Clinical Tuberculosis Problems and Management

Zulkifli Amin

ABSTRACT

Tuberculosis (TB) is a chronic disease caused by M. tuberculosis. WHO (World Health Organization) 1993 has estimated that one third of world population has been infected by M. tuberculosis bacillus. It is also estimated that 8 million people contract the disease annually and two to three million deaths occur every year due to TB. Major factors that have aggravated the spread of TB are: 1) ineffective TB control programs, leading to the development of multi drug resistant bacilli, 2) co infection with HIV (human immunodeficiency virus) where TB progress rapidly and deadly,3) existence of other co-morbid that need higher expert (Internist etc). Vaccination with BCG does not seem to protect the adult population consistently and effectively from developing pulmonary TB, and has had no significant impact on the global TB epidemiology. Tuberculosis in Indonesia results in high death rate because it is the second highest infection with national prevalence rate of 0.24%. Effective medicine standard of anti-tuberculosis is available, but many obstacles in the program from lack of knowledge among health officers, low consciousness and compliances of person with tuberculosis to carry out the treatment schedule and so on make the success of TB eradication unsatisfied. Clinical appearances of TB are multiple with non-specific symptoms, the cases that are exposed to similar source of infection but will show different clinical consequence from mild to severe. Nevertheless, with the rise of multi drug resistance strains of M. tuberculosis, the spread of HIV infection and the variation of BCG efficacy, the search for more powerful drugs, more effective vaccines, better diagnostics and other intervention strategies have become an urgent goal worldwide. Also written here how to diagnose, choose of category of treatment , cocktail anti TB according the category and some clue in handling problems during treatment.

Key words: *clinical management, WHO (World Health Organization), TB (tuberculosis), AFB (acid fast bacilli), Rifampicin, Isoniazid, Pyrazinamid, Ethambutol, Streptomycin.*

Division of Pulmonology, Department of Internal Medicine, Faculty of Medicine University of Indonesia-dr. Cipto Mangunkusumo Hospital, Jakarta

INTRODUCTION

Tuberculosis (TB) is a chronic disease caused by M. tuberculosis. World Health Organization (WHO) 1993 has estimated that one third of world population has been infected by M. tuberculosis bacillus. Respectively India, China and Indonesia are three countries with the highest prevalence of tuberculosis in the world. It is also estimated that 8 million people contract the disease annually and two to three million deaths occur every year due to TB. TB is currently the leading cause of death globally due to a single infectious agent. The distribution of TB infection and disease varies among different parts of the world.

Approximately 95% of TB cases and 98% of TB deaths are in developing countries, with the highest prevalence and estimated annual risk of TB infection in sub Saharan Africa and Southeast Asia (1,5% - 2,5% and 1%- 2% respectively). TB has become a reemerging disease. Major factors that have aggravated the spread of TB are: 1) co infection with HIV (human immunodeficiency virus) where TB progress rapidly and deadly, 2) ineffective TB control programs, leading to the development of multi drug resistant bacilli. The effect of HIV infection on TB is particularly noticeable in sub-Sahara, Africa and some parts of Western Europe countries, while in Asia, and Eastern Europe countries, the spread of TB is probably due more to social and economic problems, and ineffective TB control programs. Vaccination with BCG does not seem to protect the adult population consistently and effectively from developing pulmonary TB, and has had no significant impact on the global TB epidemiology.

Tuberculosis in Indonesia results in high death rate because it is the second highest infection with a national prevalence rate of 0.24%. Effective medical standard of anti-tuberculosis is available, but there many obstacles in the program from lack of knowledge among health officers, low consciousness and compliances of person with tuberculosis to carry out the treatment schedule and so on make the success of TB eradication unsatisfactory. Clinical appearances of TB are multiple with non-

specific symptoms, the cases that are exposed to similar source of infection but will show different clinical consequence from mild to severe. There are a lot of unanswered questions concerning TB that need explanation, i.e. what factors result in the dormant bacillus being unable to be touched by available medication and being unable to manifest disease even if the host is immunecompetent.

Nevertheless, with the rise of multi drug resistance strains of M. tuberculosis, the spread of HIV infection and the variation of BCG efficacy, the search for more powerful drugs, more effective vaccines, better diagnostics and other intervention strategies have become an urgent goal worldwide.

