Extensively Drug Resistant Tuberculosis (XDR-TB) in Chest Disease Institute, 1997-2005

Charoen Chuchottaworn MD*

** Division of Respiratory Medicine, Chest Disease Institute, Ministry of Public Health, Nonthaburi, Thailand*

Objective: *To determine prevalence of extensively drug resistant tuberculosis (XDR-TB) in Chest Disease Institute. World Health Organization has given the definition of XDR-TB as multi-drug resistant tuberculosis which also resists fluoroquinolone and aminoglycoside.*

Material and Method: *The present study was a retrospective review and conducted at Microbiology Unit, Chest Disease Institute. Drug susceptibility testing against fluoroquinolone and aminoglycoside have been done routinely since 1997. Laboratory results were studied to find XDR-TB patients and medical record information were reviewed. Laboratory results in 2006-2007 were not completed so were not included in the review.*

Results: *The result of the present study showed that from 1997 to 2005. 10,289 patients were tested for drug susceptibility. XDR-TB was found in 39 patients. Prevalence of XDR-TB was 6, 6, 9, 4, 3, 3, 2, 4 and 2 patients from 1997-2005 respectively. Most of XDR-TB patients were also resistant to Streptomycin and 39% resistant to Ethambutol. No data of resistance to second line drugs of XDR-TB was done in the present study.*

Conclusion: *The present study confirmed the existing of XDR-TB in Thai patient for a long time but not in increasing rate. The authorized TB Control organization should take XDR-TB as an important problem and developed capacity of tuberculosis laboratory in order to be able to diagnose XDR-TB*

Keywords: *Prevalence, MDR-TB, XDR-TB, Thailand*

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Pulmonary tuberculosis is an important communicable disease in Thailand. Cure rate of pulmonary tuberculosis is lower than 85% as targeted by the World Health Organization (WHO). Several factors were responsible for this low cure rate and one factor was drug resistant tuberculosis. WHO reported a primary drug resistant rate and secondary drug resistant rate of 1.6% and 34% in Thailand respectively[1]. These rates are the highest in South East Asia Region of WHO. The problem of drug resistant tuberculosis was a phenomenon observed since the discovery of the first anti-tuberculosis drug, Streptomycin[2]. The discovery of many new drugs and the success of short course 6 month regimen had obscured the drug resistant problem. Drug resistant tuberculosis became a re-emerging disease in the past decade after the recognition of a new type of drug resistant tuberculosis, multi-drug resistant tuberculosis (MDR-TB). MDR-TB was defined as *M. tuberculosis* strain which resists Isoniazid and Rifampicin that resulted as ineffectiveness of a short course treatment regimen[3]. In March 2006, WHO/Center for Disease Control (CDC) declared a new type of drug resistant tuberculosis, extensively drug resistant (XDR-TB). The definition of XDR-TB was re-defined in October 2006 as *M. tuberculosis* strain which is MDR and plus resistant to one member of the fluoroquinolone antibiotic class and resistant to one of injected anti-tuberculosis drug of Kanamycin, Amikacin or Capreomycin[4]. XDR-TB is an extremely difficult to treat and cure from tuberculosis. Currently there is no direct study of XDR-TB prevalence in Thailand. The chest Disease Institute (CDI) had done susceptibility of Ofloxacin and Kanamycin in routine drug susceptibility testing (DST) of *M. tuberculosis* since 1997. The present study has an objective to determine prevalence of XDR-TB in CDI.

Correspondence to: Charoen Chuchottaworn, Division of Respiratory Medicine, Chest Disease Institute, Ministry of Public Health, Nonthaburi 11000, Thailand.

Matereial and Method

The present retrospective study was conducted at the Microbiology Unit, Chest Disease Institute which had done DST for *M. tuberculosis* strains isolated from every new tuberculosis patient. Routine DST was done by standard absolute concentration method on Lowenstein-Jensen medium against Isoniazid, Rifampicin, Streptomycin and Ethambutol including Ofloxcacin at 2.0 microgram/milliliter (mcg/ml) and Kanamycin at 40 mcg/ml[5]. No Pyrazinamide susceptibility test was done. A retrospective review of tuberculosis laboratory record was done to find the results of drug susceptibility back to 1977 manually. Number of drug testing, number of MDR and XDR testing results were retrieved. Medical records of patients who had XDR were reviewed for medical informations. Because DST results in 2006-2007 were not completed, they were not included in the present study. Data were summarized as frequency and percentage.

