group was poor, even when second-line anti-TB drugs were used; less than half showed clinical improvement.

The diagnosis of DR-TB relies on drug susceptibility testing, which is not routinely performed in high TB burden settings. Proper management of these patients reduces the risk of escalating drug resistance to be MDR-TB or XDR-TB (Chiang and Schaaf, 2010). Standard short-course chemotherapy, based on first-line anti-TB drugs, is inadequate treatment for some patients with DR-TB (Espinal *et al*, 2000).

Based on our study, sputum culture and susceptibility testing should be carried out in patients with HIV infection or those who have previously been treated for TB. For patients who fail to respond to Category 1 treatment, drug susceptibility testing should be carried out before changing the regimen (Chiang and Schaaf, 2010). Adjusting the anti-TB drugs based on culture results should increase success rates and decrease spread of resistant infections.

Mono-drug resistance can be treated initially with standard first-line drugs, although the clinical course may be worse during the maintenance phase, especially if there is resistance to rifampicin. For two, three, or four drug resistance, the recommended regimen is second-line anti-TB drugs, based on the susceptibility pattern. Unfortunately, in MDR-TB, the treatment outcome is poor even when second-line anti-TB drugs are used (Orenstein *et al*, 2009). Every patient infected with DR-TB needs strong patient support, treatment compliance, and follow-up (Ahmad and Mokaddas, 2009). HIV co-infection with MDR-TB results in a higher mortality rate (Anunnatsiri *et al*, 2005; Gandhi *et al*, 2010). The efforts to reduce mortality must focus on early diagnosis and early initiation of second-line anti-TB drugs and early intervention with antiretroviral drug therapy.

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