DEFINITION

Distinction Between Tuberculous Infection and Tuberculous Disease

Tuberculous infection (or latent tuberculous infection) is defined by a positive tuberculin skin test but no evidence of active disease. Patients with latent tuberculous infection have therefore been exposed to the organism, but the initial infection was controlled by the host defense mechanisms and can only be subsequently traced by the positive delayed hypersensitivity skin test response. The small number of remaining organisms are in a dormant or latent state, but they do pose a risk for reactivation at a later time, especially with any impairment in the host's cellular immunity.

Tuberculous disease (or active tuberculosis), on the otherhand, is defined by the presence of clinically active disease in one or more organ systems, ideally with confirmation of the diagnosis by isolation of the organism M. tuberculosis.

Distinction Between The Terms Primer and Reactivation Tuberculosis

The distinction between the terms primary and reactivation tuberculosis, referring respectively to disease following the initial exposure and disease that reactivates after a period of latency. Several other terms are sometimes used to describe clinical disease based on the presumed pathogenesis. The term **progressive primary** tuberculosis reflects primary disease that has not been controlled by host defense mechanisms and has continued to be active beyond the point at which delayed hypersensitivity has developed. As a general rule, cellular immunity develops from 2 to 10 weeks after the initial infection, and continuing active disease beyond this time has many of the features of reactivation tuberculosis. The term **post-primary** tuberculosis refers to disease beyond the initial primary infection. Although this term usually refers to reactivation disease, it sometimes is also used to include cases of progressive primary tuberculosis.

Distinction Between The Term Reinfection and Reactivation.

Reinfection tuberculosis refers to disease in a previously infected person that results not from **reactivation** of dormant tubercle bacilli but rather from new exposure to another source of organisms. This type of infection has traditionally been considered uncommon; it is believed that individuals with prior exposure to tuberculosis, who manifest delayed hypersensitivity to the organism, are relatively resistant to exogenous reinfection from another source. However, studies using DNA fingerprinting techniques suggest that reinfection with another organism is more common than previously thought, particularly in patients who are infected with human immunodeficiency virus.

Mode of Transmission

Most infection with M. tuberculosis is through inhalation, so the lungs will be the most common organ affected compared to others. Transmission of the disease is via inhalation of droplet acid fast bacilli nuclei, particularly derived from patients with productive cough open lung TB. Other ways of transmission via direct inoculation may play a role in skin and soft tissue TB. Infection with M. tuberculosis in humans may also due to poorly sterilized or contaminated milk. Over crowded living conditions and urban settlement probably have facilitated transmission and contributed to the increased number of cases in TB. It has been shown that better living conditions and effective chemotherapy reduced the rate of morbidity and mortality in developed countries during the year 1950-1960.

Table 1. Risk Factors for Tuberculosis

Increased Risk of Exposure	Increased Risk of Active Disease
Contacts of suspected cases	HIV-positive patients
Foreign-born patients	Recent infectious exposure
Group settings	Organ-transplant patients and other
Health care workers with high-risk clients	immunosuppressed hosts
Medically underserved populations	Silicosis
High-risk racial or ethnic groups	Patients with head and neck cancer
Infants and children exposed to high-risk adults	Patients with hematologic Malignancy
Intravenous drug users	Patients with renal failure diabetes
	Gastrectomy patients
	Weight loss as a complaint
	Previously inadequately treated
	Tuberculosis

DIAGNOSIS

Clinical Manifestations

Diagnosis in TB sometimes maybe difficult because of the absence of specific signs and symptoms of the disease. The tuberculin skin testing may be helpful, but it is of limited value when applied in highly endemic areas and countries with national BCG vaccination programs, because it produces cross reactivity with antigens of environmental mycobacteria and with BCG itself. Patients with advanced disease may present with a false negative test, as they are anergic, and even in immunocompromised patients, up to 25 may have negative tuberculin skin test. Pulmonary TB mostly presents as nonproductive cough at early stages and only later becomes productive as tissue inflammation occurs. The systemic manifestations usually are night sweats, mild fever, malaise/fatigue and gradual weight loss over several months. The hematological indicators are anemia, lymphocytosis, increased blood leukocyte count, and an increased erythrocyte sedimentation rate, which is an indication of inflammation process (25). The subsequent symptoms may include chest discomfort, dyspnea, and hemoptysis, and pneumothorax. Dyspnea results from large areas of parenchymal lung involvement, whereas hemoptysis may result from ruptured blood vessels in cavity, which can be minor or gross hemorrhage . By auscultation, we may heard rales/ cracles, bronchial breath sounds, or amphoric breath sounds.

