INVITED ARTICLE

TUBERCULOSIS – FIGHTING A LOSING BATTLE?

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ABSTRACT

Tuberculosis has resurfaced as a "global emergency" in recent years not only in terms of increase in number of cases world-wide but also the emergence of the deadly multidrug-resistant tuberculosis. World Health Organisation (WHO) has issued a call for the global community to step up its vigilance against the disease. Chemotherapy is the most powerful tool in the fight against tuberculosis and should be used with utmost care and under stringent conditions. It is not enough just to prescribe the correct medication, but more importantly, the patient must be closely monitored for compliance and progress. Any facility which provides for the treatment of tuberculosis must have a good working mechanism to detect treatment defaulter and take immediate remedial action. Only then can we maintain a high standard of control of the disease and prevent the emergence of drug-resistant organisms.

Keywords: *tuberculosis chemotherapy, treatment compliance, prevention of multidrug-resistant tuberculosis.*

SINGAPORE MED J 1995; Vol 36: 209-211

INTRODUCTION

At a time when developed countries were talking about the elimination of tuberculosis (TB)[1], the disease returned with a vengeance so devastating that World Health Organisation (WHO) early last year declared it a "global emergency"[2]. The battle against this age-old disease began with the discovery of the infective agent by Robert Koch in 1882. The promise of victory with the advent of chemotherapy, especially rifampicin, and the improved social conditions was manifested by dramatic fall in the incidence of TB in developed countries. This led to complacency and a drop in vigilance against the disease. Promise turned into nightmare when indiscriminate use of these drugs and poor compliance by patients caused the emergence of resistant strains of the mycobacteria, compounded by the global epidemic of human immunodeficiency virus infection over the last decade.

Singapore is fortunate in that multidrug-resistant tuberculosis is not a big problem, human immunodeficiency virus infection has not reached epidemic proportions, and there is no slack in vigilance against TB.

The incidence of TB in Singapore has declined from 307 cases per 100,000 population in 1960 to 55 per 100,000 in 1993. The average annual rate of decline is about 4% between 1981 and 1993. Since 1987, the incidence rates have fluctuated around 55 per 100,000[3]. This plateauing is probably not due to a real increase in number of cases, but rather because of a more efficient surveillance of unnotified cases with computer linkage of the TB registry and the central TB laboratory since 1991. However, it is of vital importance for us to be constantly aware of the problem of TB in our midst and for clinicians to ensure that every case of TB diagnosed is treated well. The road from diagnosis to cure is often fraught with obstacles which cannot be ignored if control of the disease is to be maintained and further improved.

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CASE DETECTION

With the presence of classical signs and symptoms and typical X-ray appearance, the diagnosis of TB is not difficult to make. However, in the early stages, the disease is often discovered incidentally on medical screening for some other purpose. Therefore screening by chest X-ray has its place in certain situations. Diabetics are well-known to be prone to TB, and initial chest X-ray on first diagnosis of diabetes mellitus is therefore useful. Conversely, newly diagnosed TB patients should be screened for diabetes mellitus. The incidence of TB among diabetics has been reported to be in the region of 5-10% before the 1960's, but has fallen to about 1%[4]. Data from the Department of Tuberculosis Control over the last 3 years show that about 20% of our newly diagnosed TB patients are diabetics. In 1986, the figure was only 15%[5]. This rising trend is in tandem with the sharp rise in the prevalence of diabetes mellitus in Singapore from 4.7% in 1984 to 8.6% in 1992[6].

Besides diabetes mellitus, patients with silicosis, gastrectomy, end-stage renal failure, haematologic or reticulo-endothelial diseases, malignancies, immunosuppression due to long-term steroid therapy or human immunodeficiency virus infection should also be screened for TB periodically because of the increased risk of TB in these conditions.

Screening for new admissions to institutions where there is communal living, eg homes for the aged and destitute, correctional and mental institutions, etc is also advisable. It has been well documented since the early 1900s that TB is an important health problem among the homeless and residents of cheap lodging houses and shelters[7,8]. Institutional outbreaks of TB have been reported and these can be serious if multidrug-resistant organisms are implicated[9,10]. Chest X-ray survey of a large drug rehabilitation centre in Singapore in 1992 revealed that the incidence of new active pulmonary TB was 0.3% or 300 per 100,000[5], compared to the national figure of 55 per 100,000 for 1993[3].

