EXPLORATIVE STUDY OF ADVERSE DRUG REACTIONS AND DRUG-RESISTANT TUBERCULOSIS AMONG TUBERCULOSIS PATIENTS IN HOSPITAL PULAU PINANG, MALAYSIA

By

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ADRs	Adverse Drug Reactions
AFB	Acid-Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BCG	Bacille Calmette Guerin
CADR	Cutaneous Adverse Drug Reaction
CDC	Centers of Disease Control and Prevention
DOT	Direct Observed Therapy-Short Course
DR-TB	Drug-Resistant Tuberculosis
EPTB	Extra-pulmonary Tuberculosis
ETB	Ethambutol
FNA	Fine Needle Aspiration
HIV	Human Immunodeficiency Virus
HUSM	Hospital Universiti Sains Malaysia
INH	Isoniazid
LFT	Liver Function Test
MAC	Mid-Arm Circumference
MDR-TB	Multidrug-Resistant Tuberculosis
MMWR	Morbidity and Mortality Weekly Report
MOH	Ministry of Health
MREC	Ministry of Health Research Ethics Committee

NIH	National Institute of Health
NMRR	National Medical Research Register
PAS	Para-aminosalicylic
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
RIF	Rifampicin
SM	Streptomycin
TB	Tuberculosis
TST	Tuberculosis Skin Test
WBC	White Blood Cell
WHO	World Health Organization

KAJIAN EKSPLORASI PADA KESAN ADVERS DAN KERINTANGAN UBAT TUBERCULOSIS DALAM KALANGAN PESAKIT TUBERCULOSIS DI HOSPITAL PULAU PINANG, MALAYSIA

ABSTRAK

Tuberculosis (TB), penyakit berjangkit disebabkan oleh *Mycobacterium tuberculosis* yang banyak menyebabkan banyak kematian sepanjang sejarah hidup manusia, kini menjadi penyebab kedua terbesar penyebab kematian antara penyakit berjangkit yang ada setelah HIV-AIDS. Rawatan TB memerlukan kombinasi ubat anti-TB. Kesan advers drug anti-TB menjadi penting kerana kegunaan jangka masa panjang ubat anti-TB. Selain kesan advers drug anti-TB, munculnya bakteria TB rintang ubat anti-TB dapat menyulitkan rawatan TB pesakit.

Kajian ini adalah kajian retrospektif lintang secara pengamatan. Subjek penyelidikan kajian ini adalah pesakit yang dirawat sebagai pesakit TB di Klinik Dada, Hospital Pulau Pinang, Malaysia. Kajian ini bertujuan untuk menyiasat kesan advers drug anti-TB, adanya bakteria TB rintang ubat anti-TB, dan menyiasat faktor yang berkaitan dengan kesan advers drug TB dan rintang ubat anti-TB serta keluaran klinikal pesakit TB. Kesan advers drug anti-TB dilihat berdasarkan gejala klinikal, keputusan ujian makmal, dan maklumat lain yang berkaitan, sementara adanya bakteria TB rintang ubat anti-TB dilihat berdasarkan diagnosis yang bergantung kepada hasil ujian kecenderungan ubat atau ujian sensitiviti bakteria. Data demografi pesakit, sejarah perubatan, diagnosis TB dan rawatan, tanda dan gejala kesan advers drug, keputusan ujian makmal, ujian sensitiviti bakteria, dan maklumat lain yang berkaitan dikumpulkan. Data yang diperoleh dianalisis dengan menggunakan Statistic Package for Social Science (SPSS® versi 1.15).

Hasil analisis kajian menunjukkan bahawa daripada 653 pesakit termasuk dalam kajian ini, TB banyak terjadi pada lelaki, usia produktif, dan dikalangan China. Jenis TB yang paling umum ialah TB paru dengan kebanyakan pesakit mengalami batuk, kahak smear positif, dan x-ray dada tidak normal. Tuberculosis kasus baru ialah yang banyak terjadi dan separuh dari pesakit memiliki penyakit lain. Hampir 1/3 (26.0%) pesakit TB ialah pesakit DM dan 8.1% pesakit HIV/AIDS. Sepenuhnya ada 103 (15.8%) pesakit mengalami kesan advers drug dan 17 (2.6%) pesakit muncul bakteri rintang ubat anti-TB. Kesan advers drug yang banyak terjadi ialah reaksi kulit, diikuti reaksi gastrointestin, reaksi hepatic, reaksi neurologi, dan reaksi lain. Kebanyakan pola bakteria rintang ubat anti-TB adalah yang rintang satu ubat anti-TB. Ujian statistik chi-square dilakukan untuk menganalisa faktor yang berkaitan dengan kesan advers drug dan bakteria rintang ubat anti-TB. Hasil kajian menunjukkan bahawa kesan advers drug berkaitan dengan pesakit dengan sejarah penggunaan alcohol, penyalahgunaan dadah, pesakit DM, dan pesakit HIV/AIDS. Bakteria rintang ubat anti-TB berkaitan dengan pesakit yang pernah mendapatkan rawatan TB sebelumnya. Rawatan untuk kesan advers drug yang terjadi sebagian besar adalah dengan memberi tambahan ubat untuk mengatasi munculnya kesan advers drug dan rawatan pada pesakit dengan bakteria rintang ubat anti-TB bergantung kepada keputusan ujian sensitiviti pesakit. Keputusan klinikal pesakit menunjukkan bahawa kebanyakan pesakit telah sembuh daripada jangkitan TB dan faktor yang berkaitan dengan keputusan klinikal adalah adanya bakteri rintang ubat anti-TB.

EXPLORATIVE STUDY OF ADVERSE DRUG REACTIONS AND DRUG-RESISTANT TUBERCULOSIS AMONG TUBERCULOSIS PATIENTS IN HOSPITAL PULAU PINANG, MALAYSIA

ABSTRACT

Tuberculosis, an infectious disease caused by *Mycobacterium tuberculosis* claimed for human life throughout history today become second leading infectious diseases caused death after HIV-AIDS. Treatment of tuberculosis required combination of anti-tuberculosis drug. Anti-tuberculosis adverse drug reactions (ADRs) become important as longer use of these drugs. In addition to anti-tuberculosis ADRs, the presence of tuberculosis bacteria that resistant to anti tuberculosis drug may complicate on tuberculosis treatment.

