

STUDY ON DRUG-RESISTANT TUBERCULOSIS AND TUBERCULOSIS TREATMENT ON PATIENTS WITH DRUG RESISTANT TUBERCULOSIS IN CHEST CLINIC OUTPATIENT DEPARTMENT

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ABSTRACT

Background and Objective: Tuberculosis treatment's more difficult with occurrence of tuberculosis bacilli that resistant to anti-tuberculosis drug, as it occurred patients cannot be treated with standard therapy regimen and switched to second line anti-tuberculosis drugs that less effective and less safety. This study aimed to investigate drug-resistant tuberculosis cases and its treatment among tuberculosis patient treated in chest clinic.

Method: This study was a cross-sectional observation study with retrospective analysis. Patients included for this study was treated for tuberculosis in Chest Clinic on Hospital Pulau Pinang, Malaysia that in our inclusion criteria. Data was descriptively analyzed by using statistical package for social sciences (SPSS 15).

Result: Among 653 tuberculosis patient included to this study, drug-resistant problem occurred on 17 patients or 2.6% from total number of patient included to this study, among drug-resistant tuberculosis patients, 10 patients (58.8%) with mono drug-resistant tuberculosis and 7 patients (41.2%) with multidrug-resistant tuberculosis. Drug-resistant tuberculosis treatment on initial phase 9 patients (52.9%) with EHRZ, 4 (23.5%) with HRZ, and 4 (23.5%) with other combination, continuation phase 4 patients (23.5%) with H2R2, 9 patients (52.9%) with HR, 3 patients (17.6%) with others combination, and 1 patients (5.9%) was not on continuation phase, for treatment duration there are 1 patients (5.9%) <6 months (consider defaulted), 10 patients (58.8%) 6-9 months, and rest of 6 patients (35.3%) >9 -12 months.

Conclusion: Drug-resistant tuberculosis cases in Malaysia is slightly increase in 2010 and on drug-resistant tuberculosis there are some cases that required change to second line anti-tuberculosis drugs.

Keywords: Tuberculosis, Drug-resistant tuberculosis, Monodrug-resistant, Multidrug-resistant.

INTRODUCTION

Tuberculosis remains as a leading infectious killer worldwide that can appear as either silent, latent infection or a progressive, active disease. When this disease was untreated or improperly treated, tuberculosis could cause progressive tissue destruction, even death¹. Tuberculosis case until today still become worldwide health problem, there are many reason of this including poverty and social deprivation also lack of health services in certain country². Increasing incidence of *Mycobacterium tuberculosis* strain resistance or less responsive to first line anti-tuberculosis drugs is a major contributed factor to the current tuberculosis epidemic worldwide²⁻³. Drug-resistant tuberculosis has become a major problem in tuberculosis treatment worldwide^{4,5}. Multidrug-resistant tuberculosis (MDR-TB) is defined as bacilli resistant to at least two first-line agents, isoniazid (INH) and rifampin (RIF). Drug-resistant has increased especially in regions where TB control programs are poorly enforced⁶. In 2008, an estimated 390 000–510 000 cases of MDR-TB emerged globally (best estimate, 440 000 cases). Among all incident tuberculosis cases globally, 3.6% (95% confidence interval (CI): 3.0–4.4) are estimated to have MDR-TB. These estimates, which lie in the same range as the previous ones, are based on more data and a revised methodology. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. In 2008, MDR-TB caused an estimated 150 000 deaths⁴. Drug-resistant tuberculosis developed due to improper previous treatment or interruption of tuberculosis treatment^{3, 5}. In recent years, drug resistant TB has emerged as an expanding threat, with an estimate 489000 new cases in 2006. Treatment of multidrug-resistant TB (MDR-TB) is more than 100 times as costly as treatment of drug susceptible TB, difficult, less effective, requiring intensive care management for its prolonged (18-24 months) and more toxic treatment course⁷⁻⁸. Isoniazid (INH) is a critical component of the first line combination therapy of tuberculosis. Mutations in several genes and genomic regions of *Mycobacterium tuberculosis* are involved in the occurrence of resistance to INH⁹. That is why Tuberculosis until this day still became burdensome in worldwide

health problems. In Malaysia there are still less study about drug-resistant tuberculosis.

