Antituberculosis

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Antituberculosis

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Abstract

Tuberculosis (TB) is an airborne infection caused by Mycobacterium tuberculosis which can be fatal. The first antituberculosis agent discovered is streptomycin. Combination of drug therapy is used to prevent resistance. BCG vaccine prevents TB in children. Symptoms of TB are coughing, fever, weight loss, night sweats and chest pain. High risk population includes elderly, baby and patient with weak immune system. Two types of TB are childhood-type tuberculosis and adult-type tuberculosis. There are 4 types of first-line antituberculosis drugs: isoniazid, rifampin, pyrazinamide and ethambutol. Isoniazid is used in latent tuberculosis and preventive treatment. It inhibits biosynthesis of mycolic acid. It is absorbed in gastrointestinal tract, distributed into all body fluids include CNS, metabolised in liver, and excreted in kidney. Side effects of isoniazid include peripheral neuritis and hepatotoxicity. Rifampin belongs to rifamycin group which inhibits bacterial enzyme for DNA transcription. It is absorbed orally, distributed into many organs and body fluids, metabolised in liver, and excreted through bile. Side effect of rifampin is gastrointestinal disturbance. Pyrazinamide is usually used in combination with isoniazid and rifampicin. It inhibits fatty acid synthetase in bacteria. It is absorbed in gastrointestinal tract, distributed into most fluid and tissues, and excreted by kidney. Side effects of pyrazinamide include stomach upset and jaundice. Ethambutol is a bacteriostatic agent which inhibits synthesis of metabolites important in cell metabolism. It is absorbed orally, distributed widely, metabolised in liver and excreted in kidney. Side effects of ethambutol include hyperuricemia and optic neuritis. Preventive measures for tuberculosis include awareness campaign, administration of antibiotic and isolation of TB patient. In conclusion, TB is fatal and contagious disease that can caused death and has infected one-third of the world’s population. It is a windborne disease and can be transmitted from an infected person to another through coughing, sneezing, spitting, discharging mucus or even kissing. [2] Recently, the case of tuberculosis increased due to the owing to HIV infection, immigration, increased trade and globalization. [3] The cell wall of Myobacterium tuberculosis is made up of two segments, upper and lower. The peptidoglycan of Myobacterium tuberculosis is covalently attach to arabinogalactan which in turn is attached to mycolic acid with their long meromycolate and short alpha chains. This is the cell wall core of Myobacterium tuberculosis and is known as mycolyarabinogalactan-peptidoglycan complex. The upper segment of cell wall is made up of free lipids, some with longer fatty acids complementing the shorter alpha chain and vice versa. Cell wall proteins, phosphatidylinositol mannosides, the phthiocerol containing lipids, lipomannan, and lipoarabinomannan also can be found at upper segment of cell wall. [4] The cell envelope of M.tuberculosis also contain an additional layer beyond peptidoglycan that rich in unusual lipids, glycolipids and polysaccharides. [5] M.tuberculosis is an intracellular pathogen. M.tuberculosis is able to parasite human mononuclear phagocytes. [6] M.tuberculosis will spend most of its life cycle in macrophages. [7] M.tuberculosis has the ability to multiply inside the macrophage phagosome. M.tuberculosis can remain dormant for few years without the symptoms. When the immune system of the hosts is low, the dormant M.tuberculosis will become active and cause the infection. [8] There are two types of tuberculosis that is childhood-type tuberculosis and adult-type tuberculosis. Childhood-type tuberculosis occurs in infants or immunosuppressed patients such as HIV patients. Adult-type tuberculosis often occurs in immunocompetent adults. The immune system of host is strong enough to resist the activation of tuberculosis. [9] Multi drug resistant tuberculosis is defined as tuberculosis that caused by the strain of M.tuberculosis is resistant to two or more anti-tuberculosis drugs. M.tuberculosis can develop resistant to an antituberculosis agent spontaneously or under the selective pressure of antibiotics. [10] The resistance is due to the highly hydrophobic cell envelope act as permeability barrier. The hydrolytic or
drug modifying enzymes present in M. tuberculosis also contribute to drug resistance. [5] The combination of therapy effective in preventing the emergence of resistance compare to monotherapy. The rate at which resistance emerges for ethambutol is the highest while the lowest for rifampin and quinolones. [11]