This study was a retrospective cross-sectional observation study. Research subjects of this study were patients who were treated as active tuberculosis in Chest Clinic, Hospital Pulau Pinang, Malaysia. The aim of the study was to investigate anti-tuberculosis ADRs, drug-resistant tuberculosis (DR-TB), and all associate factors related to ADRs and DR-TB, also patients' treatment clinical outcomes. Adverse drug reactions were detected from patients' complains, clinical symptom, laboratory test result, and any other related information and DR-TB detected from patients' sensitivity test result. Patients' socio-demographic, medical history, tuberculosis diagnosis and treatment, clinical sign and symptom of ADRs, laboratory test result, sputum smear test, radiology test result, and other relevant information were collected. Obtained data then exported to excel and analyzed by using Statistical Package for Social Sciences (SPSS® version 15).

The study result showed that out of 653 patients included, TB cases most likely happened in male, productive age, and among Chinese. Most common type of TB was pulmonary TB with most of the patients had cough, sputum smear positive, and abnormal chest x-ray result. The most common of TB case was new diagnosed and half of the patients included had co-morbidity. Almost one third (26.0%) of TB patients were DM patients and 8.1% were HIV/AIDS patients. Totally 103 (15.8%) patients had an experience on ADRs and 17 (2.6%) patients with DR-TB. Common type of ADRs occurred was skin reaction, followed by gastrointestinal reaction, hepatic reaction, neurological reaction, and other reaction. Most of DR-TB pattern was mono-resistant tuberculosis in 10 patients. Chi-square test was implemented in order to asses associated factor related to ADRs and DR-TB. Study result showed that ADRs more likely related to alcohol consumption, drug abuse, patients with DM, and patients with HIV/AIDS infection. Drug-resistant tuberculosis more likely related to patient who had previous tuberculosis treatment (relapse patients). Adverse drug reaction management was mostly by giving other drug to overcome ADRs upon occurred and management on DR-TB depend on sensitivity test result. Clinical outcomes showed that most of the patients were cured from tuberculosis infection and factor that may affect on patients' clinical outcome was ADRs occurrence.

CHAPTER 1

INTRODUCTION

1.1 Background

Tuberculosis (TB), a well known infectious disease caused by *Mycobacterium tuberculosis* today has become the second leading cause of death among infectious diseases in the world (Dale, 2003; Allman, 2007). Tuberculosis bacteria commonly infects human lungs (pulmonary TB), but it may also involve any other organ. Active pulmonary TB incidence globally is estimated around 8 million new cases per year (Gulbay *et al*., 2006). *Mycobacterium tuberculosis* infects one third of global population (Tang *et al*., 2006) and TB continues to kill an estimated 1.8 million people globally each year (Anderson *et al*., 2010).

Active TB has been noted as a complex and unpredictable disease that caused severe disabilities even death. On the other hand, the TB bacteria can also hide within the human body for decades without causing any harm to the body (Allman, 2007). Tuberculosis causative bacteria can easily spread through air droplets while infected patients cough or sneeze, variety of hosts and environment related-factors to TB spreading (Parekh, 2009). Complexity of TB makes this disease remain as a global health problem not only in developing countries but also in developed countries, but a greater proportion of the illness lies in developing countries (Allman, 2007; Nissapatorn *et al*., 2007). Tuberculosis remains a disease associated with crowded population, decreased immunity, and poverty (Tang *et al*., 2006).

1.2 Tuberculosis History and Epidemiology

1.2.1 Tuberculosis History

Tuberculosis already claimed human life for centuries throughout human history than any other diseases (Daniel, 2006; Allman, 2007; Kaufmann and Helden, 2008). Earliest evidence of the occurrence of TB was an archeological excavation dated back to the Neolithic period (Kaufmann and Helden, 2008). Scientists discovered other evidences of TB in the bones of Egyptian mummies and prehistoric cave people. Tuberculosis seemed to have affected society independently in all part of the world (Allman, 2007). It reached epidemic proportion in Europe and North America during the 18th century then began to decline in the 19th century (Daniel, 2006). In Malaysia, TB became the leading cause of death in early 1940s and 1950s (MOH, 2002).

Pathogenesis of TB began to be understandable in the beginning of 19th century by the work of Laennec (Shampo and Rosenow, 2009). Transmission ability of *Mycobacterium tuberculosis* was demonstrated by a French physician, Jean Antoine Villemin in 1867 and identification of *Mycobacterium tuberculosis* as a causative agent or as the etiologic agent of TB was discovered by Robert Koch in 1988, and was awarded a Nobel Prize in Physiology and Medicine for this (Daniel, 2006; Shampo and Rosenow, 2009).

Tuberculosis diagnosis uses tuberculin test which was developed by Clemens von Pirquet in 1907 and 3 years after that it was used to demonstrate latent TB infection in asymptomatic children (Shampo and Rosenow, 2009). Effective anti-TB agents have been available since 1940s (Volmink and Garner, 2009). Streptomycin and para-aminosalicylic acids were invented in the 1940‟s, in 1950‟s Isoniazid and Pyrazinamide, and in 1960‟s Ethambutol and Rifampicin (Parekh, 2009).

1.2.2 Tuberculosis Epidemiology

Tuberculosis globally was monitored every year by the World Health Organization (WHO) and published TB reports since 1997 to outline the course of TB and to evaluate TB control worldwide (WHO, 2006). Tuberculosis cases which occurred from 2005 to 2010 can be seen in figure 1.1.

Tuberculosis cases on a global scale were estimated to be around 8.8 million in 2005 with a total of 1.6 million people dying due to TB (WHO, 2007). In 2006, TB cases increased to 9.2 million new cases on a global scale with a total 1.7 of million deaths due to TB (WHO, 2008), while in 2007 TB new cases were estimated at 9.3 million with 1.8 million deaths from TB (WHO, 2009). In 2008 TB new cases were estimated to be 9.4 million of TB global scale, which increased from 9.3 million TB case occurred in 2007 (WHO, 2009). Tuberculosis incidence cases in 2009 were estimated to be 9.4 million of TB globally, same number of incidence cases in 2008 (WHO, 2010a). Globally, in 2010 new TB cases were estimated at 8.8 million with 1.1 million deaths due to TB (WHO, 2011).

Top five countries with TB incidence in 2008 were India (1.6–2.4 million), China (1.0–1.6 million), South Africa (0.38–0.57 million), Nigeria (0.37–0.55 million) and Indonesia (0.34–0.52 million). An estimated 35% TB cases globally occurred in India and China alone (WHO, 2009).

Tuberculosis cases globally in 2008 and 2009 was estimated to be about 9.4 million most of the estimated number of TB cases occurred in Asia (55%) and Africa (30%), small proportions of TB cases occurred in the Eastern Mediterranean Region (7%), the European Region (5% in 2008, 4% in 2009) and the Region of the Americas (3%) (WHO, 2009; 2010a).