METHODS

Study design

The study was conducted as a 30 months retrospective cross-sectional study by conducting observation on tuberculosis patient treated on Chest Clinic Respiratory Department, Hospital Pulau Pinang, Malaysia. This study was carried out by collecting patient's medical record from year January 2008 to June 2010. Research subjects were patient that treated as tuberculosis patient (an outpatient) in Chest Clinic, Respiratory Department, General Hospital Pulau Pinang, Malaysia. Objectives of the study were to investigate drug resistant tuberculosis cases among tuberculosis patient treated in chest clinic and to evaluate tuberculosis management on drug resistant tuberculosis patient.

Sample size and sampling technique

Sample size for this study was calculated using Raosoft® Inc. Recommended sample size is 306 patients, with tuberculosis patient population treated in General Hospital Pulau Penang around 1500 patients with confidence level 95% and margin of error that can be accepted 5%. Precise population of tuberculosis patients was unknown. Sampling techniques used in this study was the universal sampling technique by collecting patient's medical record that available in medical record office. There was no information gathered directly from patients. Patients' medical record were sorted and selected according to the inclusion and exclusion criteria. Inclusion criteria for this study were patient that diagnosed tuberculosis, adult patient (18 years of age and above), and normal liver function test before start taking anti-TB drugs regimen. Exclusion criteria of this study were patient with abnormal liver function test before start taking anti-TB drugs regimen, pediatric patient (below than 18 years of age), serological evidence of an acute infection with hepatitis B or C and was diagnosed hepatitis, and inadequate medical record to allow complete analysis.

Study procedure

Malaysia has a tuberculosis control program which is called TB Negara. Under this program, patients that suspected have tuberculosis should do some test series to develop a diagnosis, those test such as tuberculin test, sputum AFB test, culture test, chest x-ray and any other test that necessary for diagnosed. Patients who were diagnosed with tuberculosis before taking treatment they have to do some more test series such as baseline liver function test, renal function test and hematology test including HIV screening test. In some certain case, reactivation tuberculosis patient have to undergo sensitivity test also for high risk tuberculosis patient. All tuberculosis patients were reviewed at first two week after started treatment and thereafter every month except if they have an experience of worseness sign and symptom, they were informed to visit the doctor immediately.

Ethical clearance

Approval for ethical clearance obtained from the local institutions where the study conducted and from the Ministry of Health Research Ethics Committee (MREC). This study also registered with the National Medical Research Register (NMRR).

Analysis

Collected data analyzed using Statistical Package for Social Sciences version 15.0. Categorical variables such as patient's gender, race, type of tuberculosis, treatment regimen, treatment duration, drug resistant tuberculosis, and others expressed in frequencies and percentage. Numerical categories such as age expressed in mean. Socio-demographic, lifestyle and habits patients that related to drug resistant tuberculosis was analyzed with chi-square, p-value <0.05 considered statistically significant.

RESULTS

Demographic characteristics

653 patients were included in this study with range of age 18 – 91 years old, median age 48 years. There are 402 patients or 61.6% of total number of patients with age between 18 – 54 years of age and 251 or 38.4% of total number of patient with age above than 54 years of age. 71.1% of total number patients are male and the rest 28.9% are female. Patients distribution according to race, Chinese (52.4%) followed by Malay (33.4%), Indian (9.0%), and other races. Other races here stands for other than Malaysian citizens which are 16 Indonesian, 9 from Myanmar, 3 from Thailand, 2 Bangladeshi, 1 from China, 1 France, 1 Vietnamese, and 1 Taiwanese.

Table 1: Shows patients distribution according to patients' demographic characteristics

| Demographic characteristic | n (%) | |
|----------------------------|----------------------|------------|
| Age | 18 – 54 years of age | 402 (61.6) |
| | >54 years of age | 251 (38.4) |
| | Minimum age | 18 |
| | Maximum age | 91 |
| Gender | Median age | 48 |
| | Male | 464 (71.1) |
| Race | Female | 189(28.9) |
| | Chinese | 342 (52.4) |
| | Malay | 218 (33.4) |
| | Indian | 59 (9.0) |
| | Others | 34 (5.2) |

Patients' lifestyle and habits

Lifestyle and habits recorded from patients form and medical record also from doctor and nurse note. Lifestyle and habits are necessary to be recorded that it might be related to risk factor of the disease and disease transmission. In this study patient that admitted smoking was found in 313 (47.9%) of total patients and other 340 (52.1%) of patients denied smoking. Patients admitted on consuming alcohol were 79 patients (12.1%) and 574 patients (87.9%) denied on alcohol consuming. Patients with drug abuse were 60 patients (9.2%) and 593 (90.8%) denied as drug abuser.