**History of drug discovery and role of vaccine**

Streptomycin is the 1st antituberculosis agent that discovered by Waksam and his team in the year 1943. Following Streptomycin, there is several antituberculosis agents that is being discovered. For example, p-aminosalicylic acid(1949), isoniazid(1952), pyrazinamide(1954), cycloserine(1955), ethambutol(1962) and rifampin(1963) that serve as antituberculosis agents.[12] Due to the present of drug resistant M. tuberculosis, the combination therapy was introduced to overcome this problem.[13]

Vaccine plays an important role to control and eliminate tuberculosis worldwide. The effective vaccine against tuberculosis has not been developed. The currently available vaccine is BCG, an attenuated M. bovis which only effective in reducing childhood tuberculosis but not for adult tuberculosis. So, the people who have been vaccinated with BCG still can be infected by M. tuberculosis. [14]

**Symptom and diagnosis of Tuberculosis**

The patients that have been infected with tuberculosis will have cough, fever, feel tired, weight loss, sweats, anorexia or loss of appetite, chest pain, diarrhea, and hemoptysis or coughing out of blood. [15]

Tuberculin Skin Test and Interferon-Gamma released assays can be used to determine whether a person is infected by M. tuberculosis. [16] The person is indicated with the infection by tuberculosis when tuberculin injection caused the area of injection become hard, swollen and red within one to three days.

Purified protein derivative (PPD) or known as Mantoux can also be used to indicate the presence of tubercular infection. [17] Tuberculosis can also be diagnosed based on the two specific antigens ESAT-6 and CFP 10 of M. tuberculosis. [18]

**Population of high risk**

Population that has high risk for tuberculosis of infection are the old man, baby, HIV patients, diabetes patients, cancer patients, organ transplant recipients, people with kidney disease, people that have treatment for autoimmune disease, malnourished individual and people that expose to TB most of the time. [19] Alcohol and drug abuse will increase the chances for reactivation of latent tuberculosis. [20]

### Anti-tuberculosis drugs

**ISONIAZID**

Isoniazid is a synthetic isonicotinic acid-derivative antimycobacterial agent, used for the treatment of tuberculosis caused by Mycobacterium tuberculosis. It has been prescribed for use in latent tuberculosis treatment or preventive treatment of clinical tuberculosis in HIV patients [20]. It is bactericidal towards fast-growing mycobacteria, but is bacteriostatic to slow-growing mycobacteria [21].

**Trade name:** INH, Laniazid, Nydrazid

**Generic name:** Isoniazid

**Chemical name:** 4-Pyridinecarboxylic acid, hydrazide

**Mechanism of action and resistance**

Isoniazid act as a prodrug and it is activated by the mycobacterial catalase-peroxidase. The production of INH-NAD and INH-NAPD will inhibit the different steps in biosynthesis of mycolic acid, which is the cell wall lipid [22]. This makes the M. tuberculosis more susceptible to reactive oxygen radicals. Isoniazid is active to mycobacterium only during the bacterial cell division. The bactericidal or bacteriostatic action on mycobacterium depends on the concentration of drug at the site of infection and the susceptibility of the infecting organism [21]. Resistance to isoniazid may be due to the mutation of Ser315THR in an enzyme, which makes the enzyme unable to activate isoniazid but still retains its catalase-peroxidase activity [23].

**Dose**

Isoniazid is available in tablets (50, 100, 300mg), syrup (50mg/5ml) and aqueous solution (100 mg/ml) intravenous or intramuscular injection. The recommended dose for adult is 5mg/kg (maximum 300mg) daily or 15mg/kg (maximum 900mg) once, twice, or three times weekly. For children, the recommended dose is 10-15 mg/kg (maximum 300mg) daily or 20-30 mg/kg (900mg) twice weekly [24].

**Pharmacokinetic**

Isoniazid is absorbed from the gastrointestinal tract after taken orally [20]. The peak plasma concentration of drug is reached within 1 to 2 hours after ingestion. The extent of absorption and bioavailability will be reduced when isoniazid is administered with food [25]. Only about 0% to 10% of isoniazid bind to protein. It distributes readily into all body fluids and tissues, which includes cerebrospinal fluid, skin, sputum, lungs, saliva, muscle [1]. Skin contains a large amounts of drug and acts as a storage depot. Isoniazid also crosses placenta and breast milk [25].