TREATMENT

It is now universally accepted that six-month short course chemotherapy is the best and most cost-effective form of treatment for TB. WHO has recommended that adults with smear-positive pulmonary TB should be given six months of rifampicin and isoniazid, supplemented in the first 2 months by pyrazinamide and either injection streptomycin or oral ethambutol[11]. In Singapore where primary drug resistance is

low, streptomycin and ethambutol in the initial phase is not essential for newly diagnosed patients. Drugs for the 2-month initial phase are given daily, and either daily or three times a week during the 4-month continuation phase. The drugs, dosages and frequencies for 6-month short-course regimens are summarised in Table I.

For smear-negative cases, the WHO recommendation is a 4-month regimen consisting of 2 months of rifampicin, isoniazid and pyrazinamide followed by 2 months of rifampicin and isoniazid. This regimen could be given daily or three times a week throughout[11].

Although the same 6-month regimens can be used for extrapulmonary TB[11], there is less evidence that they are fully effective. TB of the lymph nodes[12] and the less extensive form of urinary TB[13] have been treated with apparent success with 6-month regimens. In severe forms of the disease, like miliary TB and tuberculous meningitis, the duration is generally prolonged for more than 6 months because of the question of penetration of different anti-tuberculous drugs into organ-tissues. The blood-brain barrier is a good example[14,15].

Contraindications to the use of short-course therapy include known hepatic disease, alcoholism and hypersensitivity to any of the drugs. Although isoniazid and rifampicin are safe during pregnancy, little is known about the safety of pyrazinamide and therefore this drug is better avoided in pregnant women. Ethambutol would be a good substitute. Hepatitis B carriers are reported to have a higher risk of developing severe rifampicin-isoniazid-induced hepatitis[16]. Short-course therapy should also be used with caution in the elderly with malnutrition in whom liver function may be deficient.

COMPLIANCE

Effective chemotherapy is the key to the control of TB. To prescribe a correct regimen is only the first step. What is more important is to ensure that patients comply strictly to the prescribed regimen. Non-compliance with medication is found to be a major cause of relapse[17]. Fully supervised treatment regimens are strongly advocated, and partially or unsupervised regimens are only allowed for valid reasons and for patients deemed to be reliable. To encourage compliance, the health care worker must be willing to spend time explaining in simple language to the patient what his illness is all about, when and how the medicine should be taken, and possible side effects of the drugs. Simple written instructions would be helpful. If patients have genuine problems preventing them from complying with a daily supervised treatment regimen, the health care personnel should help to find a solution and tailor the treatment regimen to suit the patient.

Patients must have easy access to the physician at any time in case of adverse side effects which is an important cause of non-compliance. For recalcitrant patients, confinement by persuasion or legal means may have to be resorted to[18].

Any facility which provides for the treatment for TB must have a good working mechanism to detect any defaulter and take prompt action. Non-compliance is a major cause of acquired drug resistance which is becoming a big problem in many developing countries[19]. When a patient's sputum smear fails to convert after 3 months of treatment, non-compliance should be suspected and remedial action taken immediately.

MONITORING DRUG TOXICITY

There should be regular monitoring for toxicity and response to therapy. Baseline measurements of hepatic enzymes should be a routine when patients are on rifampicin, isoniazid and pyrazinamide. The enzyme levels will show a slight increase above the pre-treatment level, but will return to normal on completion of treatment[20]. If there are no signs and symptoms of liver impairment, treatment need not be interrupted or changed because of such increases. Another serious but rare adverse side effect of rifampicin is thrombocytopenia. If purpura occurs, the drug should be stopped immediately and never used again on the patient[21].