Table 2: Shows patients distribution according to patients' lifestyle and habits

| Patient lifestyle and habits | n (%) | |
|------------------------------|-----------------|------------|
| Smoking | Smoker | 313 (47.9) |
| | Non smoker | 340 (52.1) |
| Alcohol use | Alcoholic | 79 (12.1) |
| | Non alcoholic | 574 (87.9) |
| Drug abuse | Drug abuser | 60 (9.2) |
| | Non drug abuser | 593 (90.8) |

Drug resistant tuberculosis

Drug resistant tuberculosis is when *Mycobacterium tuberculosis* bacteria resistant to first line anti-tuberculosis. Drug-resistant potentially can interrupt tuberculosis patients' treatment. In this study we want to investigate are there any drug resistant problems that occur among tuberculosis patients treated in location of the study.

Incidence of drug-resistant tuberculosis among tuberculosis patients treated in hospital Pulau Pinang according to the record year can be seen in table 3. In 2008 there are 6 patients with drug-resistant cases or 2.2% from total patients treated from tuberculosis in the same year. The same number of drug-resistant tuberculosis in 2009 and in 2010 case of drug-resistant tuberculosis increased to 4.1% from all total patients that treated for tuberculosis in first 6 month in 2010. The result shows that only few drug resistant problem that occur among tuberculosis patient, only 17 (2.6%) patient that had an experience on drug resistant problem from total number of patient included to this study.

Table 3: Shows number of drug resistant case according to year

| Drug resistant | Year | | | Total |
|----------------|------------|------------|-------------|-------------|
| | 2008 | 2009 | 2010 | |
| yes | 6 (2.2%) | 6 (2.3%) | 5 (4.1%) | 17 (2.6%) |
| no | 268(97.8%) | 252(97.7%) | 116 (95.9%) | 636 (97.4%) |
| Total | 274 (100%) | 258 (100%) | 121 (100%) | 653 (100%) |

Tuberculosis culture resistant shows 7 patients (1.1%) resistant to streptomycin, 4 patients (0.60%) resistant to isoniazid and streptomycin, 2 patients (0.30%) resistant to rifampicin and other 4 patients resistant to other first line anti-tuberculosis. Those 4 patients are 1 (0.20%) resistant to isoniazid, 1 (0.20%) resistant to both ethambutol and streptomycin, 1 (0.02%) resistant to both isoniazid and ethambutol while 1 (0.20%) resistant to three first line anti-tuberculosis, isoniazid, rifampicin and ethambutol.

Table 4 shows correlation between patients' demographic characteristics and drug resistant tuberculosis. There are 9 (1.4%) male patients that resistant to anti-tuberculosis drug while there are 8 (1.2%) female patients that resistant to anti-tuberculosis drug. Chi square test result showed no significance correlation between patient gender and drug resistant 0.095 (beyond 0.05).

Correlation between patients' age and drug-resistant tuberculosis also can be seen on table 4, there are 13 (2.0%) patients age between 18-54 years old and 4 (0.6%) patients age >54 years old that resistant to anti-tuberculosis drug. Chi square test result showed no significant correlation on patient gender and drug resistant 0.200 (beyond 0.05).

Drug resistant tuberculosis correlate with patients' gender showed that there are 7 (1.1%) of total patient in this study are Chinese, 6 (0.9%) of total patient in this study are Malay, 3 (0.4%) of total patient of this study are Indian, and 1 (0.2%) of total patient with other race resistant to anti-tuberculosis drug. Chi square test result showed no significant correlation on patient race and drug resistant 0.597 (beyond 0.05).

