STUDY OF DRUG RESISTANT CASES AMONG NEW PULMONARY TUBERCULOSIS PATIENTS ATTENDING A TUBERCULOSIS CENTER, YANGON, MYANMAR

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Abstract. A cross-sectional descriptive study was carried out at a tuberculosis center, Yangon, Myanmar from October 2003 to July 2004 to analyze the drug susceptibility of new sputum smear positive pulmonary tuberculosis patients. A total of 202 *Mycobacterium tuberculosis* isolates were tested for resistance to isoniazid, streptomycin, rifampicin and ethambutol. Resistance to at least one anti-tuberculosis drug was documented in 32 (15.8%) isolates. Mono-resistance (resistance to one drug) was noted in 15 (7.4%) isolates and poly-resistance (resistance to two or more drugs) was noted in 17 (9.4%) isolates, including 8 (4.0%) multi-drug resistant isolates (resistance to at least isoniazid and rifampicin). Total resistance to individual anti-tuberculosis drugs were: isoniazid (29, 14.3%), streptomycin (11, 5.4%), rifampicin (10, 4.9%) and ethambutol (1, 0.5%). The demographic data and possible contributing factors of drug resistance were evaluated among the drug resistant patients. Poly-resistant cases had significantly longer intervals between symptom appearance and achieving effective anti-tuberculosis treatment than mono-resistant cases (p = 0.015).

INTRODUCTION

The prevalence of tuberculosis (TB) is very high in many parts of the world and has reached epidemic proportions. Approximately one third of the global population is estimated to be infected with *Mycobacterium tuberculosis*, the causal bacterium of tuberculosis. The global TB problem has been further complicated by a substantial increase in multi-drug resistant tuberculosis (MDR-TB), which is defined as TB that is resistant to at least isoniazid and rifampicin (Drobineski and Wilson, 1998).

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In Myanmar, TB is described as a second priority disease in the National Health Plan. The estimated incidence of all TB cases and new smear positive TB cases for Myanmar are 154/100,000 population and 68/100,000, respectively. The TB mortality is 26/100,000 and MDR-TB among new cases is 1.5% (WHO, 2004).

Due to the chronicity of the disease and long-term treatment, tuberculosis problems can be compared to an iceberg, with only the part floating above the sea can be seen, it is difficult to know its real magnitude. Long-term treatment of this disease can result in multi-drug resistant cases, which further decrease the cure rate of tuberculosis.

Development of resistance to the two most potent drugs, isoniazid and rifampicin, is a serious threat not only to individual pa-

tients but also to the community, as one index case can infect 10-20 persons a year. Patients with untreatable anti-tuberculosis drug resistant disease become the vectors for additional generation of drug resistant tuberculosis, spreading resistant infection primarily to their contacts (WHO Regional Office for SEA, Speakers notes by Dr UM Rafei, 1999).

The objective of this study was to analyze the drug susceptibilities of *Mycobacterium tuberculosis* isolates from new smear positive pulmonary TB patients. The demographic data, laboratory results and possible contributing factors of drug resistance were evaluated.

MATERIALS AND METHODS

This study was a cross-sectional descriptive study which was conducted at TB Center, Yangon Division, Myanmar from October 2003 to July 2004.

Case definition

New. A patient who has never had treatment for TB or who has been taking anti-tuberculosis drugs for less than 1 month.

Pulmonary tuberculosis, sputum smear-positive (PTB+)

a. two or more initial sputum smear examinations positive for acid-fast bacilli (AFB), or

b. one sputum smear examination positive for AFB plus radiographic abnormalities consistent with acute PTB as determined by a clinician, or

c. one sputum smear positive for AFB plus sputum culture positive for *M. tuberculosis* (WHO, 2003).

New sputum smear positive pulmonary tuberculosis patients were selected according to the case definition.

Patients who gave informed consent were interviewed using pre-tested questionnaires designed to elicit the social demographic data and other contributory factors of drug resistance by a trained interviewer at the TB Center. The data include age, sex, occupation, education, income, history of TB contact, how did they reach the TB Center, history of taking treatment at a private clinic, history of self medication, length of time between the appearance of symptoms and receiving anti-TB treatment and history of investigations done in the private sector. All the data were coded, checked for consistency and analyzed using SPSS software at the Epidemiology Research Division, Department of Medical Research (Lower Myanmar).