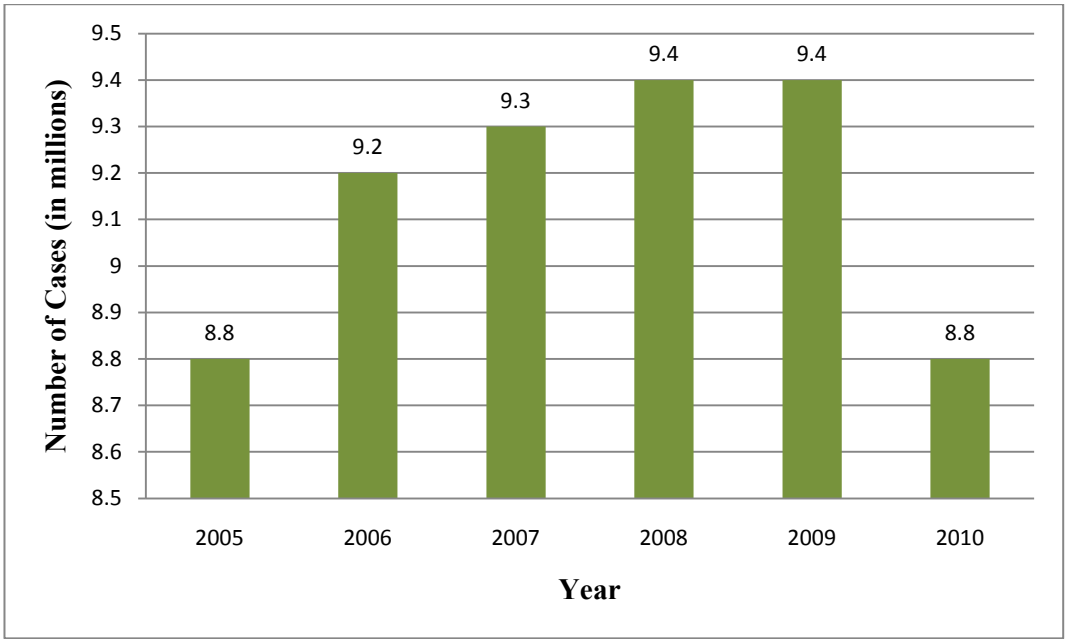

Figure 1.1 World Health Organizations, Tuberculosis Case Report 2005-2010

Tuberculosis became the leading cause of death in Malaysia in early 1940s and 1950s**.** Malaysia is a multi-ethnic country that consists of three major ethnic groups Malay, Chinese, and Indian (MOH, 2010). In 1999, Malaysia was ranked 46th in total number of TB cases globally with 14908 new cases of TB reported. Most of the TB cases were in the 15-50 age groups in Malaysia. Incidence rate of TB cases in Malaysia is 47 per 100,000 population per year with prevalence of 136 cases and mortality rate is estimated 17 cases per year (Marzuki *et al*., 2008), reported a total number of deaths due to TB was 853. This makes TB the single most important killer among other infectious disease in Malaysia (MOH, 2002).

1.3 Tuberculosis Etiology and Pathology

Tuberculosis caused by *Mycobacterium tuberculosis*, is an obligate aerobe bacillus with a size of about 0.2 x 5.0 µm. It most successfully grows in human tissues that have highest oxygen tension (PO_2), such as the lung apexes; a slowly growing organism with generation time estimated to be 12 to 18 hours; has a high

cell-wall lipid content so the organism is impermeable to the usual bacteriologic stains and even this organism require special enriched media to grow in the laboratory, this organism is extremely resistant to physical stress (Dale, 2003).

Tuberculosis pathogenesis is unique due to many related variables but mostly long latency period from someone infected to the clinical illness manifestation. A single TB bacillus theoretically can cause infection but it needs to pass the upper airway defense mechanism to reach alveoli of the pulmonary (Dale, 2003).

Transmission of *Mycobacterium tuberculosis* is commonly spread from infected persons to another person by cough or sneeze that is dispersed by droplet nuclei in which each droplet may contain one to three bacilli (Peloquin, 2005). Development of TB infection may occur after inhalation of the infected droplets that has been sneezed out by infected by *Mycobacterium tuberculosis* (Actor *et al*., 2008).

Primary infection is initiated when inhaled infectious droplets may escape from host‟s upper airway defenses and reach the alveoli (Peloquin, 2005), then the lungs exposed to TB bacteria (Actor *et al*., 2008). After inhalation, the TB bacteria grows intracellular in the host‟s alveolar macrophages, then followed by the recruitment of new macrophages and lymphocytes, and the formation of a tuberculous granuloma (Ridzan and Kizza, 2002). Disease progression on clinical manifestation depends on the number of organisms inhaled, virulence factors of the organism and host cell-mediated immune system (DiPiro *et al*., 2008).

Growth periodicity of the bacilli is logarithmic in which single bacilli will duplicate every 24 hours. The bacilli can be spread from the initial lesion to the other parts of the body through lymphatic and or circulating system. The centre of the cell mass or granuloma become caseous and necrotic as the cellular infiltration continue (Nicholas *et al*., 2010).

The period of infectiousness on a patient may be prolonged due to late diagnosis, poor adherence to medications or inappropriate TB treatment that is caused by drug-resistant organisms (Ridzan and Kizza, 2002).

1.4 Tuberculosis Risk Factors

There are several factors that are responsible for developing TB infection including poverty, lack of modern treatment methods and AIDS epidemic (Allman, 2007). Tuberculosis is mainly a disease of adults and it affects men more than women (Kaufmann and Helden, 2008), with high risk for TB in males within the age group 25 and 44 (Dale, 2003). In the United State, in 2002, 35% among TB cases was within the age group 25 to 44 years, followed between 45 to 64 years (28%), and 65 years of age above (21%) (Peloquin, 2005).

Tuberculosis cases in relation to ethnicity and age, TB is more common in older whites and Asians compared to younger people from these groups. Older blacks and Hispanics also have more TB than younger folks, but the differences by age are not as pronounced. Until the age of 15, TB rates are similar for males and females, but after that, the male predominance increases with each decade of life (Peloquin, 2005).

Tuberculosis disproportionately affects ethnic minorities in United States, non-Hispanic blacks accounted for 30% of all TB cases, followed by Hispanics at 27%. Asians and Pacific Islanders accounted for 22%, whereas non-Hispanic whites accounted for only 20% of the new TB cases in 2002 (Peloquin, 2005).