When ethambutol is used, pre-treatment visual acuity and colour vision should be recorded, and blood urea and creatinine levels obtained, especially in the elderly, to assess renal function since ethambutol is mainly excreted by the kidneys. Subsequent measurements are only necessary when drug toxicity is suspected. The visual effects are reversible if the drug is stopped as soon as they are detected. Visual impairment as a result of ethambutol is uncommon if the drug is given in the recommended dosage of 25 mg/kg body weight for 2 months, and subsequently 15 mg/kg body weight if the drug is to be continued beyond 2 months[21]. Ethambutol is not recommended for young children who are unable to complain of any visual changes.

Complaints of drug toxicity, no matter how trivial, should be taken seriously by the health care personnel and some kind of active intervention taken. If they are brushed aside, the patient will often lose confidence and default treatment. Symptomatic medications and reassurance are usually all that is needed. Only with serious toxic side effects like hepatitis, thrombocytopenic purpura, visual impairment, or symptoms causing the patients undue distress should the regimen be modified.

Rifampicin has the ability to induce the action of detoxifying or conjugating liver enzymes. This may result in increased clearance of certain drugs by the liver, for example, oral contraceptives, oral hypoglycaemic agents, corticosteroids, digoxin, phenytoin, anti-coagulants, theophylline, beta-blockers and ketoconazole[22]. Therefore, patients on oral contraceptive pills must be advised to use alternative method of birth control. Diabetics, epileptics and patients on any of these drugs should be monitored and dose of drugs adjusted if necessary.

MONITORING RESPONSE TO TREATMENT

Patients being treated for uncomplicated pulmonary tuberculosis

Table I – Six-month short course regimen for treatment of tuberculosis in adults

Adult body weight	Initial phase – 2 months				Continuation phase – 4 months			
	Daily				Daily		3 times a week	
	Rifam	INH	PZA	Strep*	Rifam	INH	Rifam	INH
< 50 kg	450 mg	300 mg	1.5 g	750 mg	450 mg	300 mg	600 mg	15 mg/kg
⩾ 50 kg	600 mg	300 mg	2.0 g	1 g	600 mg	300 mg	600 mg	15 mg/kg

*Optional

Rifam = rifampicin
INH = isoniazid
PZA = pyrazinamide
Strep = streptomycin injection

do not require frequent chest X-rays. Bacteriological examination of sputum is a better indicator of response to treatment. Monthly sputum examination should be done for patients who have initial positive smears until conversion is noted. Patient is considered cured at completion of treatment when two consecutive sputum examinations are negative, one at the fourth month and the second at the end of treatment[11].

After two months of daily initial treatment phase with at least 3 drugs (rifampicin, isoniazid and pyrazinamide), sputum should convert in more than 90% of cases[20]. Sputum remaining positive at the third month of treatment could suggest possibility of treatment failure due to non-compliance or drug-resistant organisms. Corrective measure should be taken immediately by implementing strict supervision of treatment to ensure patient compliance. Drug sensitivity results must be available before modification to the regimen is made. It cannot be over-emphasised that when modification to a failing regimen is indicated, on no account should a single drug be added at a time as this will only promote the development of further drug resistance. Two or 3 new drugs to which the organisms are susceptible should be chosen. Many of these second-line drugs are less effective, associated with significantly greater risks of toxicity, and therefore best left in the hands of the experts.

CONCLUSION

"Treatment of tuberculosis is as easy as A B C – one bacteria, two lungs, three drugs."

Tuberculosis is one of the great medical paradoxes of our age. There are powerful drugs to cure the disease, yet it is far from being eradicated. Instead, it has re-emerged with the deadly form – the multidrug-resistant tuberculosis that is threatening and challenging countries with the most resources and expertise and it is gaining the upper hand unless other new effective drugs are discovered soon. Even then, it may be just a matter of time before these in turn become useless. The vicious cycle will only be broken when physicians realise the crucial importance of proper management of tuberculosis. It is easy to blame the patients for non-compliance with treatment, causing drug resistant tuberculosis and spreading the disease, when in fact, the physician bears the greater responsibility. His duty is to educate and motivate the patient. Diagnosis and treatment of TB may appear easy, but it often needs a lot of patience, commitment and understanding to achieve a cure and hence interrupt the chain of transmission of the disease. As physicians, this much we owe to the community.

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