MULTIDRUG-RESISTANT TUBERCULOSIS AT SRINAGARIND HOSPITAL, KHON KAEN, THAILAND

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Abstract. Pulmonary tuberculosis is a very common infectious disease in Thailand. Multidrug-resistant tuberculosis (MDR-TB) is the most serious form of the disease. Failure to control resistant tuberculosis is associated with its resurgence. The objective of this study was to analyze the drug susceptibility pattern of *M. tuberculosis* and to study the clinical characteristics and outcome of patients diagnosed with MDR-TB at Srinagarind Hospital. Between January 1995 and December 2000, 899 isolates of *M. tuberculosis* were recovered. Rifampicin (RIF) resistance was the most common finding (8.2%). Twenty-two patients (2.4%) were infected with MDR-TB. Other susceptibility results showed resistance to isoniazid (INH) (4.2%), ethambutol (EMB) (4.3%), streptomycin (SM) (3.7%), kanamycin (Kana) (3.0%), and ofloxacin (Oflox) (2.3%).

Twenty MDR-TB patients were retrospectively reviewed. The mean age was 37 years (range: 17 to 64). The male to female ratio was 3:1. The mean duration of symptoms before treatment was 3.8 months (range: 3 days to 2 years). The commonest comorbidity was HIV-infection (7 patients). Eleven patients (55%) had a past history of treatment with anti-TB drugs. In addition to INH and RIF resistance, many organism also resisted EMB (35%), SM (30%), Oflox (30%), and Kana (10%). Only five patients (25%) responded to medical treatment. Seven patients (35%) died, and the other eight were unavailable for an evaluation of clinical outcome.

Although the prevalence of MDR-TB was not high in Srinagarind Hospital, the treatment was costly and the outcomes were poor. Preventing new cases of MDR-TB by using effective treatment strategies for patients with drug-sensitive TB is a priority.

INTRODUCTION

The World Health Organization (WHO) declared tuberculosis (TB) a global emergency in 1993 (World Health Organization, 1994). The global TB problem has been further complicated by a substantial increase in multidrug-resistant tuberculosis (MDR-TB), which is defined as TB that is resistant to at least isoniazid and rifampicin (Pablos-Mendez *et al*, 1998). Approximately 1.7 billion people (*ie* one-third of the world's population) are infected with *Mycobacterium tuberculosis* and, despite the availability of effective chemotherapy in the latter half of the 20th century, 10.2 million new TB cases and 3.5 million TB deaths occur annually (Raviglione *et al*, 1995).

In Thailand, TB cases and deaths were in decline until 1992, when cases began to rise because of the spread of HIV. The annual risk of infection in 1997 was estimated at 1.4%, with approximately 100,000 new TB cases developing each year (Ministry of Public Health, 1998); at that time, between 2,000 and 3,000 TB-related deaths were recorded annually.

In order to cope with the resurgence of TB, something other than short-course chemotherapy is needed. Patients' adherence to drug regimens must be promoted and monitored by directly-observed treatment (DOT). Medical errors in the prescribing of chemotherapy and unreliable drug supplies must be corrected; in

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addition, consideration of regional variations in resistance is essential to the guidance of local treatment and prevention programs. The high rate of drug-resistant TB implies to poor national tuberculosis control programing (Heymann *et al*, 1999).

The objective of this study was to analyze the drug susceptibility of *M. tuberculosis* isolates made at Srinagarind Hospital between 1995 and 2000. The demographic data, laboratory results, and clinical outcomes of the treatment of MDR-TB patients, were evaluated.

MATERIAL AND METHODS

This study was a cross-sectional retrospective study that was conducted between January 1995 and December 2000 at Srinagarind Hospital. The culture and sensitivity patterns of *M. tuberculosis* isolates were reviewed.

Potentially contaminated specimens, such as sputum, were decontaminated using NALC-NaOH. A conventional method of mycobacterial culture in Lowenstein-Jensen medium was used. *M. tuberculosis* was identified by growth rate, pigmentation, and biochemical tests (niacin, nitrate reduction, catalase, tween hydrolysis, and urease tests). The susceptibility of the *M. tuberculosis* isolates was determined by the absolute concentration method. A level four times that of the minimum inhibitory concentration (MIC) of isoniazid (INH), rifampicin (RIF), streptomycin (SM), ethambutol (EMB), kanamycin (Kana) and ofloxacin (Oflox) (*ie* 1 μg/ml, 40 μg/ml, 16 μg/ml, 20 μg/ml, 40 μg/ml, 4 μg/ml respectively) was used as the cut-off point.

We defined MDR-TB as *M. tuberculosis* that was resistant to at least isoniazid and rifampicin. The patients' charts were reviewed for the following information: demographic data, duration of symptoms before treatment, HIV status, underlying diseases, organs of involvement, past history of tuberculosis contacts, past history of tuberculous infection, compliance with treatment, results of acid-fast smear and culture of sputum etc, duration of therapy, and the final clinical outcome.

The study was approved by the Ethics Committee of the Faculty of Medicine, Khon Kaen University.