The major route of isoniazid metabolism is hepatic N-acetylation in liver to produce acetylisoniazid. It undergoes several process and finally concerted to reactive metabolite by hepatic microsomal enzyme,
this active metabolite may cause hepatotoxicity. The isoniazid acetylation is genetically determined and may varies from one individual to another [25]. Isoniazid is excreted as unchanged drug and metabolites primarily by kidneys. It is also excreted though breast milk. Other than that, small amounts of isoniazid are excreted in saliva, sputum and feces[25]. The plasma half-life of isoniazid ranges from 1 to 4 hours in patients with normal renal and hepatic function. The half life may be prolonged to 4.3 hours in patient with liver or renal failure.

**Side effect**

One of the most common adverse effect of isoniazid is peripheral neuritis, the signs and symptoms include clumsiness and burning or paresthesia of the hands and feet[20]. This effect is dose-related. The other most common adverse drug reaction is hepatotoxicity. The drug is metabolized to mono-acetylyhydrizine and probably responsible for the hepatotoxicity[26]. Another adverse effect is hypersensitivity reaction with symptoms such as fever, skin eruptions and hypotension. Other isoniazid-induced effects include gastrointestinal disturbances, dryness of mouth, hyperglycemia, urinary retention, pyridoxine deficiency, pellagra and gynecomastia in males[20]. Central nervous system effects such as dysarthria, seizures, dysphobia and inability to concentrate also have been reported with the use of isoniazid[24].

**Precaution, contraindication and drug interaction**

Isoniazid may cause severe hepatotoxicity, if signs and symptoms of hepatotoxicity occur the use of drug should be stopped immediately. Isoniazid should be taken with meals when gastrointestinal irritation occurs. Breast milk is one of the route of excretion of isoniazid, thus, breast-feeding is not encouraged. Patients who are slow acetylators may require a lower dose because slow acetylation results in higher serum concentration of isoniazid which will lead to toxicity. Renal failure patients with the use of isoniazid should be given supplemental pyridoxine to reduce isoniazid-induced neurotoxicity. If hypersensitivity reaction occurs at first sign, the drug has to be discontinued promptly. Isoniazid is contraindicated in patients with hypersensitivity to isoniazid. Cross sensitivity also may occur in patients hypersensitive to ethionamide, pyrazinamide, niacin or other chemically related medications [20]. Isoniazid should not be used in patients with acute liver disease as isoniazid will precipitate porphyria. In patients with epilepsy, convulsions may be precipitated[25]. Its drug interactions include the administration of isoniazid with carbamazepine, it may result in the increase of serum carbamazepine levels as isoniazid inhibit the metabolism of carbamazepine. This will cause carbamazepine toxicity. The use of isoniazid in patients receiving cycloserine and ethionamide may lead to the ineffectiveness of BCG vaccine. Daily use of alcohol will increase the metabolism of isoniazid and the risk of hepatotoxicity. Thus, dosage adjustment is necessary in patients who are alcoholics. Concurrent use of ketoconazole also has been reported to reduce serum concentrations of ketoconazole. The concurrent use of phenytoin with isoniazid will increase phenytoin serum concentrations and toxicity may occur. Hydroxide-containing antacids may delay and decrease the absorption and serum concentration of isoniazid.

**RIFAMPIN**

Rifampin is an antibiotic belongs to rifamycin group that is usually used to treat tuberculosis. Its effect is usually bactericidal. It is a semisynthetic drugs produced by fermentation of a strain of Streptomyces mediterranei[27].

**Trade name : Rifampicin**

**Generic name : Rifampin, Rifamycin AMP**

**Chemical name :** 3-[[4-Methyl-1-piperazinyl]imino[methyl]rifamycin

**Mechanism of action and resistance**

Rifampin selectively inhibit the bacterial cell DNA-dependent RNA polymerase, the enzyme which is responsible for DNA transcription, by binding its beta-subunit, thus preventing transcription to mRNA and subsequent translation to protein[29]. It works by forming a stable drug-enzyme complex. However, it does not affect mammalian RNA polymerase and hence not interfere with the RNA synthesis in the human being. Rifampin is found to be most active during cell multiplication[28]. Bacteria resistant to rifampin as a result of mutations leading to a change in structure of B-subunit[29].