After interviewing, the sputum specimens of those patients were collected and transported to the Bacteriology Research Division, Department of Medical Research (Lower Myanmar), for isolation of *Mycobacterium tuberculosis*.

The sputum specimens were decontaminated with 4% sodium hydroxide and inoculated onto egg based Lowenstein-Jensen (LJ) medium, then incubated at 37ºC for 6-8 weeks. *Mycobacterium tuberculosis* isolates were identified by growth rate and pigmentation. Drug susceptibility testing of culture isolates was carried out at the Reference TB Laboratory, National Tuberculosis Program by the proportion method as described by Center Venkatareman and Paramasiven (1999).

The tested anti-TB drugs and their minimum inhibitory concentrations are: isoniazid 0.2 mg/l, rifampicin 40 mg/l, dihydrostreptomycin 4 mg/l and ethambutol 2 mg/l. The results were interpreted at 42 days of incubation at 37ºC and the proportion of bacilli resistant to a given drug was determined by expressing the resistant portion as a percentage of the total proportion tested. A result of 1% or more the proportion above drug concentration was interpreted as resistant.

This study was approved by the Ethics Committee on Medical Research involving

human subjects, Department of Medical Research, with letter No.13/Ethics 2003.

Statistical analysis

Descriptive statistics was used to describe the data. Means and ranges were calculated for continuous data, numbers and percentages were calculated for the categorical data.

RESULTS

Drug susceptibility pattern

Susceptibility to first line anti-TB drugs, isoniazid (I), rifampicin (R), streptomycin (S) and Ethambutol (E) was tested on 202 *Mycobacterium tuberculosis* strains isolated from new PTB+ patients. One hundred and seventy isolates were sensitive to all tested anti-TB drugs. Resistance to at least one anti-TB drug was documented in 32 (15.8%) isolates. Mono-resistance (resistance to one drug) was noted in 15 (7.4%) isolates and polyresistance (resistance to 2 or more drugs) was noted in 17 (9.4%) isolates, including 8 (4.0%) MDR-TB isolates.

Of the monoresistant strains, 13 (6.4%) isolates were resistant to I, 1 (0.5%) isolate each was resistant to R and E. Of polyresistant strains, IR resistance was found in 6 (3.0%) isolates, SR resistance in 1 (0.5%) isolate, SI resistance in 8 (4.0%) isolates and SIR resistance was noted in 2 (1.0%) isolates (Fig 1). The total resistance of individual anti-TB drugs was I (29, 14.3%), S (11, 5.4%), R (10, 4.9%) and E (1, 0.5%).

Demographic data and relevant history of the drug resistant patients

The demographic data and relevant histories of the 32 drug resistant patients are shown in Table 1. The mean age was 33.6 years (range 13-70 years). There were 21 men and 11 women, 18 (56.2%) were skilled workers and 15 (46.9%) patients had a middle school education level. The mean family number of resistant patients was 5 (range 2-10).
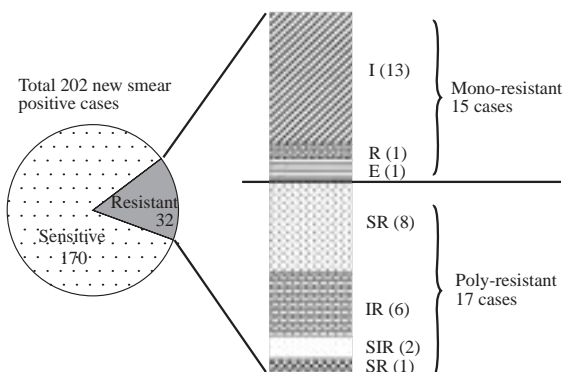
I=Isoniazid; R=Rifampicin; E=Ethambutol; S=Streptomycin

Fig 1–Drug susceptibility pattern among new sputum smear positive pulmonary tuberculosis patients (n=202).