People that have close contact history of pulmonary TB patients are most likely to be infected, including family members, co-workers, or co-residents in places such as prisons, shelters, or nursing homes. The longer the contact with TB patients

the greater risk to be infected, with infection rates as high as 30%. Although many circumstances exist to be infected with TB, most TB patients have limited access to health care, living in crowded condition or homeless (DiPiro *et al*., 2008).

Other groups of populations with high incidence of TB such as immigrants, alcoholic, drug dependant person, homelessness, people who travel to TB endemic countries, and hospital employees, including physicians are also at increased risk of infections with TB (Dale, 2003).

Newly acquired TB infections cases occur every second in the world and in addition, one third of the world population is currently infected with *Mycobacterium tuberculosis*. Due to lack of healthy nutrition, crowded living conditions, and lack of access to health care, the highest incidence rate of TB cases is among developing countries (Tang *et al*., 2006).

1.5 Tuberculosis Transmission

Tuberculosis is a disease that can easily spread through air (Frieden *et al*., 2003). Tuberculosis bacteria can spread by airborne droplets from patients that have been infected by TB to other humans. Passive case patients are identified mostly in high-burden countries when they visit health care facilities. Contact with patients with TB is a high-risk group for developing the disease, so that actively screening contacts with patients that confirmed TB may improve on case detection and control the disease (Fox *et al*., 2011).

Air travel also gives opportunities for TB to spread rapidly between countries and continents. There may be potential risk of transmission during flights, notably airborne and droplet borne respiratory infection. Infected passengers may act as

disease vectors, bringing the infectious agents to the destination (Martinez *et al*., 2007).

There are some factors that determine the possibility of *Mycobacterium tuberculosis* transmission including number of organisms being expelled into the air, organisms concentration in the air, length of time an exposed person breathes the contaminated air, and presumably the immune status of the exposed individual. People with HIV-infection or with low immunity status more likely to become infected with *Mycobacterium tuberculosis* after exposure than persons with normal immunity and more likely to develop disease if they are infected (Dunlap *et al*., 2000).

1.6 Tuberculosis Clinical Manifestations

1.6.1 Pulmonary Tuberculosis

Definition of pulmonary TB is an active infection of the lung, means that the bacteria can located in the lung. Pulmonary infections are critically important because they are highly contagious and life threatening to patients that get affected (Davies *et al*., 2008). Suggested symptoms of pulmonary TB are cough (usually more than three weeks), cough with sputum, loss of appetite, loss of weight, fever, dyspnea, night sweats, chest pain and hoarseness of voice, all of which are not common. Patients with all these symptoms should be screened for TB (MOH, 2002).

1.6.2 Extra-pulmonary Tuberculosis

Extra-pulmonary TB is defined as tuberculosis infection in other organs besides the lung (Davis *et al*., 2008). Extra-pulmonary TB symptoms are often non-specific, including lassitude, anorexia, fever, and weight loss. The specific features are related to the organ involved (MOH, 2002).

1.7 Tuberculosis Investigation

The first technique in TB diagnosis was in 1882, Dr. Robert Koch, and Dr. Paul Erlich developed the acid-fast strain to identify *Mycobacterium tuberculosis* (Dye *et al*., 1999). Earlier diagnosis of TB is important to control the infection, to introduce timely manner of the treatment, and to determine bacteria resistance profile. Over the past two decades, dedicated efforts have resulted in enhancing TB diagnosis techniques (Tang *et al*., 2006).

The main tool for diagnosis of adult pulmonary TB is the sputum smear examination by direct microscopy for acid-fast bacilli (AFB). Once someone experiences most of the common symptoms of TB (persistent cough for 3 weeks or more) they need to follow some screening tests by submitting 3 sputum samples. Diagnosis on adult TB is described in figure 1.2 (WHO, 1999).