Result

Labortatory data was available from 1997-2005. By using WHO/CDC definition of XDR-TB in October 2006, rom 1997-2005, Microbiology Unit, CDI, had done DST in 10,289 tuberculosis patients. MDR-TB was found in 909 (8.8%) patients. XDR-TB was found 2-9 patients in each year (Table 1). In 1999, XDR-TB had the highest number of 9 patients. The proportion of XDR-TB in MDR-TB was 2.3-8.0% as shown in Table 1. Co-resistant rate of Streptomycin and Ethambutol in XDR-TB were 94.9% and 41.0% as shown in Table 2. Medical records were found for 24 patients. XDR-TB patients in the present study were 27 male and 12 female. Three patients had HIV co-infection. The average duration of treatment before XDR was diagnosed was 6-48 months. Four patients didn't have any tuberculosis treatment before diagnosis of XDR. Ten patients were treated with second line drugs and 4 patients were documented as failure and another 6 patients defaulted from treatment without knowing the result. Fourteen patients never received second line drugs because the drug susceptibility testing result wasn't known before the patients defaulted from treatment. One patient died after 6 months and one patient is still being followed-up at CDI.

Discussion

Extensively drug resistant tuberculosis is a new type of drug resistant which was first defined in March 2006 as multi-drug resistant tuberculosis (MDR-TB) that was also resistant to three or more second line drug classes (second line drugs had 6 classes)[6]. This definition was not practical because there are no standard methods for second line anti-tuberculosis drug testing, few laboratories can do second line drug susceptibility and stability of second line drugs in the media are poor. WHO/CDC declared in October 2006 a new definition of XDR-TB as MDR-TB that was also resistant to one member of the fluoroquoinolone antibioticclass and one injected drug of Kanamycin, Amikacin or Capreomycin. This definition is more practical because fluoroquinolone and aminoglycoside are more stable and reliable test results. Ofloxacin was used as the representative of fluoroquinolone class in testing. Fluoroquinolone and aminoglycoside are two core drugs for treatment of MDR-TB and resistant to these drugs made treatment of XDR-TB far more from successful. The present study demonstrates clearly that XDR-TB was existing

Table 1. Prevalence of MDR-TB and XDR-TB in chest disease institute from 1997-2005

Year	No. of patients	No. (%) MDR-TB	No. (%) XDR-TB
1997	1,345	150 (11.15)	6 (4.0)
1998	1,438	97 (6.74)	6 (6.2)
1999	1,082	113 (10.44)	9 (8.0)
2000	1,342	108 (8.05)	4 (3,7)
2001	1,276	88 (6.90)	3 (3.4)
2002	1,013	78 (7.70)	3 (3.8)
2003	919	72 (7.83)	2 (2.8)
2004	1,006	115 (11.43)	4 (3.5)
2005	868	88 (10.14)	2 (2.3)

Table 2. Prevalence of Streptomycin and Ethambutol co-resistant in XDR-TB

Year	No. XDR	No. (%) of Steptomycin resistant	No. (%) Ethambutol resistant
1997	6	6 (100.0)	3 (50.0)
1998	6	3 (50.0)	3 (50.0)
1999	9	9 (100.0)	5 (55.5)
2000	4	4 (100.0)	2 (50.0)
2001	3	2 (66.7)	2 (66.7)
2002	3	3 (100.0)	0 (0.0)
2003	2	2 (100.0)	1 (50.0)
2004	4	4 (100.0)	0 (0.0)
2005	2	2 (100.0)	0 (0.0)
Total	39	37 (94.9)	16 (41.0)

in Thailand and dated back ten years ago. The prevalence of XDR-TB was not high and comparable to other reports. A survey conducted by CDC/WHO of 17,690 isolates collected between 2000-2004 showed an overall prevalence of XDR-TB of 2%[3]. Kim et al reported a prevalence of XDR-TB of 5.3% in 140 patients with MDR-TB during 2000-2002 from Korea[7]. In February 2008, WHO released a report indicating that XDR-TB has been reported from 45 countries including Thailand. Prammananan reported susceptibility results against second line drugs in Thai MDR-TB but no direct report of XDR-TB. Approximately 5% of MDR-TB in this report were resistant to fluoroquinolne[8]. Kanamycin concentration used in the testing is higher than recommended in the textbook[9].