Table 4: Shows correlation between patients' demographic characteristics and drug-resistant tuberculosis occurrence

| Demographic characteristics | | Drug-resistant tuberculosis | | Total | p-value |
|-----------------------------|---------|-----------------------------|--------------------|------------|---------|
| | | Yes, n (%) (N = 17) | No, n (%) (N= 636) | | |
| Gender | Male | 9 (1.4) | 455 (69.7) | 189 (71.1) | 0.095 |
| | Female | 8 (1.2) | 181 (27.7) | 464 (28.9) | |
| Age | 18-54 | 13 (2.0) | 389 (59.6) | 402 (61.6) | 0.200 |
| | >54 | 4 (0.6) | 247 (37.8) | 251 (38.4) | |
| Race | Malay | 6 (0.9) | 212 (32.5) | 218 (33.4) | 0.597 |
| | Chinese | 7 (1.1) | 335 (51.3) | 342 (52.4) | |
| | Indian | 3 (0.4) | 56 (8.6) | 59 (9.0) | |
| | Others | 1 (0.2) | 33 (5.1) | 34 (5.3) | |

Table 5 shows correlation between drug resistant tuberculosis with lifestyle and habit showed that drug-resistant happened on 7 smoker patients, 4 alcoholic patients, and 3 drug abuser patients. Chi square result indicated there is no significant correlation between patient lifestyle and habit with occurrence on drug-resistant tuberculosis event, with p-value beyond 0.05.

Drug-resistant tuberculosis correlate with patients' medical history can be seen on table 6.

There are 12 newly diagnosed patient that encountered with drug-resistant tuberculosis and 5 relapse patient with drug-resistant tuberculosis. Chi square result showed that there is significant

correlation between patients' medical history with drug resistant tuberculosis occurrence in this case patients patient's tuberculosis status whether newly diagnosed patient or relapse, with p value <0.05.

Other patient's medical history such as contact with tuberculosis patient before, diabetes mellitus history or history on human immunodeficiency (HIV) co-morbidity, chi square test result showed that there are no significant correlation between drug-resistant occurrence with tuberculosis contact history, co-morbidity with diabetes mellitus and human immunodeficiency virus infection, with p value > 0.05.

Table 5: Shows correlation between patients' lifestyle-habits and drug-resistant tuberculosis occurrence

| Lifestyle and Habits | | Drug-resistant | | Total | p-value |
|----------------------|-----|---------------------|--------------------|------------|---------|
| | | Yes, n (%) (N = 17) | No, n (%) (N= 636) | | |
| Smoking status | Yes | 7 (1.1) | 306 (46.9) | 313 (48.0) | 0.572 |
| | No | 10 (1.5) | 330 (50.5) | 340 (52.0) | |
| Alcohol use | Yes | 4 (0.6) | 75 (11.5) | 79 (12.1) | 0.143 |
| | No | 13 (2.0) | 561 (85.9) | 574 (87.9) | |
| Drug abuse | Yes | 3 (0.5) | 57 (8.7) | 60 (9.2) | 0.221 |
| | No | 14 (2.1) | 579 (88.7) | 593 (90.8) | |

Table 6: Shows correlation between drug resistant tuberculosis and patients' medical history

| Patient Medical History | | Drug Resistant Tuberculosis | | p-value |
|-------------------------|--------------------|-----------------------------|--------------------|---------|
| | | Yes, n (%) (N = 17) | No, n (%) (N= 636) | |
| Tuberculosis status | New diagnose | 12 (1.8) | 554 (84.8) | 0.048 |
| | Relapse | 5 (0.8) | 82 (12.6) | |
| Contact Tuberculosis | Yes | 1 (0.2) | 89 (13.6) | 0.338 |
| | No | 6 (0.9) | 547 (83.8) | |
| Diabetes Mellitus | Yes | 5 (0.8) | 165 (25.3) | 0.748 |
| | No | 12 (1.8) | 471 (72.1) | |
| HIV | Positive | 0 (0.0) | 53 (8.1) | 0.393 |
| | Negative | 12 (1.8) | 445 (68.1) | |
| | Data not available | 5 (0.8) | 138 (21.1) | |