Table 2. Diagnosis of Tuberculosis

Laboratory criteria for diagnosis:
Isolation of M. tuberculosis from a clinical specimen or, when a culture has not been or cannot be obtained, demonstration of acid-fast bacilli in a clinical specimen
For cases that lack laboratory confirmation, all elements of the clinical case diagnosis must be met:
A positive tuberculin skin test (PPD")
Signs and symptoms compatible with tuberculosis, such as an abnormal, unstable (worsening or improving) chest radiograph or clinical evidence of disease
Treatment with two or more antituberculous medications
A completed diagnostic evaluation

'Purified protein derivative

TB that occur outside the lungs, is termed extra-pulmonary TB. Extra pulmonary cases may account for 5-30% of all TB cases, and this type of TB is more difficult to diagnose because most patients do not have detectable acid-fast staining bacilli in its specimen. There is a large variability in signs and symptoms, depending on the system/site that involved. Among many presentations that can lead us to diagnose extra-pulmonary TB are 'fever of unknown origin' and/or patients with granulomatous inflammation in their tissue biopsy. The probability of developing this form of TB influence by age (higher in teenage), gender (higher in female), and race (more prevalent in blacks). Extra-pulmonary TB can involve almost any organ of the body, including pleural, lymphatic, genito-urinary, bone, joint, abdomen and central nervous system (CNS).

Disseminated or miliary TB can occur when the bacilli spread through the blood stream, thus infecting multiple organs. This form of TB represents an inadequate host's immune response to mycobacterial infection. The term miliary derives from the millet seeds appearance in the involved tissues, and can only be seen ante-mortem on chest radiography. The clinical presentations of these patients are variable and generally are non-specific, dominated by systemic effects such as fever, weight loss, anorexia, and weakness. Other symptoms and signs depend on the site of involvement . Tuberculin skin testing is more likely to be false negative and the only well detectable specific physical abnormality is the 'choroidal tubercle', a granuloma located in the choroid of the retina.

Radiology

Radiological examination can support the diagnosis of pulmonary TB. Some of the typical features on chest X-ray can be: (1) localization of the infiltration, which is usually in the upper lung zones, (2) presence of infiltrates, typically with fibro-nodular irregular shadowing, (3) cavities with thick, moderately irregular walls, and (4) (often) rapid loss of volume within the segment (s) or lobe (s) . Other features are usually more atypical, such as lower zone infiltration, prominent pleural effusions, mass lesions, solitary pulmonary nodules, hilar/para-tracheal/mediastinal lymphadenopathy, and pneumothorax. Some of the differential diagnoses for TB on radiographic findings include lung carcinoma, pneumonia, sarcoidosis, lung abscess, progressive massive fibrosis, and other granulomatous diseases. According to the criteria from the (United States) National Tuberculosis Association, based on the radiological findings on chest X-rays, the severity of pulmonary TB can be classified into: mild, moderate-advanced and far-advanced. Mild or minimal disease presents with less than one lobe involvement of the lung. Moderate-advanced cases are those presenting with an area of infiltration in one lobe of the lung and /or a cavity of less than 4 cm in diameter, whereas far-advanced cases involve wider areas and/or cavities of more than 4 cm in diameter. In some difficult cases, a computed tomography scanning may prove to be useful.

Bacteriological Examination

The gold standard for diagnosis of TB is finding by culture the M. tuberculosis of the patient's specimen. But mostly the fnding of acid fast bacilli by sputum staining with the standard Ziehl-Neelsen or the Rhodamine Auramine method define enough for a diagnosis of lung TB. The Ziehl-Neelsen method is more widely used, as it is less expensive and laborious.