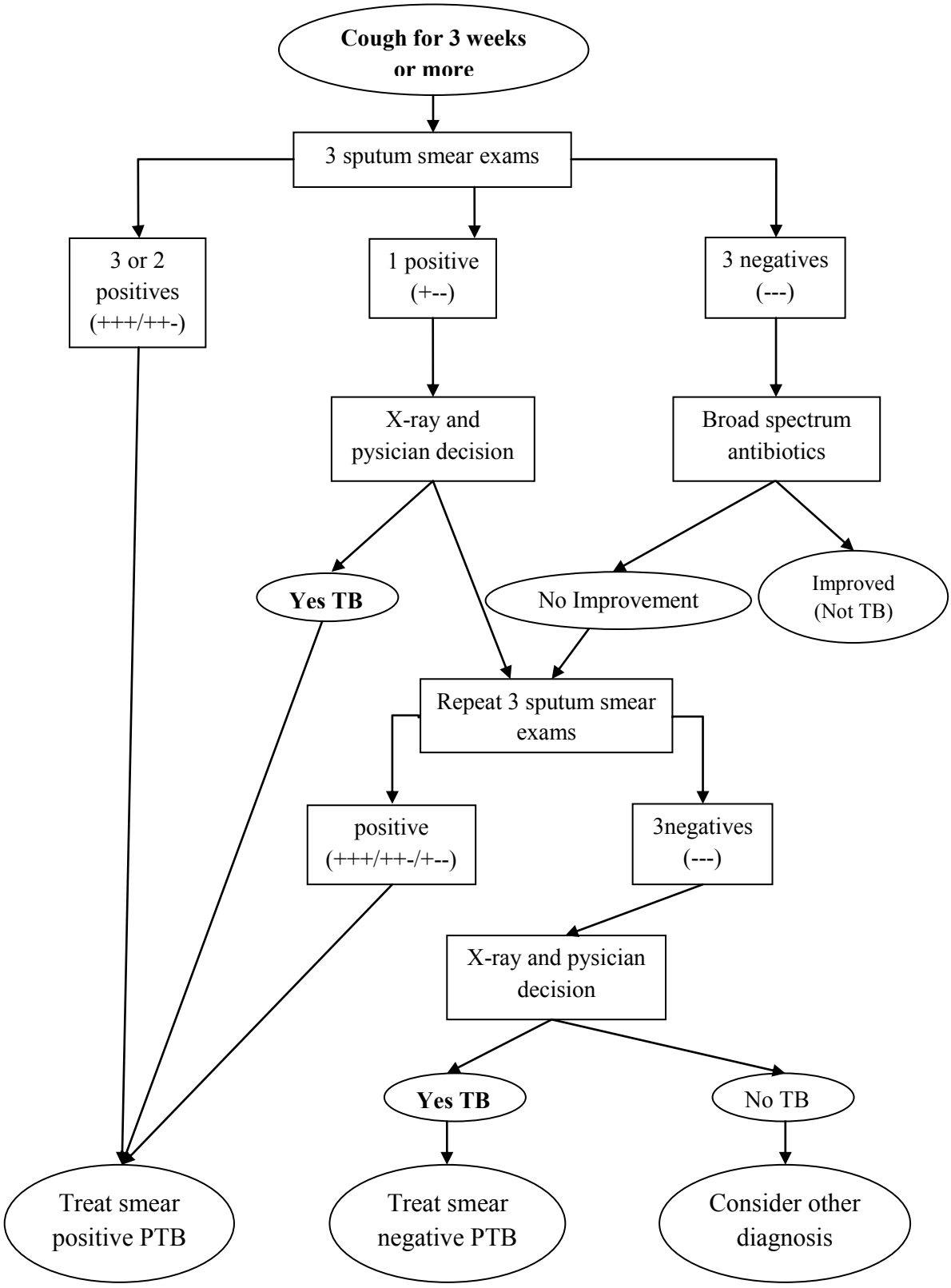

Figure 1.2 Diagnosis of Adult Pulmonary Tuberculosis (WHO, 1999)

1.7.1 Microbiological Investigation

Microbiological methods, smear, and culture for *Mycobacterium tuberculosis* remain as gold standards for definitive diagnosis but are insensitive when compared with microbiologic specimens for routine bacteria. Histology examination of tissue from various sites such as liver, lymph nodes, bone marrow, pleura or synovium that show the characteristic tissue reactions (caseous necrosis with granuloma formation) is useful for diagnosis of TB disease but not definitively indentified *Mycobacterium tuberculosis* as the causative agent, therefore culture should be obtained whenever possible. For suspected pulmonary TB, three consecutive morning sputum specimens are recommended for mycobacterial studies that include an initial smear and culture for *Mycobacterium tuberculosis* (Marion and High, 2009).

Mycobacterial culture is considerably more sensitive than microscopy for the diagnosis of TB (Lam *et al*., 2010). Classic culture using egg-based media takes up to 8 weeks for final result. There are radiometric methods such as BACTEC, which can give us result within 2 weeks that can be use for early diagnosis and in smear negative patients (MOH, 2002).

1.7.2 Chest X-Ray

A plain chest X-ray is usually preliminary radiological investigation in suspected TB (Parekh, 2009). Radiographic findings, like other diagnostic modalities, vary with age. Cavitations are more common in young than older adults with pulmonary TB. Further, young patients have more upper lobe infiltration while older patients are more likely to have a milliary or nonspecific pattern on chest radiograph (Marion and High, 2009).

1.7.3 Tuberculin Skin Test (TST)/ Mantoux

Tuberculin is a glycerin extract from the tubercle bacillus. Tuberculin skin test is important for diagnosis and prevention of TB that is more sensitive than Chest X-ray in identifying *Mycobacterium tuberculosis* infection. The tuberculin skin test should be evaluated within 48 to 72 hours after the patient is injected (Dale, 2003). Diameter of induration rather than erythema determines the interpretation. The American Thoracic Society and the Centre for Disease Control and Prevention (CDC) now proposes that different criteria must be applied to different population groups. Criteria for positive tuberculin skin testing shown in table 1.1.

Table 1.1 Criteria for Positive Tuberculin Skin Test in Different Risk Condition (DiPiro *et al*., 2008)

≥ 5 mm induration	≥ 10 mm induration	≥ 15 mm induration
HIV positive patients	Recent immigrants (within 5 years) from high prevalence countries	Any person, including persons with not known risk factors for TB.
A recent contact of a person with TB disease	Injection drug users	However, targeted skin testing programs should only be conducted among high-risk groups
Persons with fibrotic changes on chest radiograph consistent with prior TB	Residents and employees of high-risk congregate settings (includes long term care facilities)	
Patients with organ transplants	Mycobacteriology laboratory personnel	
Persons who are immune-suppressed for other reasons (e.g., taking the equivalent of >15 mg/day of prednisone for 1 month or longer, taking TNF- a antagonists	Persons with clinical conditions* that place them at high risk	
	Children <4 years of age, infants, children, and adolescents exposed to adults in high-risk categories	

Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995; 44 (RR: 11): 19-34

The disadvantage of tuberculin skin test it is time consuming. It may have more of a role in low TB-prevalent areas where HIV infection is also uncommon (Dale, 2003). Although tuberculin proved ineffective as a remedy for TB it was immediate discovery that repeated injections caused more rapid and severe skin reactions (Parekh, 2009).

1.7.4 Polymerase Chain Reaction (PCR)

Nucleic Acid Amplification Tests (NAA Test) are developed for rapid diagnosis of tuberculosis disease. In this method, mycobacterial DNA and RNA are directly detected in clinical specimens (Tang *et al*., 2006). Nucleic Acid Amplification Test by polymerase chain reaction can detect small numbers of organism. However PCR can give positive result in patients who are already on anti-TB treatment but still excreting small number of non-viable bacilli, thus this test not for patients‟ follow up of treatment (MOH, 2002).

1.8 Anti-Tuberculosis Drugs Regimen

The chemotherapy for pulmonary and extra-pulmonary TB is similar and should proceed according to 1). Cultures and drug sensitivity test results, 2). Combination of anti-TB drugs must be used. The most important reason for using two or more chemotherapy agents simultaneously is to prevent the emergence of drug-resistant TB organism, 3). Daily single dose of anti-TB drugs is preferred. Single-dose therapy is as effective as divided-dose therapy, because due to slow generation time of the tubercle bacillus achieves greater patients‟ acceptance and compliance, 4). Prolonged chemotherapy is necessary. Previous regimens used multiple drugs for period of 18 to 24 months, but with combinations of newer agents,

shorter regimens of 6 months have been found to be equally effective, and 5) Patients are closely followed up to ensure patients compliance, also to monitor drug efficacy and toxicity (Dale, 2003).

Treatment for TB of active disease, initial four-drug therapy is recommended, but, if the organism is isolated and susceptibility testing results are available, can be tapered to two-drug specific combination therapies (Marion and High, 2009).

Modern anti-TB drug was started by the discovery of streptomycin in 1944 by Schatz, Bugie, and Waksman, then para-amino-salicylate was discovered by Lehmann two years later (Zhang and Amzel, 2002). Main aims of anti-tuberculosis drug therapy are to eradicate all active metabolites bacteria in the pulmonary and eliminate less active replicates and near dormant bacteria that may cause disease relapse (Rivers and Mancera, 2008). Anti-TB drugs can be divided into first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide, and streptomycin) and second line drugs (para-amino-salicylic acid, cyloserine, ethionamide, quinolones, etc) (Peloquin, 2005). First-line anti-TB drug regimen primarily consists of isoniazid and rifampicin, and has already been used for many years for TB treatment and evidently effective in active, drug-susceptible TB, when patients have completed their course of treatment (Rivers and Mancera, 2008).