Table 7: Shows correlation on patients' treatment with and without drug-resistant tuberculosis

| Patients' Treatment | | Drug-resistant tuberculosis | | p-value |
|---------------------|------------------------------|-----------------------------|--------------------|---------|
| | | Yes, n (%) (N = 17) | No, n (%) (N= 636) | |
| Initial Phase | EHRZ | 9 (52.9) | 521 (81.9) | 0.000 |
| | HRZ | 4 (23.5) | 82 (12.9) | |
| | Others* | 4 (23.5) | 33 (5.2) | |
| Continuation Phase | H2R2 | 4 (23.5) | 240 (37.7) | 0.019 |
| | HR | 9 (52.9) | 274 (43.1) | |
| | Others** | 3 (17.6) | 24 (3.8) | |
| | Not on continuation phase*** | 1 (5.9) | 98 (15.4) | |
| Treatment Duration | < 6 months | 1 (5.9) | 132 (20.8) | 0.004 |
| | 6-9 months | 10 (58.8) | 441 (69.3) | |
| | >9-12 months | 6 (35.3) | 54 (8.5) | |
| | >12 months | - | 5 (0.8) | |
| | Not mention**** | - | 4 (0.6) | |

E : Ethambutol; H : Isoniazid; R : Rifampicin; Z : Pyrazinamide; S : Streptomycin; O : Ofloxacin; L : Levofloxacin

*Others combination than EHRZ and HRZ;

Without drug resistant tuberculosis, 5 patients with EHZ, 2 patients with SHRZ, 2 patients with HR, 1 patient with EHRZ + HER, 1 patient with EH+O, 1 patient with ERZ, 1 patient with EH, and 1 patients with E3HZ

With drug resistant tuberculosis : 1 patients with SRZ+ O, 1 patients with EHZ, 1 patient with SHRE, and 1 patient with EHRZ +L+ ethionamide

**Others combination than H2R2 and HR ;

Without drug resistant tuberculosis, 11 patients with EH, 4 patients with ER, 2 patients with HER, 2 patients with EHZ, 1 patient with H3E3, 1 patient with S2H2, 1 patient with E3H, 1 patient with EH + ofloxacin, and 1 patient with SHR

With drug resistant tuberculosis, 1 patient with EH and 2 patients with HER

***Patients not taken medication for their continuation phase, usually defaulted patient

****Length of treatment unknown precisely cause patients stop the medication by them self

Treatment for patient with drug-resistant tuberculosis can be seen in table 7. Chi-square test result showed that there are significant correlation between patients' treatment for initial phase, continuation phase, and treatment duration with drug-resistant tuberculosis, with p value <0.05. Patients with drug-resistant tuberculosis, that not resistant to isoniazid or rifampicin still can be treated with first line anti-tuberculosis drugs. The result showed that among drug-resistant tuberculosis patients there are 4 patients that treated with other than standard treatment regimen for initial phase treatment and for continuation phase there are 3 patients with other treatment regimen (not on standard regimen) while 1 patient not on continuation phase treatment.

DISCUSSION

Tuberculosis still became world health problem until now, in this study we investigated drug resistant tuberculosis cases among tuberculosis patient treated in hospital Pulau Pinang, Malaysia. We analyzed 653 tuberculosis patients that met our inclusion and exclusion criteria. All patients taken for this study was given medication on normal dosage use. The result showed that tuberculosis mainly happened in male patients in this study 71.1% patients are male and the others are female patients. Other study also showed the same results that male is a high risk gender on getting tuberculosis while female have less risk¹⁰⁻¹⁴. Age related to tuberculosis between 18-54 years of age which is productive age with mean age on 48 years of age. Other studies also have same result that productive age highly related on tuberculosis disease^{10, 13-15}. Race that related to tuberculosis is Chinese, it might be happened because of most of Pulau Pinang citizens are Chinese. If the study conducted in other part of Malaysia maybe there are different number of tuberculosis patient related to race, such as when the research conducted in Kuala Lumpur Malaysia the large number tuberculosis patient happened in Malay race¹². Risk factors for tuberculosis that well known are living in crowded population, poverty, poor nutrition, alcoholism, patients with diabetes mellitus, and human immunodeficiency virus infection. In this study we recorded patients' lifestyle and habit including cigarette smoking, alcoholism, and drug abuse. The result showed that almost half of total patients in this study were smoker. Even smoking status not one of well known risk factor of tuberculosis but it might be can increase risk of patients to get tuberculosis. Patients who were smoker mostly related to pulmonary tuberculosis. In study that conducted in India 81.5% of pulmonary tuberculosis were smokers¹⁶. In other study also shown that current or who had ever smoking have higher prevalence to be infected by *Mycobacterium tuberculosis*. This study result determined that 84.1% tuberculosis cases are pulmonary tuberculosis, this result is consistent with other research results^{12, 17}.