Under the microscope, the bacteria will appear as red rods with blue and white background. This is often difficult, especially when there are not many bacteria in the specimen. Another problem is that this appearance does not distinguish between M. tuberculosis and other mycobacteria. Thus, sputum-staining methods require equipment and well-trained laboratory personnel in order to obtain optimal case findings in the population.

Culture of mycobacteria takes approximately 6-8 weeks before colonies become visible, which is due to the slow generation time of many mycobacteria. The standard culture technique is by using Lowenstein-Jensen (L-J) slant media. The obtained culture can be used for several purposes, such as species identification, drug susceptibility testing and monitoring response to therapy. Specimens for staining and culture are usually obtained from sputum, but when sputum is not available specimens can be collected from gastric lavage, bronchoalveolar lavage and aspirates of pleural fluid or cerebrospinal fluid, pus or tissue biopsies. In genitourinary TB, bacilli sometimes can be found in the urine, whereas for gastro-intestinal TB, a feces specimen is sometimes needed.

Other Methods of Diagnosis

Recent advances in molecular biology, mycobacterial genomics and related biomedical research are opening up opportunities for more accurate diagnosis of TB. Identification of the mycobacteria can be performed by the amplification of nucleic acid in the specimen. One of the main molecular techniques is the Polymerase Chain Reaction (PCR), which amplifies a specific fragment of DNA (deoxyribo nucleic acid) that is specific for the pathogen. The repetitive insertion element IS 6110 and IS 1081 have been identified to be specific for M. tuberculosis complex, and this element can be used as target for PCR. Other non-PCR molecular techniques include ligase chain reaction, transcription-mediated amplification (TMA) and strand displacement amplification; some of which are commercially available.

Furthermore, the sensitivity of sputum-smear examination can now be improved by molecular techniques such as immunomagnetic separation. The time of culture can be minimized by using the Accuprobe system (Gen-Probe, San Diego), in combination with BACTEC (Becton Dickinson, Oxford). Nucleic acid amplification can also be applied for detection of drug resistant strains as well as strain typing of M. tuberculosis. The main limitation in using those nucleic acid amplification techniques, is the 'carry-over' contamination i.e. contamination of samples by products of previous amplifications, and the possibility of inhibitors which may be present in the sample. Another drawback is that it is too costly for screening a population, especially in the developing countries which are often high endemic areas.

Serological diagnosis is one of the immune-based assays that has long been studied. This method is based on the detection of specific antibodies in serum or other body fluids, because it has been recognized that TB patients produce high amounts of antibody. Although this method may be a promising strategy for simple and rapid diagnosis applicable for field use, the lack of M.tuberculosis-specific antigens has hindered development of such tests with high sensitivity and specificity. The other immunologic-based approach of diagnosis of TB is measuring recognition of specific M. tuberculosis antigens by patients' T cells, instead. A first requirement for such a test, like the serological method, is to define the antigens that are unique for M. tuberculosis complex. These tests are based on the same principle as tuberculin skin testing, i.e. the detection of T cells that have been primed to M tuberculosis antigens previously. In tuberculin skin testing with Purified Protein Derivative (PPD), a mixture of proteins which is shared with many other mycobacterial species, however, it has a low specificity.

Attempts are made to identify M. tuberculosis-specific antigens that are not present in other mycobacteria, now that the M. tuberculosis genomic nucleotide sequence is elucidated. Overall, diagnosis in TB is still hampered by the absence of specific clinical signs and symptoms and the lack of rapid, simple, cheap and robust, yet accurate, diagnostic tools. The applicability of immune-based diagnosis still needs solid proof, and in the mean time, sputum smear and culture will remain the optimal diagnostic tools in hospital and community settings.

Chemotherapy of Tuberculosis

Chemotherapy for TB can be classified into two types of regimens, i.e. first-line and second-line drugs. Both lines of drugs are directed toward eradicating growing bacilli, eliminating dormant bacilli and preventing drug resistance to occur. The first line drugs consist of Isoniazid (INH), Rifampicin, Pyrazinamide,

Ethambutol, and Streptomycin. The second line drugs consist of Rifabutin, Ethionamide, Cycloserine, Para-Amino Salicylic acid, Clofazimine, Aminoglycosides other than Streptomycin and Quinolones. Isoniazid (INH) is the most potent bactericidal agent for TB. Its mechanism of action is to inhibit the cell-wall biosynthesis pathway. INH is considered a safe drug; its major side effects may be hepatitis and peripheral neuropathy due to the interference with the biological function of vitamin B6 or pyridoxin.