Isoniazid, one of the most important anti-TB drugs, that is highly specific for mycobacteria (Peloquin, 2005), is a pro-drug that needs to be activated by bacterial catalase-perokxidase to generate reactive oxygen species and reactive organic radicals, that then attack multiple targets in the tubercle bacillus (Zhang and Amzel, 2002).

Rifampicin interrupts on RNA synthesis by binding to the bacterial DNA-dependent RNA polymerase β-subunit (Zhang and Amzel, 2002) while streptomycin

inhibits initiation of mRNA translation, and facilitates genetic code misreading and ribosome inefficient proofreading (Zhang and Amzel, 2002).

Ethambutol affects the biosynthesis of major polysaccharide of mycobacterial cell wall (arabinoglactan) (Zhang and Amzel, 2002).

Pyrazinamide mechanism of action is by disruption of membrane function and energy metabolism, pyrazinamide is a nicotinamide analog also a prodrug that needs to be activated as pyrazinoic acid by the nicotinamidase enzyme (Zhang and Amzel, 2002). Mechanism action of anti-TB drugs can be seen in table 1.2.

Table 1.2 Anti-tuberculosis Drugs and their Targets (Zhang and Amzel, 2002)

Drugs	Mechanism of action	Targets
Isoniazid	Inhibition of cell wall mycolic acid synthesis, and other potential multiple effects on DNA, lipids, carbohydrates, and NAD metabolism	Multiple target including acyl carrier protein reductase (InhA), β-ketoacyl synthase (KasA)
Rifampicin	Inhibition of RNA synthesis	RNA polymerase unit
Pyrazinamide	Distruption of membrane function and energy	Membrane function and energy metabolism
Ethambutol	Inhibition of cell wall arabinogalactan synthesis	Arabinosyl transferase
Streptomycin	Inhibition of protein synthesis	Ribosomal S12 protein and 16SrRNA
Amikacin/Kanamycin /Capreomycin	Inhibition of protein synthesis	16SrRNA
Fluoroquinolones	Inhibition of DNA gyrase	DNA gyrase
Ethionamide	Inhibition of mycolic acid synthesis	Acyl carrier protein reductase (InhA)
Cycloserine	Inhibition of peptidoglycan synthesis	D-alanine racemase/synthase
Para-amino-salicylic acid	Inhibition of folic acid synthesis	Unknown

1.8.1 World Health Organization Tuberculosis Treatment's Guidelines

According to WHO, the aims of TB treatment are to cure patients and to restore patients‟ quality of life and productivity; to prevent patients‟ death due to active TB or its late effects; to prevent TB relapse; to reduce TB transmission to other person and to prevent drug resistant TB development and transmission (WHO, 2010b). Most TB treatments need more than one drug combination to eradicate TB bacteria. First line anti-TB drugs recommended for TB treatment by WHO are combination between isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin (WHO, 2010b). Anti-TB drugs standard regimens recommended by WHO can be seen on the table 1.3.

Table 1.3 Standard Treatment Regimens for TB Treatment (WHO, 2010b)

Tuberculosis status	Intensive Phase Treatment		Continuation Phase Treatment	
	Regimens	Freq/Duration	Regimens	Freq/Duration
New tuberculosis patient (presumed, or known, to have drug susceptible TB				
Standard regimen new TB patients	HRZE	Daily/2 months	HR	Daily/4 months
Acceptable alternative for any new TB patient receiving directly observed therapy	HZRE	Daily/2 months	HR	Three times per week/4 months
Acceptable alternative provided that patient is receiving directly observed therapy and is not living with HIV or living in an HIV prevalent setting	HRZE	Three times per week/2 months	HR	Three times per week/4 months
In setting where the level of isoniazid resistance among new TB cases is high and isoniazid susceptibility testing is not done (result not available) before the continuation phase begins	HRZE	Daily/2 months	HRE	Daily/4 months
Previously treated patients (relapse or defaulted) Standard regimens for previously treated patients depend on specimen for culture and drug susceptibility testing (DTS) result. DTS should be taken for at least isoniazid and rifampicin.				
In setting with conventional DTS method yield result within weeks or month, need to establish empirical regimens	HRZES	Daily/2 months	HRZE HRE	Daily/1 months Daily/5 months
In country with rapid DTS method	Depend on DTS result if there are any drug resistant tuberculosis occurred use the drug resistant regimens			

Recommended standard doses of each first-line anti-TB drug for adult by WHO can be seen in table 1.4.

Table 1.4 Recommended Doses of First-Line Anti-Tuberculosis Drugs for Adult

Drug	Recommended dose			
	Daily		3 Times per week	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Maximum (mg)
Isoniazid	5 (4-6)	300	10 (8-12)	900
Rifampicin	10 (8-12)	600	10 (8-12)	600
Pyrazinamide	25 (20-30)	-	35 (30-40)	-
Ethambutol	15 (15-20)	-	30 (25-35)	-
Streptomycin[a]	15 (12-18)		15 (12-18)	1000

[a]Patients aged over 60 years may not be able to tolerate more than 500–750 mg daily, so some guidelines recommend reduction of the dose to 10 mg/kg per day in patients in this age group (*2*). Patients weighing less than 50 kg may not tolerate doses above 500–750 mg daily (*WHO Model Formulary 2008*, www.who.int/selection_medicines/list/en/

Recommended second-line anti-TB drugs are cycloserine, ethionamide, streptomycin, amikacin-kanamycin, capreomycin, p-aminosalicylic acid (PAS) and levofloxacin, this second line drugs to substitute first-line anti-TB drugs in some certain case (DiPiro *et al*., 2008).

1.8.2 Ministry Of Health Malaysia Treatment's Guidelines

Modern therapy should cure almost all new diagnosed patients if an effective regimen is prescribed for an adequate period of time and if the patient ingests the prescribed medication regulary. A six months course of therapy has proven highly effective and reliable. Purposes of the treatment are to reduce morbidity, to prevent mortality, to prevent relapse of TB, to decrease transmission, and to prevent the emergence of multidrug-resistant TB (MDR-TB) (MOH, 2002).