**Dose**

Rifampin can be administered via oral route or parenteral route (intravenous injection). The recommended dose for treatment of tuberculosis is 10mg/kg (maximum 600mg/day) intravenously once daily, twice weekly or 3 times a week[2]. A 6 months regimen which include rifampin, isoniazid, pyrazinamide, ethambutol for the first 2 months, isoniazid and rifampin for the following 4 months, is recommended[28].

**Pharmacokinetic**

Rifampin has approximately 90-95% bioavailability. It is readily absorbed from the gastrointestinal tract. Peak serum level achieve between 2 to 4 hours after the oral administration of the drug. The intake of food may delayed but not decrease the absorption of the drug[28]. About 60 to 90% of the drug is bound to the plasma protein. It is distributed widely throughout the
body in many organs and body fluids such as lungs, liver, bile, and urine. Rifampin can used to prevent and treat meningitis as it can enter the cerebrospinal fluid. It can as well enter the breast milk[27]. Approximately 60% to 80% of the drug was metabolized in the liver. Rifampin undergoes enterohepatic recirculation and is rapidly metabolized to its main and active metabolite, desacetyltrifampin. Small amount of the drug was metabolized to Formylrifampin which has 10% of antibacterial activity[28]. About 15% to 30% of the drug are cleared via renal route, but only 7% of the drug will be excreted unchanged in the urine. Approximately 60% to 65% of the drug is excreted via bile in the faeces[27]. The half life of rifampin is between 1.5 to 5 hours and prolonged in presence of hepatic impairment[27].

Side effect
Gastrointestinal disturbance such as heartburn, anorexia, nausea, diarrhea, vomiting and cramp can occur. Severe condition may even lead to pseudomembranous colitis[28]. Headache, drowsiness, fatigue, mental confusion, visual disturbance, fever, generalized numbness and menstrual disturbance have been reported regarding the use of rifampin[28]. Hypersensitivity reaction is commonly seen in patient who use rifampin. Patient will exhibit a flu-like syndrome such as fever, chills, decrease in the blood pressure and shock. Occasionally, rash, erythema, urticaria, pruritus, eosinophilia, sore mouth and exudative conjunctivitis have also occurred[28]. Thrombocytopenia, leukopenia, purpura, hemolytic anemia and hemolysis have occurred with rifampin[28]. The occurrence of mortality associated with the hepatotoxicity has been reported to be 16 in 500,000 patients who receiving rifampin[28].

Precaution, contraindication and drug interactions
Concomitant use with etravirine or nevirapine, patient should be reminded that they should not coadminister with rifampin. Concurrent use with halothane should be avoided if possible. Patients who take rifampin are not recommended to concomitant use with maraviroc, if can’t be avoided, dose adjustment is necessary. Patient who suffers from diabetes mellitus should be advised not to take rifampin as this can make the diabetes management more difficult. Taking higher than normal doses (doses higher than 600mg once or twice weekly) will increase the risk of serious side effect, including shortness of breath, shock, anaphylaxis, and renal failure. Intentional or accidental interruption of daily regimen might lead to renal hypersensitivity reaction[28]. Rifampin was contraindicated in patient with known hypersensitivity to rifampin, any component of the product, or any of the rifamycin. Rifampin was also contraindicated in patient who are receiving atazanavir,darunavir, fosamprenavir, sequinavir, or topranavir due to the potential of rifampin to decrease plasma concentration of these antiviral drugs[28]. Its drug interaction include concurrent consumption of alcohol which may increase the risk of hepatotoxicity[27]. Rifampin is a potent inducer of hepatic p450 oxidative enzymes. It may decreased the half life and serum level of numerous drugs, such as oral anticoagulants, oral contraceptives, cyclosporine, ketoconazole, anticonvulsants (phenytoin), digitoxin, antiarrhythmics, antifungal,B-blocker, antidiabetics, antibiotic and corticosteroid[27]. Concurrent use of isoniazid with rifampin may greatly increase the risk of hepatotoxicity, patients should be monitored closely for signs of hepatotoxicity during the first 3 months of therapy[27]. The concomitant antacid administration such as aluminum hydroxide, magnesium trisilicate or sodium bicarbonate may reduced the oral absorption of rifampin[27]. Rifampin might reduce the efficacy of oral contraceptives because of the rapid destruction of oestrogen by rifampin[27].