Rifampicin is also a very potent antituberculous agent, inhibiting the DNA dependent ribonucleic acid (RNA) polymerase of M. tuberculosis. The main adverse reaction is hepatitis, flu-like syndrome's and thrombocytopenia. Pyrazinamide is a bactericidal agent for intracellular organisms and it is the third most potent antituberculous agent. Ethambutol has only bacteriostatic effect, but when combined with INH and Rifampicin can be effective in preventing the development of drug resistance. Streptomycin was one of the first anti tuberculous agent discovered. It is an aminoglicoside antibiotic administered parenterally and active against growing extra cellular organisms. Its main limitation is the toxic effect in the eighth cranial nerve, which may cause vestibular dysfunction and/or hearing loss. The second line drugs are reserved for the treatment of multi drug-resistant cases.

Treatment of TB requires at least 6 months of constitutive therapy to prevent the development of drug resistance. For this, the WHO has implemented the DOTS strategy, in which health care personnel closely supervises (directly-observed) patients taking the medicine to ensure compliance. The WHO also has provided a standard treatment regimen, which divides patients into four different categories, based on the case definition.

SOME USEFUL NOTES IN TREATING TB

When to stop medications without further consideration:

1. **Generalised reactions** including shock, purpura and fever. This is very rare but may be caused by rifampicin, pyrazinamide or streptomycin. The medication thought to be responsible for the reaction should never be given again.
2. **Impairment of vision in a patient on ethambutol.** Patients developing impaired vision should report immediately for examination. If ethambutol is thought to be responsible, it should never be given again.
3. **Patients who are pregnant** must never be given streptomycin due to risk of vestibulo-cochlear damage to the foetus.
4. **Skin irritation or rash in any patient on thioacetazone**. The medication must be stopped immediately and never given again (it should be replaced with ethambutol).

What to do when you think there may be an adverse effect:

1. **Dizziness** may be caused by vestibular damage due to streptomycin. This is most frequent in older individuals. Correct dosage and duration of treatment is important to prevent occurrence of these side effects. If a patient develops the following symptoms, medications may need to be stopped while the cause is investigated.
2. **Jaundice or severe abdominal discomfort** may be caused by hepatitis. It is most frequently due to isoniazid, but may also be caused by rifampicin and pyrazinamide. Any patient with these symptoms should be referred to the Internist for further investigation.
3. **Skin rash in a patient not on thioacetazone.** This is most frequently due to isoniazid, streptomycin or pyrazinamide. If the patient is clinically well (does not suffer from advanced tuberculosis or serious forms such as meningitis or disseminated disease), it is best to stop all medications and recommence them when the reaction has subsided. If the symptoms recur. the patient should be referred Internist.

Reactions not requiring interruption of treatment:

1. **Numbness or tingling** may be caused by isoniazid. When it occurs. it can be treated by supplementing the isoniazid with vitamin B, at a dose of 5 mg daily.
2. **Joint symptoms** may be caused by pyrazinamide. Check the dosage by weight; it is usually caused by overdosage. It may be easily alleviated with acetyl salicylic acid.
3. **All patients on rifampicin:** inform each patient to expect a red/orange colour to body fluids (tears, saliva, sputum, urine and sweat) which is not dangerous.

Determine if the patient is taking birth control medications, anti-epileptic medications, corticosteroids, oral treatment for diabetes, or oral anticoagu lants. These may require adjustment of dosage, or the use of alternative methods in the case of birth control.