Table 1.5 Anti-Tuberculosis Drugs and Recommended Dosage (MOH, 2010)

First line drug	Daily dosage		Biweekly dosage	
	mg/kg	max (mg)	mg/kg	max (mg)
Isoniazid (H)	5 – 8	300	15 - 20	1200
Rifampicin (R)	10 – 15	600	15 – 20	600
Pyrazinamide (Z)	20 – 40	1500	50	3000
Ethambutol (E)	15 – 25	1200	50	2000
Streptomycin (S)	15 – 20	1000	15 – 20	1000
Note : For patient more than 65 years of age, the dose of streptomycin should not exceed 750 mg				

Dosage regimen from MOH is almost the same as the dosage form recommended by World Health Organization. Figure 1.3 showed TB treatment categories in Malaysia accordingly to Ministry of Health Malaysia 2002. There are no newest guidelines regarding to TB treatments regimen. MOH categorizes TB into three categories, category I: new TB case, category II: for relapse patients and failure after interruption patients, and category III: patients with chronic case.

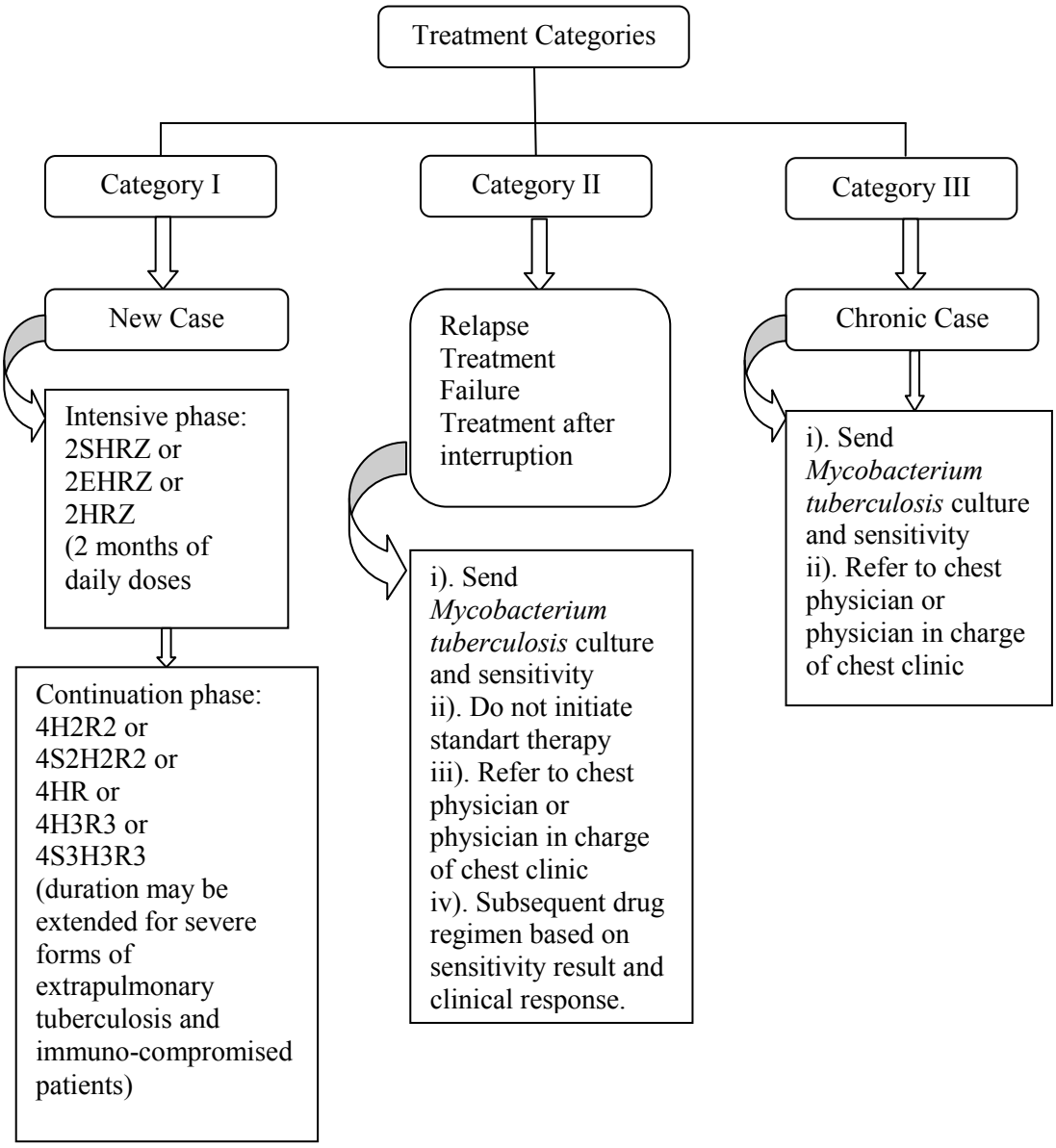

Figure 1.3 Treatment Categories and Regimen (MOH, 2010)

1.9. Adverse Drug Reactions (ADRs)

1.9.1. Definition of Adverse Drug Reactions

Adverse drug reaction is unwanted or unintended effect of medicines which occur during proper use of drugs. Definition of ADRs according to WHO is any noxious and unintended response of drugs that occurs at doses used for prophylaxis, diagnosis or therapy. Drug side effect definition, is any unintended effect of a pharmaceutical product that occur at normal dose usage which is related to the

pharmacological properties of the drug (Badyal and Bhatia, 2006). The simplest classification of ADRs is into type A and B reactions. The differences of those 2 types of ADRs can be seen in table 1.6.

Table 1.6 Differences of ADRs Type (Badyal and Bhatia, 2006)

	Type A	**Type B**
Drug response	Augmented	Bizarre
Pharmacologically predictable	Yes	No
Possible to reproduce in animals	Usually possible	Difficult
Dose-dependent	Yes	No
Dependence on host	Often independent	Usually dependent
Incidences	High	Low
Morbidity	High	Low
Mortality	Low	High
Treatment	Dose adjustment	Stop

Adverse drug reactions are common and often preventable causes of hospital admission, which has become an important challenge in today‟s modern medicine in terms of early recognition, proper management, and avoidability (Farcas *et al*., 2010). Although prescribers aim to use medicines that help patients and do no harm, no drug is administered without risk. Minimizing the occurrence of ADRs is the main challenge to do this effectively requires an understanding of their frequency, severity, predictability and reversibility. It is also helpful to have an appreciation of the patient groups that are predisposed to drug toxicity (Lee, 2001).