**PYRAZINAMIDE**
Pyrazinamide is a nicotinamide analogue which is one of the essential first-line drug in combination with isoniazid and rifampicin for the treatment of tuberculosis[34]. Pyrazinamide kills 95% population of semi-dormant microorganism which only active in acidic environment found at the site of inflammation[30,34].Pyrazinamide is a becteriostatic agent[32].

**Trade name: Rifater**
Generic name: pyrazine-2-carboxamide
Chemical name: Pyrazinecarboxamide

**Mechanism of action resistance**
Pyrazinamide is a prodrug that is converted into pyrazinoic acid by bacterial pyrazinamidase[31]. Pyrazinonic acid and its analog 5-chloro-PZA inhibited the fatty acid synthetase I (FASI) of M. Tuberculosis[32]. Pyrazinonic acid disrupted membrane energetics and inhibited membrane transport function in Mycobacterium tuberculosis[31]. Accumulation of pyrazinoic acid in acidic conditions leads to acidification of the cytoplasm and damage the cell[35].Mycobacterial pyrazinamidase is encoded by pncA, and mutations in this gene have been demonstrated as the major mechanism of PZA resistance[35].M bovis and M bovis BCG, are naturally resistant to pyrazinamide. In these organisms, pyrazinamide resistance is due to a unique C to G point mutation in codon 169 of pncA[36].

**Dose**
Daily regimen : 25 mg/kg (20-30 mg/kg) body weight
as a single daily dose.

Intermittent regimen : 35 mg/kg (30-40 mg/kg) body weight 3 times a week as a single dose[37].

Pharmacokinetic

Pyrazinamide is well absorbed from the gastrointestinal tract[33]. The mean pyrazinamide tmax value is 1.6 hours[37]. Pyrazinamide is widely distributed to most fluids and tissues, including liver, lungs, kidneys, and bile. Pyrazinamide has excellent penetration into CSF[33]. The volume of distribution is 0.57-0.84 l/kg. The plasma protein binding of pyrazinamide is low, which is approximately 10-20%[37]. Pyrazinamide is hydrolyzed by a microsomal deamidase to pyrazinoic acid, an active metabolite, and then hydroxylated by xanthine oxidase to 5-hydroxy pyrazinoic acid[33]. Pyrazinamide is eliminated renally, mostly in the form of metabolites[37]. Within 72 hours, approximately 3% of unchanged pyrazinamide, 33% of pyrazinoic acid, and 36% of remaining identifiable metabolites excreted in urine[33]. In dialysis, A single 3- to 4-hour hemodialysis session reduces serum pyrazinamide concentrations by approximately 55% and pyrazinoic acid concentrations by 50 to 60%[33]. The half-life of pyrazinamide is approximately 10 hours. The half-life for the active metabolite pyrazinoic acid after a single dose is approximately 10-20 hours[37].

Side effect

The main side effects cause by pyrazinamide are stomach upset such as nausea, vomiting and diarrhoea[41]. It also may cause flu like symptoms such as chills, fever, dizziness and bone pain[37]. Jaundice is one example of adverse effect which is the yellowing of the skin or eyes[43].