Table 3. Standard Antituberculosis Medications for Adults

Drug	Daily	Usual Adult Dose Three Times (or Twice) a Week	Toxicity	Special Considerations	Comments
Isoniazid (INH)	300 mg orally	600 (900) mg	Hepatitis, neuritis, mood/ cognition, lupus reaction	Pregnancy: safe Liver disease: caution Renal impairment: decrease dose if severe	Monitor liver function tests monthly in most patients; clinically significant interactions with phenytoin and anti fungal agents (azols)
Rifampin (RIF)'	600 mg orally; 450 mg in persons < 50 kg body weight	600 (600) mg	Hepatitis, thrombopenia, nephritis, flu syndrome	Pregnancy: acceptable Renal impairment: safe	Key: multiple, profound drug interactions possible (see later); turns urine and fluids red
Rifapentine (RPT)	Not recommended	Not recommended (600 mg orally once weekly)	Similar to RIF	Similar to RIF	The primary role for RPT is in once-weekly therapy for patients with non-cavitary TB; not indicated for persons with AIDS
Rifabutin (RBU)	150-300 mg orally	300 (300) mg	Similar to RIF; modestly more neutropenia and thrombopenia than RIF	Similar to RIF	The primary role for RBU is in persons with AIDS to lessen drug-drug interactions.
Pyrazinamide (PZA)	25-30 mg/kg orally	30-35 mg/kg (same)	Hepatitis, arthralgias and arthritis secondary to hyperuricemia, gastro-intestinal (GI) distress, rash	Pregnancy: unknown avoid) Liver disease: caution Renal impairment: caution	Urate levels always rise; do not treat or stop PZA unless unmanageable gout develops
Ethambutol (EMB)	15 mg/kg orally	35 (50) mg/kg	Optic neuritis; GI distress; rare peripheral neuritis	Pregnancy: safe Liver disease: safe Renal impairment: decrease dose/frequency	Monitor visual acuity and color vision regularly
Streptomycin (SM)	12-15 mg/kg intra muscularly	15 mg/kg (same)	Vestibular and auditory, cation depletion	Pregnancy: high risk (avoid) Liver disease: safe Renal impairment: decrease dose/frequency	Reduce dose and/or frequency in case of renal impairment

Rifampin drug interactions have been reported with antiretroviral agents including protease inhibitors and nonnucleoside reverse vanscripmneinhibitors, oral contraceptives.
Coagulants, methadone, corticosteroids, estrogen replacement, calcium channel blockers, b-blockers, cyclosporine, antifungal (ozols) phenytoin, theophylline, sulfonylureas, haloperidol, and others (see Physicians' Desk Refference)

Table 4. Category TB for Treatment Grouping

Category	TB patients	Treatment regimens*	
		Initial phase	Continuation phase
1	New sputum smear-positive PTB	2 SHRZ (EHRZ)	6 HE
	Severe forms of TB,extra-pulmonary TB (severe), smear-negative PTB	2 SHRZ (EHRZ)	4 HR
		2 SHRZ (EHRZ)	4 H3R3
2	Relapse'	2 SHZE/ 1HRZE	5 H3R3E3
	Treatment failure	2 SHRZE / 1 HRZE	5 HRE
	Return after default		
3	Smear-negative PTB	2 HRZ or 2 H3R3Z3	6 HE
	Extra-pulmonary TB (less severe)	2 HRZ or 2 H3R3Z3	2 FIR / 4 H
		2 HRZ or 2 H3R3Z3	2 H3R3 / 4 H
4	Chronic case (still smear-positive After supervised re-treatment)	Not applicable (consideration of using second-line drugs)	

Abbreviations: TB = tuberculosis; PTB = pulmonary tuberculosis; S = Streptomycin; H = Isoniazid; R =Rifampicin; Z = Pyrazinamide; E = Ethambutol

Table 5. Common Errors in The Management of Tuberculosis

Addition of a single drug to a failing regimen
Failure to identify preexisting or acquired drug resistance
Chest radiographic findings absent or misinterpreted
Inadequate primary regimen
Failure to identify and address noncompliance
Inappropriate isoniazid preventive therapy

WHAT FACTORS MIGHT AFFECT TREATMENT ?

How does HIV Affect Treatment?

Patients infected with HIV usually have a response to treatment similar to that of patients who are not infected with HIV with a few exceptions:

- they are more likely to die during the course of treatment, usually from causes other than tuberculosis
- they may be more likely to experience toxic reactions to medications (and particularly to thioace tazone) than those who are not HIV infected, and their treatment must be adjusted for this reason;
- they are more likely to relapse if treated with the twelve-month regimen.