Tuberculosis treatment now became more complex with occurrence of tuberculosis bacteria that resistant to first line anti-tuberculosis drugs, called as drug-resistant tuberculosis. In this study among 653 patients included to this study there are 17 patients or 2.6% of total patients included to this study were diagnosed as drug-resistant tuberculosis patient determined with culture sensitivity test, 6 patients were detected in 2008 (2.2% of total tuberculosis patients included in this study), 6 patients were detected in 2009 (2.3% of total tuberculosis patients included in this study), and the rest 5 patients were detected in first 6 month by the year 2010 (4.1% of total tuberculosis patients included in this study). All factors that related to tuberculosis infection recorded and correlate with drug resistant. Chi-square test was used to determine whether tuberculosis risk factor related to drug resistant tuberculosis, in this study we analyzed patients' demographic characteristics, lifestyle and habit, patients' medical history, and patients' treatment and it's correlation with drug resistant tuberculosis cases. Chi-square test result showed that patients' age, gender and race have no correlation with drug-resistant tuberculosis occurrence. It means that drug-resistant tuberculosis can happen in every age, gender and race. Other studies also suggest the same with our study, that there are no correlation between patients' age, gender, and race with drug-resistant tuberculosis. Drug-resistant tuberculosis on correlation with patients' age, other previous study also showed similar results^{8, 18-19}. There was study that suggested that patients

with age 45-64 years old likely to be infected with drug-resistant tuberculosis bacteria strain²⁰. Drug-resistant tuberculosis in correlation with gender and race, other study also suggested same result^{8, 18-20}. Patients' lifestyle and habit recorded and correlate with drug-resistant tuberculosis by using chi-square test. Patients' lifestyle and habit recorded including smoking status, alcohol use, and drug abuse. The chi-square test result showed that there are no correlation between patients' lifestyle and habit with drug-resistant tuberculosis.

Patients' medical history including tuberculosis status, contact tuberculosis, diabetes mellitus status, and HIV status were collected and correlated with drug resistant tuberculosis case whether patients' medical history had association with patients' medical history or not. Chi-square test result showed that only patients' tuberculosis status (new diagnosed or relapsed) had an association with drug-resistant tuberculosis case occurrence. There were previous study had similar result^{18, 20}. There are no correlation between contact tuberculosis and drug-resistant tuberculosis case, so whether patients had contact with tuberculosis patients or not before it was not related to drug-resistant tuberculosis case occurrence. Some other studies also suggested the same results^{18, 20}, even though contact tuberculosis may increase probability of people get infected by *Mycobacterium tuberculosis*. We did not find correlation between drug-resistant tuberculosis with HIV status. Our result is similar with other previous study²⁰.

Patients' treatment was recorded including initial treatment, continuation treatment, and treatment duration. Patients' treatment was recorded to see whether there are any relationship between patients' treatment and drug-resistant tuberculosis case occurrence. Association between patients' treatment and drug-resistant tuberculosis occurrence was analyzed by chi-square test. Chi-square test result showed that there are significant correlation between patients' treatment and drug-resistant tuberculosis. In patients with drug-resistant tuberculosis treatment there are 4 patients (23.5%) of drug-resistant tuberculosis patients that required change other than standard regimen. Treatment duration on our result maximum period for drug-resistant tuberculosis treatment was 12 months, it was quite difference with other study that some of them said that the treatment duration may prolonged into 18-20 months^{3, 21-22}. This differences maybe because in our study most of the patients were resistant to streptomycin, so the treatment still can use standard regimen so it not prolonged the treatment duration.

There were some limitations in this study because it was designed as retrospective study. We only able to analyzed data that were recorded, for compliance and adherence or other factor that might related to drug-resistant tuberculosis we were not able to analyze.

CONCLUSION

Drug-resistant tuberculosis case in hospital Pulau Penang was slightly increase, need attention from all health practitioners to overcome this case and early detection is very necessary to decide most appropriate treatment on patients.