The diagnosis of an adverse reaction is the difficult part, if a patient taking medicines in differential diagnosis should include the possibility of ADRs (Edwards and Aronson, 2000). The most important problem in assessing ADRs is whether there is a causal relationship between the drug and the untoward clinical event

(Naranjo *et al*., 1981). The Naranjo Algorithm is a questionnaire designed by Naranjo *et al* in order to determine the possibility of whether an ADRs is actually due to the drugs rather than the result of other factors. The probability is defined through a score termed definite, probable, possible, and doubtful (Doherty, 2009).

Study on ADRs showed that antibiotics were responsible for 44.9% out of 250 episodes of ADRs observed in two pulmonology division of Catanzaro, Italy (Gallelli *et al*., 2002).

1.9.2 First-line Anti-tuberculosis Drugs Profile

First-line anti-TB that is commonly used in TB treatment is a combination of two or more anti-TB drugs such as isoniazid, rifampicin, pyrazinamid, ethambutol, and streptomycin. The necessity of using of multidrug regimens has been associated with increased incidence of ADRs of anti-TB drugs. This ADRs may be mild as well as fatal (Gulbay *et al*., 2006).

Anti-TB agent that is commonly used such as, isoniazid, rifampicin and pirazinamide are highly effective but also can cause hepatotoxicity (Singla *et al*., 2010). Treatment of people with TB requires treatment for at least six months, and sometimes patients may find difficulty in completing their treatments. This poses a major constraint to eradicating the disease (Volmink and Garner, 2009). Drug‟s profile of first-line anti-TB drugs is listed on table 1.7.

Table 1.7 First-line Anti-Tuberculosis Drugs Profile (Lacy *et al*., 2008).

Anti-tuberculosis Drugs	Drugs Profile (Precaution, ADRs and Monitoring)
Isoniazid	Warnings/precaution: use with caution in patients with severe renal impairment and liver disease Adverse Drug Reactions: a. Cardiovascular: hypertension, palpitation, tachycardia, vasculitis b. CNS: depression, dizziness, encephalopathy, fever, lethargy, memory impairment, seizure, slurred speech, c. Dermatologic: flushing, rash, Endocrine and metabolic: hyperglycemia, metabolic acidosis, pellagra, pyridoxine deficiency, d. GI: anorexia, nausea, vomiting, stomach pain e. Hematologic: agranulocytosis, anemia (sideroblastic, hemolytic or aplastic), eosinophilia, thrombocytopenia f. Hepatic: hyperbillirubinemia, billirubinuria, jaundice, hepatitis, hepatic dysfunction g. Neuromuscular and skeletal: athralgia h. Ocular: blurred vision, loss of vision, optic neuritis and atrophy i. Miscellaneous: Lupus-like syndrome, lymphadenopathy, rheumatic syndrome. Monitoring parameters: baseline and periodic LFT; sputum cultures monthly
Rifampicin	Warnings/precaution: in liver impairment (caution n modify dosage) Adverse Drug Reactions: a. Cardiovascular: edema, flushing b. CNS: ataxia, behavioral changes, concentration impairment, dizziness, drowsiness, fatigue, fever, headache, numbness, psychosis. c. Dermatologic: pemphigoid reaction, pruritis, urticaria d. Endocrine and metabolic: adrenal insufficiency, menstrual disorder e. Hematologic: agranulocytosis (rare), DIC, eosinophilia, hemoglobin decreased, hemolysis, hemolytic anemia, leukopenia, thrombocytopenia f. Hepatic: hepatitis (rare), jaundice g. Neuromuscular and skeletal: myalgia, osteomalacia, weakness h. Ocular: exudative conjungtivitis, visual changes i. Miscellaneous: flu like syndrome j. GI (1-2%): anorexia, cramps, diarrhea, epigastric distress, flatulence, heart burn, nausea, pancreatitis vomiting Monitoring parameters: periodic (baseline and every 2-4 weeks during therapy) LFT, CBC, hepatic n mental status, sputum culture, chest X-ray
Pyrazinamide	Warnings/precaution: use with caution in patients with history of alcoholism, renal failure, chronic gout, DM or porphyria Adverse Drug Reactions: 1% to 10% a. CNS : malaise b. GI : anorexia, nausea, vomiting c. Neuromuscular and skeletal : athralgia, myalgia <1% (limited to important to life-threatening) : acne, angiodema (rare), anticoagulant effect, dysuria, fever, gout, hepatotoxicity, interstitial nephritis, itching, photosensitivity,

	porphyria, rash, sideroblastic anemia, thrombositopenia, urticaria Monitoring parameters : periodic LFT, serum uric acid, sputum culture, chest X-ray 2-3 months into treatment and at completion.
Ethambutol	Adverse Drug Reactions: a. Cardiovascular: myocarditis, pericarditis b. Central Nervous System: headache, confusion, disorentation, malaise, mental confusion, fever, dizziness, hallucination c. Dermatologic: rash, pruritis, dermatitis, exfoliative dermatitis d. Endocrine and metabolic: acute gout or hyperuricemia e. Gastrointestinal: abdominal pain, anorexia, nausea, vomitting f. Hematologic: leukopenia, thrombocytopenia g. Hepatotoxicity, hepatitis h. Neuromuscular and skeletal: Arthralgia i. Ocular: optic neuritis ; symptom may include decrease acuity, scotoma, color blindness, or visual defects (usually reversible with discontinuation, irreversible blindness has been described) j. Renal: nephritis k. Respiratory: infiltrates, pneumonitis l. Anaphylaxis Monitoring parameters, baseline and periodic (monthly) visual testing (each eye individually as well as both eyes tested together); baseline and periodic renal, hepatic and hematopoietic tests.
Streptomycin	Warnings/precaution: May cause neurotoxicity, nephrotoxicity, and/or neuromuscular blockade and respiratory paralysis Adverse Drug Reactions: a. Cardiovascular: hypotension b. CNS: neurotoxicity, drowsiness, headache, drug fever, paresthesia c. Dermatologic: skin rash d. GI: nausea, vomiting e. Hematologic: eosinophilia, anemia f. Neuromuscular and skeletal: athralgia, weakness, tremor g. Otic: ototoxicity (auditory), ototoxicity (vestibular) h. Renal: nephrotoxicity i. Respiratory: difficulty in breathing Monitoring parameters: hearing (audiogram), BUN, creatinine; serum concentration of the drug should be monitored

1.10. Drug-Resistant Tuberculosis (DR-TB)

There are many reasons that TB still became world health problem including poverty, social deprivation and also lack of health services in certain countries (Breathnach *et al,* 1998). Increasing incidence of *Mycobacterium tuberculosis* strain