HIV infection is spread most frequently by sexual intercourse, through exchange of blood or blood products and from mother to child. Because of the association between tuberculosis and HIV infection, greater attention must be given in general to prevent the spread of both of these infections. The highest standards of hygiene must be observed, particularly when there is a risk of exposure to blood or blood products, when caring for tuberculosis patients. The use of injections should be limited as much as possible. Where they cannot be avoided, every health care worker should strictly adhere to the principle: a sterilised needle and syringe for each injection in each individual patient.

Any patient who is infected with HIV should be carefully protected from exposure to other patients with tuberculosis. Moreover, wherever HIV positive patients come together (in hospital wards, hospices and community support groups), a great deal of attention should be paid to any possibility of the occurrence of tuberculosis in these patients and every effort should be made to quickly diagnose and treat tuberculosis which may occur.

How does Drug Resistance Affect Treatment?

Large populations of tuberculosis microorganisms, such as those in patients who are sputum smear positive, always contain some mutants naturally resistant to medications. If a correct combination of medications is prescribed and is taken by the patient, this resistance is overcome and does not pose a problem. This is the reason for using a greater number of medications during the intensive phase of treatment until the population of micro-organisms has been rapidly reduced. This important principle must be respected in order to prevent development or extension of clinically important resistance to medications.

Once developed, resistance to antituberculosis medications can have an influence on the impact of treatment of tuberculosis cases, by causing the emergence of further resistance (where an insufficient combination of medications is used) or by rendering the patients incurable (where resistance to isoniazid and rifampicin coincide in an individual patient). The recommendations put forward in this Guide propose the

steps most likely to be successful in preventing multidrug-resistant tuberculosis and thus preventing the development and spread of incurable tuberculosis.

What if The Patient is Pregnant or Breast Feeding?

Pregnant women with tuberculosis should start or continue their treatment for tuberculosis in the same way as other patients. However, streptomycin should not be used because of the risk of toxicity to the unborn child. When the patient has a nursing infant, it is of particular importance to continue breast feeding, as its discontinuation poses a serious risk for the development of the infant.

What About Those Exposed to Tuberculosis?

Those who live in the same household with any patient who is smear positive have a higher risk of having tuberculosis themselves. If they have any symptoms, they should be asked to attend a medical examination. Any child in the household under 5 years of age who has symptoms and sign that suggest tuberculosis should be given treatment as a case of tuberculosis. All of the other children under 5 years of age should be given preventive chemotherapy, even if they have previously been vaccinated.

What is Preventive Therapy and Its Role?

Preventive therapy is the treatment of those infected with Mycobacterium tuberculosis (tuberculous infection) who do not have the disease (tuberculosis). The infection can be identified with a tuberculin skin test. The risk of developing tuberculosis in those who are tuberculin skin test positive is relatively low unless the infection has been acquired relatively recently or the person is also HIV positive. Preventive therapy in such persons can prevent the development of tuberculosis to an important extent.

This Guide recommends preventive treatment with isoniazid daily for a period of 6 months at a dose of 5 mg/kg body weight.

Often tuberculin is not available. The most important group that can be identified as needing preventive therapy are children under the age of 5 years who are living in the same household as a newly discovered smear positive tuberculosis patient. The chance that the child has been infected is high, as is the chance of the development of tuberculosis. New smear positive patients must be questioned carefully to determine if there are children in their household. These children must then be examined and treated as outlined above.

Can a Patient on Treatment Infect You?

Treatment is effective in rapidly diminishing the infectiousness of any patient with susceptible micro-organisms. This is because the medications rapidly reduce the number of micro-organisms, and the patient's cough rapidly subsides, resulting in fewer micro-organisms expelled into the air. In most settings, no special precautions for preventing the spread of infection need be taken once the patient is on treatment: the best prevention is to ensure that the medication is being taken regularly.