Statistical analysis

Descriptive statistics were used to describe the data. Means and ranges were calculated for the continuous data; number and percentage were calculated for the categorical data.

RESULTS

Between January 1995 and December 2000, *M. tuberculosis* was recovered from 899 isolates. The sensitivity of each drug and the rates of MDR-TB are shown in Table 1. Drug-resistant tuberculosis was at its highest in 1995: in this year, isolates were found to resist INH (11.6%), RIF (21.8%), EMB (6.8%), SM (6.8%), Kana (2.7%), Oflox (4.8%); MDR-TB accounted for 6.8% of the isolates. During the 6-year study, the drug most often resisted was rifampicin (8.2%). The average resistance to the other drugs was INH 4.2%, EMB 4.3%, SM 3.7%, Kana 3.0%, Oflox 2.3%, and MDR-TB 2.4%.

Twenty-two patients had MDR-TB, although only 20 charts could be reviewed (Table 2). The mean age was 37 years (range:17 to 64 years); there were 15 men and 5 women. The mean duration of symptoms was 3.8 months (range: 3 days to 2 years). Ten patients were tested for anti-HIV: seven were positive. Comorbidity other than HIV infection was found in 3 patients (1 case of diabetes mellitus; 1 case of autoimmune hemolytic anemia while on high dose prednisolone; 1 case of chronic obstructive pulmonary disease).

Pulmonary involvement was a common finding, affecting in 15 patients. Other infected organs included the lymph nodes (in 3 patients), joints or spine (in 3), gastrointestinal tract (in

Table 1
M. tuberculosis isolated of Srinagarind Hospital (1995-2000): drug sensitivity.

Resistant to	1995 (N=147)	1996 (N=161)	1997 (N=182)	1998 (N=165)	1999 (N=127)	2000 (N=117)	Total (N=899)
INH (%)	11.6	1.9	3.8	1.2	3.9	3.4	4.2
RIF (%)	21.8	8.7	3.8	6.7	6.3	1.7	8.2
EMB (%)	6.8	9.3	1.6	1.8	5.5	0.9	4.3
SM (%)	6.8	4.3	3.8	4.2	0.8	0.9	3.7
Kana (%)	2.7	8.7	1.6	2.4	0	1.7	3.0
Oflox (%)	4.8	3.7	2.7	1.2	0	0.9	2.3
MDR-TB (%)	6.8	1.2	2.7	1.2	1.6	0.9	2.4

Table 2
The demographic data of the 20 MDR-TB patients.

Mean age in years (range)	37 (17-64)
Male: Female	15:5
Mean duration of symptoms (months)	3.8
Co-morbidity (No.)	
Anti-HIV positive	7
Diabetes mellitus	1
High-dose steroids	1
COPD	1
Organ involvement (%)	
Pulmonary	75
Lymph nodes	15
Joints or spine	15
GI tract	10
Meninges	5
Pericardium	5
Bone marrow	5
Skin	5
Tuberculosis contact history (%)	15
Previous tuberculosis treatment (%)	55
Drug allergy (%)	5
Poor compliance (%)	20

Table 3
Laboratory results of the 20 MDR-TB patients.

Laboratory results	No.	%
Initial positive acid-fast stain	8	40
Any drug resistance:		
INH	20	100
RIF	20	100
EMB	7	35
SM	6	30
Kana	2	10
Oflox	6	30
Combined drug resistance		
INH + RIF	7	35
INH+RIF+EMB	3	15
INH+RIF+SM	2	10
INH+RIF+Kana	1	5
INH+RIF+Oflox	2	10
INH+RIF+EMB+Oflox	1	5
INH+RIF+SM+Oflox	1	5
INH+RIF+EMB+SM+Kana	1	5
INH+RIF+EMB+SM+Oflox	2	10

2), meninges (in 1), pericardium (in 1), bone marrow (in 1), and skin (in 1). Three patients had a family history of tuberculosis. Eleven patients (55%) had a past history of TB and treatment with antituberculous drugs. One patient had a drug allergy; four patients were poor compliance with therapy.

Initial acid-fast staining of specimens was positive in 8 patients (40%). The drug sensitivity patterns of 20 MDR-TB patients revealed resistance to INH (100%), RIF (100%), EMB (35%), SM (30%) Oflox (30%), SM (30%), and Kana (10%) (Table 3). All patients received treatment. Table 4 shows the medical treatment

Table 4
Treatment outcomes of the 20 MDR-TB patients.

Outcome	No.	%
Cured	5	25
Died	7	35
Others		
still on medication	1	5
lost to follow-up	4	20
referred elsewhere	3	15

outcomes of these patients. Treatment, lasting from 18 months to 2 years, resulted in the resolution of five cases (25%): five to six antituberculous drugs were used. Seven patients (35%) died as a result of serious infection. The other 8 patients either continued with medication or were lost to follow- up or were referred to other hospitals.