The importance of XDR-TB is the treatment success rate which was very poor and mortality rate is extremely high. Gandhi et al reported 53 patients of XDR-TB with HIV infection who had a mean survival time of 16 days[10]. Kim reported a cohort of MDR/XDR in Korea with a cure rate of 46.2% in MDR-TB and 29.3% in XDR-TB. Default rate was quite high 32.2% in this cohort[7]. In the present study, most of the patients defaulted from treatment and although ten patients had been treated with second line drugs, none of the patients could be documented as cured. Another interesting finding is 14 patients didn't receive any treatment with second line drugs because DST results came back too late and the patients defaulted before knowing the DST results.

Conclusion

Extensively drug resistant tuberculosis has actually existed in Thailand for a long time but with no in increasing rate. The authorized TB Control organization should take XDR-TB as an important problem and develop the capacity of tuberculosis laboratories in order to be able to diagnose XDR-TB.

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วัณโรคดื้อยาชนิดรุนแรง (XDR-TB) ในสถาบันโรคทรวงอกปี พ.ศ. 2540-2548

เจริญ ซูโซติถาวร

วัตถุประสงค์: *เพื่อศึกษาความชุกของการดื้อยาวัณโรคชนิดรุนแรงในสถาบันโรคทรวงอก องค์การอนามัยโลก (WHO) ได้ให้คำจำกัดความของวัณโรคดื้อยาชนิดรุนแรง (XDR-TB) ว่าเป็นวัณโรคดื้อยาชนิด MDR-TB ที่มีการดื้อต่อยากลุ่ม fluoroquinolone และ aminoglycoside*

วัสดุและวิธีการ: *การศึกษานี้เป็นการศึกษาย้อนหลังที่งานจุลชีววิทยา สถาบันโรคทรวงอก เป็นสถาบันเดียวในประเทศไทยที่มีการทดสอบความไวของเชื้อวัณโรคต่อยา fluoroquinolone และ aminoglycoside ในผู้ป่วยใหม่ทุกรายตั้งแต่ปี พ.ศ. 2540–2548 ผลการทดสอบการดื้อยาทางห้องปฏิบัติการได้รับการตรวจสอบ เพื่อหาผู้ป่วยที่มีการดื้อยาวัณโรคชนิดรุนแรง และประวัติการรักษาของผู้ป่วยที่มีการดื้อยาชนิดรุนแรงจะได้รับการทบทวน ผลการทดสอบการดื้อยาในปี พ.ศ. 2549-2550 มีไม่สมบูรณ์จึงไม่ได้นำมาศึกษา*

ผลการศึกษา: *พบว่าตั้งแต่ปี พ.ศ. 2540 ถึง พ.ศ. 2548 ห้องปฏิบัติการวัณโรค ได้ทำการทดสอบเชื้อวัณโรคทั้งหมดในผู้ป่วยวัณโรครายใหม่จำนวน 10,289 สายพันธุ์และความชุกของการดื้อยาชนิด XDR-TB จำนวน 39 ราย ตั้งแต่ปี พ.ศ. 2540-2548 ตามลำดับดังนี้ 6, 6, 9, 4, 3, 3, 3, 5 และ 2 ราย เชื้อ XDR-TB จากการศึกษานี้พบว่าส่วนใหญ่จะมีการดื้อยา Streptomycin ร่วมด้วยยา Ethambutol จะพบว่ามีการดื้อยาเพียงร้อยละ 39 ไม่มีข้อมูลของการดื้อยาสำรองอื่น ๆ ร่วมด้วย*

สรุป: *การดื้อยาของเชื้อวัณโรคชนิดใหม่ที่เพิ่งมีการให้คำจำกัดความจากการศึกษานี้พบว่ามีมานานในผู้ป่วยไทย แต่อัตราการดื้อยาพบว่าไม่มีแนวโน้มที่เพิ่มขึ้นผลจากการศึกษาครั้งนี้แสดงว่ามีเชื้อวัณโรคดื้อยาชนิดรุนแรง (XDR-TB) ในประเทศไทยจริงและจำเป็นที่หน่วยงานทางด้านการควบคุมวัณโรค จะต้องให้ความสำคัญโดยเฉพาะการพัฒนาห้องปฏิบัติการเพื่อให้มีขีดความสามารถในการตรวจสอบเชื้อวัณโรค XDR*