REFERENCES

1. Amin Z. Tuberculosis. Buku Ajar Ilmu Penyakit Dalam FKUI 2006. Jakarta: Pusat Penerbitan Departemen Ilmu Penyakit Dalam FKUI; 2006. Inprint.
2. Amin Z. Peran penambahan imunomodulator ekstrak phyllanthus niruri L pada OAT standar dalam mempercepat Konversi BTA penderita tuberkulosis paru pasca primer. Disertasi FKUI, Jakarta 2005.
3. Bourke SJ and Brewis RAL. Tuberculosis. Lecture notes on respiratory medicine. 5th edition. Oxford: Blackwell Science. p. 55-64.
4. Enarson DA, Rieder LA, Arnadottir T and TrebuckA. Management of tuberculosis. 5th edition. A Guide for low income country. France: IUATLD; 2000.
5. Fishman JA. Mycobacterial infections. In: Fisman PA, et al, editor. Fishman's manual of pulmonary diseases and disorders. 3rd edition. New York: McGraw-Hill; 2002. p. 763-819.
6. Iseman MD. Mycobacterial disease of the lungs. In: Hanley ME, Welsh CH, editors. Current diagnosis and treatment in pulmonary medicine. New York: Lange Medical Books/ McGraw-Hill; 2003. p. 399-413.
7. LoBue PA. Tuberculosis: clinical manifestation and diagnosis of diseases. In: Bordow RA, Ries AL, Morris TA, editors. Manual of clinical problems in pulmonary medicine. 6th edition. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 190-4.
8. Smith JA. Tuberculosis. In: Stein JH, editor. Internal medicine diagnosis and therapy. Connecticut: Appleton Lange;1993. p. 339-41.
9. Subronto YW. Antigen recocnition and Immunopathogenesis of Tuberculosis. Dissertation. Leiden 2002.
10. Weinberger SE. Tuberculosis and non tuberculosis mycobacteria. Principles of pulmonary medicine. 4th edition. Philadelphia: WB Saunders; 2004. p. 310-20.

Khomenko A.G. Tuberculosis yesterday, today and tomorrow. Probl. tub. = Problems of tuberculosis. 1997: 6; 9-11. Rudoi N.M. Lekarstvennaya ustoichivost' mikobakterii tuberkuleza [Drug resistance in Mycobacterium tuberculosis]. Moscow, 1969, 287 p. Rossman M.D., MacGregor R.R. Tuberculosis: clinical management and new challenges. N.Y., McGraw Hill Inc., 1995. Bastian I., Portals F. Tuberkulez s mnozhestvennoi lekarstvennoi ustoichivost'yu [Multi-drug-resistant tuberculosis]. Management of Tuberculosis. Federal Bureau of Prisons Clinical Practice Guidelines. January 2010. Clinical guidelines are being made available to the public for informational purposes only.Â Management of Tuberculosis Januay 2010. Screening for Latent TB Infection: The Tuberculin Skin Test (TST). Currently there are two FDA-approved methods for testing for latent TB infection (LTBI): the TST and a new blood test, QuantiFERON-GÂ®.Â A significant logistical problem associated with the test is that specimens must be processed within 12 hours of collection. The laboratory costs for QuantiFERON-G significantly exceed that of the TST; however, staff time required for testing is significantly reduced given that return visits for reading and two-step testing are unnecessary. Tuberculosis (TB) is a chronic disease caused by M. tuberculosis. WHO (World Health Organization) 1993 has estimated that one third of world population has been infected by M. tuberculosis bacillus. It is also estimated that 8 million people contract the disease annually and two to three million deaths occur every year due to TB. Major factors that have aggravated the spread of TB are: 1) ineffective TB control programs, leading to the development of multi drug resistant bacilli, 2) co infection with HIV (human immunodeficiency virus) where TB progress rapidly and deadly,3) existence of other B. Pulmonary tuberculosis. Clinical features. Cough is the commonest presentation. Initially it may be nonproductive, but as inflammation and tissue necrosis ensue, sputum is produced.Â Extrapulmonary tuberculosis usually presents a more difficult diagnostic problem. It is less common and, therefore, less familiar to most clinicians [17, 18]. Extrapulmonary tuberculosis in HIV-infected patients. The high frequency is related to the failure of the immune response to contain M. tuberculosis, thereby enabling haematogenous dissemination and subsequent involvement of single or multiple non-pulmonary sites. Disseminated tuberculosis occurs because of the inadequacy of host defenses in containing the infection.