Thirteen patients (40.6%) had a history of tuberculosis in close contacts. Twenty-five of 32 drug resistant patients (78.1%) had a history of seeking treatment at private clinics for their first symptoms. The mean duration which they spent at the private clinics was 33.1 days (range 1 to 90 days) before attending the TB Center and 6 (18.8%) of these patients had been treated with anti-TB drugs for less than a month at the private clinics. The commonest investigation done at the private clinics was a chest X ray (17/25, 68%). Blood tests were carried out in 5/25 cases, (20%) and sputum microscopy was done only in 3/25 cases (12%). The medium interval between the appearance of symptoms of the disease and receiving anti-TB treatment at the TB Center was 54.5 days (range 7-180 days).

Distribution of drug resistant cases among different age groups

Resistance is shown in Table 2. Twenty-eight (87.5%) of 32 drug resistant cases were age 20-59 years.

Drug resistance and the outcome of TB contacts

Thirteen (40.6%) of 32 drug resistant

Table 1
The demographic data and relevant history of 32 drug resistant TB patients.

Demographic data	Number (%)
Age	
Mean age in years (range)	33.6 (13-70) ± SD 13.1
Sex	
Male	21 (65.6)
Female	11 (34.4)
Occupation	
Unskilled worker	4 (12.5)
Semiskilled worker	2 (6.3)
Skilled worker	18 (56.2)
Dependent	6 (18.8)
Others	1 (3.1)
Student	1 (3.1)
Education	
Illiterate	1 (3.1)
Read and write	1 (3.1)
Primary school	6 (18.8)
Middle school	15 (46.9)
High school	7 (21.9)
Under graduate	2 (6.3)
Household number	
Average no. per household (range)	5 (2-10)
Relevant history	
Tuberculosis contact history present	13 (40.6)
Treatment seeking at private clinic before reaching TB center	25 (78.1)
Mean duration at private clinic days (range)	33.1 (1-90) ± SD 30.4
History of anti-TB treatment at private clinic	6 (18.7)
Mean internal between symptom appearance and receiving anti-TB treatment at TB center days (range)	54.50 (7-180) ± SD 46.6
Investigation done at private clinic	
Chest X ray	17 (68)
Blood test	5 (20)
Sputum microscopy	3 (12)

cases had a history of TB contacts. Among them 7 patients (1 I resistance, 2 IR resistance, 3 SI resistance and 1 SIR resistance) had a history of death of their contacts due to TB (Table 3).

Interval between symptom appearance and receiving anti-TB treatment in mono-resistant and poly-resistant cases

    The mean interval of the 15 mono-resis-tant cases was 43.4 days and 17 poly-resis-tant cases was 82.6 days. The difference is statistically significant by Anova test (p = 0.015) (Table 4).

DISCUSSION

    The World Health Organization stated Myanmar is one of the 22 high TB burden countries. The National TB Program (NTP)

Table 2
Drug resistant pattern among different age groups.

Drug resistance	Age group (in years)			Total
	<20	20-59	≥60 and above	
I	0	8	1	13
R	0	1	0	1
E	0	1	0	1
IR	0	5	0	6
SI	1	5	1	8
SR	1	0	0	1
SIR	0	2	0	2
Total	2 (6.2%)	22 (87.5%)	2 (6.2%)	32 (100.0%)

Table 3
Outcome of TB contacts in drug resistant cases.

Drug resistant cases	Outcome in TB contacts			Total
	Cured	Still on treatment	Died	
I	1	2	1	4
R	1	0	0	1
IR	0	0	2	2
SR	1	0	0	1
SI	1	0	3	4
SIR	0	0	1	1
Total	4	2	7	13

Table 4
Interval between symptom appearance and receiving anti-TB treatment in monoresistant and polyresistance cases.

Drug resistance	Number	Mean interval	Standard deviation	Difference	p-value
Mono-resistant cases	15	43.40	26.56	1	0.015
Poly-resistant cases	17	82.59	53.12	30	

Myanmar was implemented in 1968. The directly observed treatment short-course (DOTS) strategy was adopted in 1997. The DOTS detection rate of new sputum smear positive TB cases and DOTS treatment success rate were 73% and 81%, respectively in 2002 (WHO, 2004).