REFERENCES

1. DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM. Pharmacotherapy : A Pathophysiologic Approach. 6th ed. United States of America: The McGraw-Hill Companies; 2005.
2. Breathnach AS, Rutier Ad, Holdsworth GMC, et al. An Outbreak of Multidrug-Resistant Tuberculosis in a London Teaching Hospital. Journal of Hospital Infection 1998;39:111-117.
3. Ahmad S, Mokaddas E. Recent Advances in the Diagnosis and Treatment of Multidrug-resistant Tuberculosis. Respiratory Medicine 2009;103:1777-1790.
4. WHO. Global Tuberculosis Control : WHO Report 2010. In. Geneva: World Health Organization; 2010.
5. Bartu V, Kopecka E. Multidrug-resistant Tuberculosis-Prolonged Course of Disease. Respiratory Medicine 2008;1:150-152.
6. Tang YW, Stratton CW, Kilic A, Drake w. Advances in the Diagnosis of Mycobacterium tuberculosis and Detection of Drug Resistance. In: Advanced Techniques in Diagnostic Microbiology: Springer US; 2006.

7. Shah NS, Pratt R, Armstrong L, Robinson V, Castro KG, Cegielski JP. Extensively Drug-Resistant Tuberculosis in The United States, 1993-2007. *JAMA* 2008;300(18):2153-2160.
8. Sharma SK, Turaga KK, Balamurugan A, et al. Clinical and genetic risk factors for the development of multi-drug resistant tuberculosis in non-HIV infected patients at a tertiary care center in India: a case-control study. *Infection, Genetics and Evolution* 2003;3:183-188.
9. Rindi L, Bianchi L, Tortoli E, Lari N, Bonanni D, Garzelli C. A real-time PCR assay for detection of isoniazid resistance in *Mycobacterium tuberculosis* clinical isolates. *Journal of Microbiological Methods* 2003; 55:797- 800.
10. Tost JR, Vidal R, Maldonado J, Cayla JA. Effectiveness and Tolerance of Antituberculosis Treatment Regimens Without Isoniazid and Rifampicin Analysis of 85 Cases. *Arch Bronconeumol* 2008;44(9):478-483.
11. Yee D, Valiquete C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of Serious Side Effects from First-Line Antituberculosis Drugs among Patients Treated for Active Tuberculosis. *Am J Respir Crit Care Med* 2003;167:1472-1477.
12. A. MO, M. FAR, S. A, M. KI. Prevalence and Risk Factor of Anti-Tuberculosis Drug-Induced Hepatitis in Malaysia. *Singapore Medical Journal* 2008;49 (9):688-693.
13. Marra F, Marra CA, Bruchet N, et al. Adverse Drug Reactions Associated with First-line Anti-Tuberculosis Drug Regimens. *Int J Tuber Lung Dis* 2007;11(8):868-875.
14. Sharma Dk, Kulshreshtha M, maheshwari M, Yadav S. A Clinical Survey On Correlation Study Between Tuberculosis And Its Predisposing Factors In Mathura Region, *International Journal of Pharmaceutical Sciences Review and Research* 2011;Volume 9(Issue 2):150-152.
15. Singla R, Sharma SK, Mohan A, et al. Evaluation of risk factors for antituberculosis treatment induced hepatotoxicity. *Indian J Med Res* 2010;132:81-86.
16. Gajalakshmi V, Peto R. Smoking, drinking and incident tuberculosis in rural India: population-based case-control study. *International Journal of Epidemiology* 2009;38(4):1018-1025.
17. Elamin EI, Ibrahim MIM, Sulaiman SAS, Muttalif AR. Cost of illness of tuberculosis in Penang, Malaysia. *Pharm World Sci* 2008;30:281-286.
18. Melzer M, Gupta N, Petersen I, Cook S, Hall B. Previous treatment in predicting drug-resistant tuberculosis in an area bordering East London, UK. *International Journal of Infectious Diseases* 2010;14:e717-e722.
19. Kim HR, Hwang SS, Kim EC, et al. Risk Factor for Multidrug-Resistant Bacterial Infection among Patients with Tuberculosis. *Journal of Hospital Infection* 2010;xxx:1-4.
20. Suarez-Garcia I, Rodriguez-Blanco A, Vidal-Perez JL, et al. Risk factors for multidrug-resistant tuberculosis in a tuberculosis unit in Madrid, Spain. *Eur J Clin Microbiol Infect Dis* 2009;28:325-330.
21. Mukherjee JS, Rich ML, Socci AR, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. *The Lancet* 2004;363:474-481.
22. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. *Lancet Infectious Disease* 2009;9:153-161.