Precaution, contraindication and drug interactions

If hyperuricemia is accompanied by acute gouty arthritis, pyrazinamide should be discontinued[37]. Pyrazinamide should be used with caution in patients with a history of diabetes mellitus, as management may be more difficult[41]. If you become pregnant while taking this medicine, tell your doctor immediately. If you are about to be started on any new medicine, remind your doctor and pharmacist that you are taking Pyrazinamide-AFT[39]. Patient cannot stop taking pyrazinamide when they feel better because some of the causing agent may not be killed and continue to grow and TB onfection may return[42]. Pyrazinamide is contraindicated in patients with hypersensitivity to the active substance or to any of the excipients[37]. This drug is also contraindicated in severe hepatic damage patient with acute gout[41]. Pyrazinamide may interfere with administration of Probenecid and Allopurinol. Pretreatment with pyrazinamide prolonged the half-life of probenecid without changing its plasma-binding. As the rate of probenecid metabolism is decreased, its uricosuric action tends to be prolonged and the effect of PZA lessened[39]. Therefore, concomitant use should be avoided[37]. Allopurinol increased the concentration of pyrazinoic acid in blood[31]. Despite decreasing uric acid synthesis, allopurinol increased plasma concentrations of pyrazinoic acid, which is directly responsible for the inhibition of renal urate secretion[40]. Since pyrazinoic acid inhibits urate elimination, allopurinol is not effective in treating pyrazinamide-associated hyperuricaemia[37].

ETHAMBUTOL

It is an antimycobacterial agent belongs to ethylaminobutan[44]. Ethambutol effective against strains of Mycobacterium tuberculosis but it is not active against fungi, viruses, or other bacteria[45].

Ethambutol is considered as bacteriostatic[46] against tubercle bacilli, and bacteria that resistant to other antimycobacterial agents.

Trade Name: Myambutol[47]

Generic Name: Ethambutol

Chemical name : (+)-2,2’-(Ethylenedimino)-di-1-butanol dihydrochloride

Mechanism of action and resistance

It inhibits the synthesis of metabolites important in cell metabolism and bacterial multiplication by preventing the incorporation of mycolic acids. Inhibition of the cell wall synthesis occurs by inhibiting arabinosyl transferases which is involved in cell wall biosynthesis. This leads to an increase in cell wall permeability[48][49]. Resistance might develop when ethambutol is used alone for treatment of tuberculosis, resistance developed might occur in vitro susceptibility test[49].

Dose

Ethambutol should not be used alone or with single administration, in initial treatment or in retreatment[46][50][51]. Recommended doses for treatment in EMB for patient with normal function is 15 mg/kg/day, but higher doses is considered in certain condition[52].

Pharmacokinetics

Orally, it is well absorb. A peak serum concentration of approximately 4 mg/l is achieved in 2-4 hours following the intake of 15 mg/kg body weight. Volume of distribution is found to be 3.9 l/kg and plasma protein binding is 25%. It is widely distributed except in CNS. Food intake will have some influence on their absorption in gastrointestinal tract. From the recent studies, it was stated that serum concentration in children were much lower than the serum concentration in adults following the similar dose. Recent reports stated that about 10-40% of the drug is
bound to plasma protein. Metabolism of this drug occurs in the liver[44]. It is converted to inactive aldehyde and carboxylic acid metabolites[53]. Elimination of ethambutol is 50 to 70% through kidneys[44]. The elimination of the drug is delayed in subjects with renal impairment. Its half-life is about 4 hours initially and 10 hrs subsequently[54].

**Side effect**

Development of hyperuricemia is associated with prolonged drug administration[55]. Generally, uric acid is filtered by glomerulus but 98% of the filtrate will be reabsorbed back in the proximal convoluted tubule[55][56]. However, ethambutol appears to alter the excretion of uric acid by reducing its glomerular filtration rate and enhancing the tubular reabsorption of uric acid and also by blocking tubular secretion of this organic acid that leads to increase of serum urate concentration[55][57].

Another study found the effect on optic neuritis[59][60]. This visual impairment is a result of retrobulbar neuritis of the eye, which is generally reversible and is related to the dose and duration of treatment. This occur as central fibres of nerve are effected, causing blurring of vision and loss of ability to see green colour and sometimes red[53]. The frequency depends on the dose and duration of therapy[54][58][60].