Drug resistance is an important cause of treatment failure, particularly when the strains are resistant to the main bactericidal drugs isonizaid and rifampicin (MDR-TB). MDR-TB strains can be transmitted in the community and replace the susceptible strains, making the first line regimen inadequate for achieving high cure rates.

There are some studies which address the drug resistant TB situation in Myanmar. A study conducted on 400 new TB patients in

1994-1995 at the Union Tuberculosis Institute (UTI) Yangon showed that 1.2% and 18% had MDR-TB and any anti-TB drug resistance, respectively (Ti *et al*, 1995). In 2002, a second study was conducted on 51 new TB patients at UTI and reported the MDR-TB rate and any anti-TB drug resistant rate were 2% and 35%, respectively (Phyu *et al*, 2003).

The present study was carried out at a TB Center, the Yangon Division, which is situated in Yangon, the capital of Myanmar. It is a main referral center and responsible for case detection, diagnosis and treatment of outpatients. Annual reports show the diagnosis and treatment of one third of TB Clinic attendees in Yangon were from this center. The results show the MDR-TB rate in new PTB+ patients was 4.0% and any anti-TB drug resistant rate was 15.8%. MDR-TB rate is increased when it is compared to the 1994-1995 study.

The most common resistant drug was isoniazid (14.3%) and the second was streptomycin (5.4%). Rifampicin resistance was seen in (5.0%) and the least resistant drug was ethambutol (0.5%). This finding is consistent with the resistance rates of previous studies in Myanmar.

Primary resistance is difficult to determine because the patients themselves may not know or may deny they have had previous treatment for tuberculosis. Although we have constructed the interview questionnaires to screen new cases, we described our drug resistant rate as drug resistance among new TB cases, which is defined as the presence of resistant strains of *Mycobacterium tuberculosis* in patients who have never received TB drugs or had received them for less than one month.

Demographic data of drug resistant cases shows that 24 (75%) of the patients were workers and 28 (87.5%) were within the age group of 20-59 (Tables 1 and 2). Thirteen patients (40.6%) had a history of TB in a close contact. Among these, 7 patients (1 I resistance, 2 IR resistance, 3 SI resistance and 1

SIR resistance) had a history of death in their contacts due to TB (Table 3). Primary resistance is due to infection with resistant strains, originating from a patient who acquired resistance as a result of inadequate treatment. Patients with untreatable drug resistance become the vector for transmission of infection to the community. Therefore identification of drug resistant cases is important as most TB patients are from the working age group who have more exposure in the community.

Seventy-eight point one percent of cases had taken treatment at private clinics before attending the TB Center and the mean duration which they spent at the private clinics was 33.11 days (range 1-90 days). Six of these patients had been treated with anti-TB drugs for less than one month by private practitioners (PPs). The most common investigations done by PPs were chest X ray and sputum examination, were done in only 12% of cases. Sputum microscopy was the main diagnostic tool for tuberculosis case detection, and the categorization of patients for the choosing of an appropriate treatment regimen is dependent on the sputum smear results. Therefore, there were reasons for delay and inadequacy in anti-TB treatment and diagnosis of PPs, who had not kept current with TB therapy.

The mean interval between the appearance of symptoms and receiving anti-TB treatment at the TB Center was 54.5 days (range 7-180 days). Table 4 shows the mean interval in mono-resistant cases was 43.4 days and poly-resistant cases was 82.59 days and the difference was statistically significant (p = 0.015). This indicated that treatment delay may play an important role in the occurrence of poly-drug resistance.

In conclusion, our study found the prevalence of MDR-TB and anti-TB drug resistance among new smear positive pulmonary TB patients. The most common resistant drug was isoniazid. Evaluation of demographic data showed the main affected group is 20-39

years old, and a TB contact history played an important role among drug resistant cases. Poly-resistant cases had significantly longer intervals between symptom appearance and achieving effective anti-TB treatment than mono-resistant case.

This study highlights that drug resistant TB is an emerging problem and delay in correct diagnosis and effective treatment may lead to the occurrence of drug resistance cases. Moreover, patients may have socio-economic loss while they are seeking correct diagnosis and treatment. Therefore further studies should be carried out to find the bacteriological and social factors of patients with considerable delay in getting effective treatment.

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