DISCUSSION

The WHO has reported a primary MDR-TB rate in Thailand of 3.8% (Pablos-Mendez *et al*, 1998); the Central Chest Hospital has reported a rate of 4.2% (Riantawan *et al*, 1998). In this study, the average rate of MDR-TB was 2.4% (range: 0.9 to 6.8%), which included both new and relapsed cases.

Srinagarind Hospital, in Northeast Thailand, is an 800-bed teaching hospital that provides both primary healthcare and referral services. Laboratory cultures for *M. tuberculosis* are not conducted in every case of diagnosed tuberculosis. The data on MDR-TB in this study suggest that there are some problems with MDR. Unlike drug resistance in other countries, in Thailand resistance to rifampicin is often more frequent than resistance to isoniazid (Pablos-Mendez *et al*, 1998; Riantawan *et al*, 1998). The data in the present study show 8.2% rifampicin-resistance and 4.2% isoniazid resistance: this finding may be the result of inadvertent monotherapy with rifampicin, due to the selective compliance of patients, or an inappropriate regimen.

HIV infection was the commonest comorbidity found among the 20 MDR-TB patients. A previous study in the Central Chest Hospital found that HIV prevalence is high (22%) among TB patients and is associated with MDR, including a 12-times higher risk of MDR-TB (Punnotok *et al*, 2000). Previous treatment, which is also a risk factor for MDR-TB (Kritski *et al*, 1997), had been given in 55% of cases. The time between the completion of treatment and relapse was in the range of 1 month to 14 years. Only 40% of cases had positive acid-fast staining at the first visit, at which time multiple (3 to 5) specimens should be collected for acid-fast staining, especially in suspicious cases. Culture and sensitivity testing should be conducted for patients who have been treated in the past or are HIV-positive (Heifets and Cangelosi, 1999).

HIV-infected patients have poorer outcomes than those free of HIV (Telzak *et al*, 1995; Flament-Saillour *et al*, 1999). Disseminated tuberculous infection was a common features of HIV co-infection. Of the seven HIV patients with MDR-TB, five died, one was lost to follow-up, and one was still on medication. The overall response rate of MDR-TB to medical treatment was 25% during a period of 18 months to 2 years. The treatment regimen may have included previously unused drugs, such as kanamycin or streptomycin, ofloxacin, para-aminosalicylic acid, pyrazinamide, or ethambutol. An initial 5- or 6-drug regimen, including aminogylcosides, should be used (Iseman, 1999). The error of adding a single drug to a failing regimen and non-compliance with therapy are concerns that warrant prompt remedial action.

Surveillance of antituberculosis drug resistance is an important method of evaluating the quality of tuberculosis control programes and the success of MDR-TB therapy. Previous treatment with antituberculous drugs is related to the development of MDR-TB. HIV co-infection has a poorer outcome. The education

of doctors and structured treatment programs are required to prevent increases in the prevalence of MDR-TB.

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REFERENCES

Flament-Saillour M, Robert J, Jarlier V, Grosset J. Outcome of multidrug-resistant tuberculosis in France: a nationwide case-control study. *Am J Respir Crit Care Med* 1999; 160: 587-93.

Heifets LB, Cangelosi GA. Drug susceptibility testing of *Mycobacterium tuberculosis*: a neglected problem at the turn of the century. *Int J Tuberc Lung Dis* 1999; 3: 564-81.

Heymann SJ, Brewer TF, Wilson ME, Fineberg HV. The need for global action against multidrug-resistant tuberculosis. *J Am Med Assoc* 1999; 281: 2138-40.

Iseman MD. Treatment and implication of multidrug-resistant tuberculosis for the 21st century. *Chemotherapy* 1999; 45 (suppl): 234-40.

Kritski AL, de Jesus LSR, Andrade MK, *et al*. Factors associated with drug resistance and adverse outcomes. *Chest* 1997; 111: 1162-7.

Ministry of Public Health, Thailand. The national tuberculosis control program. Bangkok: Ministry of Public Health, 1998.

Pablos-Mendez A, Raviglione MC, Laszlo A, *et al*. Global surveillance for antituberculosis-drug resistance, 1994-1997. *N Engl J Med* 1998; 338: 1641-9.

Punnotok J, Shaffer N, Naiwatanakul T, *et al*. Human immunodeficiency virus-related tuberculosis and primary drug resistance in Bangkok, Thailand. *Int J Tuberc Lung Dis* 2000, 4: 537-43.

Raviglione MC, Snider DE, Kochi A. Global epidemiology of tuberculosis: morbidity and mortality of a worldwide epidemic. *J Am Med Assoc* 1995; 273: 220-6.

Riantawan P, Punnotok J, Chaisuksuwan R, Pransujarit V. Resistance of *Mycobacterium tuberculosis* drugs in the central region of Thailand, 1996. *Int J Tuberc Lung Dis* 1998; 2: 616-20.

Telzak EE, Sepkowitz K, Alpert P, *et al*. Multidrug-resistant tuberculosis in patients without HIV infection. *N Engl J Med* 1995; 333: 907-11.

World Health Organization. Tuberculosis: a global emergency. Geneva: WHO, 1994.