**Precaution, contraindication and drug interaction**

Recently, ethambutol can cause optic neuropathy, and without discontinuation, leading to optic chiasm[58]. Ethambutol is contraindicated in renal impairment patient. Excretion of ethambutol is via kidney and thus high blood concentrations may readily produce ocular toxicity in renal impairment patients. Ethambutol also contraindicated in patients with optic neuritis[53][54]. Discontinuation of taking ethambutol should be stressed when ethambutol-induced ocular toxicity is recognised and the patients should be referred to an ophthalmologist for further evaluation[58]. It is also contraindicated with the patients who hypersensitivity with this drug[54][61]. Drug interaction include disulfiram, may increase the risk for ocular toxicity if taken along with ethambutol during therapy. Aluminium hydroxide could impair the absorption of ethambutol in gastrointestinal tract. Ethambutol with combination of Isoniazid or pyridoxine might increased the concentration of uric acid in serum.

**Preventive Measure**

Anti-tuberculosis campaign is one form of society fight[62]. By this way, society can gain knowledge on how to prevent tuberculosis infection. This campaign is a very crucial way to warn and educate publics on how dangerous is the infection. By then, it will increase the awareness of community about this disease. Another way of Tuberculosis prevention is by drug therapy which is through the administration of antibiotic. This kind of therapy is for those who are in closed contact with tuberculosis patient and also their family members which have a high risk to get TB infection. Examples of antibiotics you can take to prevent from infection are isoniazid, PAS and Streptomycin[63]. TB patient should isolate themselves from public during first few weeks of treatment because they are still highly contagious. They should avoid going to the crowded place. During isolation, patient with tuberculosis have to stay away from others who may be vulnerable to acquired active TB disease. In hospital, patients are placed in a negative pressure room with closed door away from other patients[64]. Negative pressure room ensures that air can only blow in and not out because the air pressure inside the room is lower than that outside the door.

**Conclusion**

Tuberculosis is a fatal and contagious disease caused by a type of bacteria, called Mycobacterium Tuberculosis. It can affect any part of our body but mainly at lungs which is named Pulmonary Tuberculosis[66]. There are 60% of the TB patient who are unwilling or unable to receive treatment died each year. However, 90% of the TB patient are completely cured and recover after received whole course of treatment. The populations who are in high risk of getting tuberculosis include HIV infected patients, chronic alcoholic, drug addicts, infants, elderly people, diabetic patients as well as health care professionals. Tuberculosis usually spreads by airborne droplets through coughing, sneezing, speaking and kissing[82]. The diagnosis of TB made on the basis of the laboratory test results. The standard test for tuberculosis is tuberculin skin test, which also known as mantoux test. It is used to detects the presence of infection, not of active TB. Another method is through examine the chest x-ray. The first indication of TB is an abnormal chest x-ray or other test result rather than physical discomfort[69]. In addition, sputum specimen can be obtained for microscopy test and culture. Besides, tuberculosis can be detected by some clinical sign and symptoms. The clinical sign and symptoms include prolonged cough, sputum with blood stained, loss of appetite, loss of weight, breathing difficulties, chest pain, fever and night sweat. The whole course of tuberculosis treatment requires duration of 6 months to 12 months, this depend on the condition of patients. Its initial treatment include the use of 4 types of drugs, such as isoniazid, rifampin,
ethambutol and pyrazinamide for first 2 months. The continuous treatment for the last 4 months involve only 2 drugs, which are isoniazid and rifampin. Patients who does not receive treatment or take medicine regularly may causes relapse and acquired drug resistance. Multiple-Drug Resistance (MDR) TB and extensive drug resistance (XDR) TB may emerge as a result of irregular treatment. To avoid this problem, Directly Observe Treatment (DOT) must be practiced. The preventive measure that should be taken by public to avoid from getting TB disease is know more and aware about TB by participate themselves in anti-TB campaigns. This can raise their awareness about the sign and symptoms, how TB is transmitted and the treatment involved. Besides, for the family members or people who has close contact with TB patients, they should take some antibiotics such as isoniazid as prophylaxis to prevent them from getting TB. Besides, they should have regular check up in hospital to make sure themselves not infected by TB. They can also receive vaccination to prevent from infected by TB. Vaccination with BCG does not prevent infection by *M. tuberculosis* but it does strengthen the immune system of first-time TB patients. As a result, serious complications are less likely to develop.[65]

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Illustrations

Illustration 1

Chemical structure for isoniazid

Illustration 2

Chemical structure for rifampin
Illustration 3

Chemical structure for pyrazinamide

Illustration 4

Chemical structure for ethambutol
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