AMBULATORY TREATMENT AND PUBLIC HEALTH MEASURES FOR A PATIENT WITH UNCOMPLICATED PULMONARY TUBERCULOSIS

AN INFORMATION PAPER

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Summary points:

1. There are two main purposes in the management of a case of tuberculosis: to cure the patient, and to contain the spread of the infection. The attending physician has the responsibility to ensure treatment completion.
2. The process of diagnosis follows the usual steps: history, physical examination, and investigations. Chest radiograph and sputum bacteriological examination are the basic diagnostic tools, supplemented by other tests where appropriate.
3. Bacteriological examination and drug susceptibility tests should be done as far as possible in every case of tuberculosis. Susceptibility results provide a good guide to formulation of the drug regimen, as well as surveillance data on trend of drug resistance in the community.
4. The standard treatment is the short course regimen given for at least 6 months. Drug prescription should be made after assessment of contraindications and necessary precautions. Biochemical and clinical monitoring are performed where appropriate.
5. DOTS is strongly recommended by the World Health Organisation as the cornerstone of TB treatment.
6. Apart from clinical management, public health measures are also essential. These include infection control measures, notification, contact tracing, and health education.

Introduction

In Hong Kong, there are around 5,000 notified cases of tuberculosis (TB) each year. Ambulatory chemotherapy has been the mainstay of anti-TB treatment. The majority (around 80%) of notified TB cases are managed in the chest clinics of the Tuberculosis & Chest Service (TB&CS) under the administration of the Department of Health (DH). Others are treated at various medical units of the Hospital Authority (HA) and in the private sector. It is a statutory requirement for every case of active TB to be notified to DH according to the Prevention and Control of Disease Ordinance (Cap. 599), which was an update from an old Ordinance and enacted in July 2008. Broadly speaking, notification serves two main purposes, namely, epidemiological surveillance and contact investigation. Prompt notification facilitates contact tracing procedures and helps to contain the spread of the infection. Details of the notification procedure can be found in the "Guidance notes for notification of tuberculosis".[1]

Today, emphasis is placed on encouraging patients with symptoms suggestive of TB to seek medical attention early, so called "passive case finding", rather than indiscriminate screening of asymptomatic individuals. This paper provides a summary and general view of the management of a patient with uncomplicated pulmonary TB.

Management of the Patient with Tuberculosis

Aims

There are two main objectives in managing a TB patient. The first is to cure the individual patient. The second is to contain the spread of the infection. In this regard, the health care provider has a responsibility to monitor every TB patient for treatment adherence till completion.[2]

History

As TB is endemic in Hong Kong, a high index of suspicion should be maintained, especially for patients presenting with symptoms like persistent cough for over 3 to 4 weeks, blood in sputum, weight loss, persistent fever, or night sweating. In assessing a patient presenting with persistent chest and/ or constitutional symptoms, a full medical history is essential. Particularly important issues in the history include previous history of TB, coexisting medical illnesses, occupational history, contact history, and smoking habit, risk of HIV infection (e.g. venereal exposure, intravenous drug addiction). If a positive culture of *Mycobacterium tuberculosis* (MTB) has been isolated from the sputum of the probable source case, the anti-TB drug susceptibility pattern helps in the choice of initial drug regimen for the patient. Any evidence of previous BCG vaccination is to be noted especially if the patient is a child.

Physical examination

Physical examination not uncommonly yields negative findings. Some features may be worth mentioning, including: general condition, cervical lymph node enlargement, features of pleural effusion, and unilateral wheeze related to endobronchial involvement. The physical findings may help in the consideration of differential diagnoses, e.g., a lung nodule is more likely to be a carcinoma than a tuberculoma in the presence of finger clubbing.

Investigation

Chest radiograph and sputum examination for acid fast bacilli (AFB) are essential tools employed for the diagnosis of pulmonary TB. The chest radiograph is a relatively simple and sensitive test. Typical radiographic changes, like apical lesions, tend to have a higher positive predictive value for TB in an endemic area like Hong Kong. However, atypical sites of involvement, e.g. predominant lower lobe changes, may occur in elderly patients with TB or patients coinfected with HIV. Every effort should be made to trace old chest radiographs for comparison, if available. At times, symptomatic TB patients may have normal findings on chest radiographs at presentation.[3]

Diagnostic sputum samples, preferably collected on two to three consecutive mornings, are sent for direct smear and culture examination. Positive smear results should be reported back to the clinics promptly so that patients can be called back for early commencement of treatment. If direct smears are negative, clinico-radiological correlation is essential in deciding the next step of action. In certain situations, trial of antibiotics, and follow-up chest

radiograph examination in one to two weeks may be required to differentiate TB from other types of community-acquired pneumonia. However, care should be exercised to avoid certain antibiotics in particular the fluoroquinolones which may mask the features of TB resulting in delayed diagnosis.[4,5]

The use of liquid cultures and the more advanced laboratory techniques like molecular detection and amplification tests can shorten the time required for bacteriological diagnosis and/ or drug susceptibility tests, though at a higher cost. However, false positive results of nucleic acid amplification tests may occur, e.g. in cases of treated or inactive TB. In more difficult cases, it may be necessary to resort to further investigations like computerised tomography scan, fibreoptic bronchoscopy, and percutaneous transthoracic fine needle aspirate. Thus, the diagnosis of active pulmonary TB may be based on any combination of clinical, radiological, bacteriological, and sometimes histological grounds. Empirical treatment may have to be considered for some patients with compatible clinical and/ or radiological features in the absence of bacteriological confirmation. Under such situation, careful clinical evaluation of treatment response is called for to confirm the clinical diagnosis and exclude other possibilities.

Both tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are immunological tests designed primarily for the diagnosis of infection, rather than disease. Neither is sufficiently sensitive or specific to rule in or rule out active TB disease. The use of TST is rather limited in the local setting, partly as a result of widespread BCG vaccination and revaccination, although the latter has been stopped since September 2000. Despite such limitation, the test may still give useful information in certain clinical situations, especially among the younger age group, and in case assessment is required for need of treatment of latent TB infection. Regarding the use of IGRAs for the diagnosis of latent TB infection, the World Health Organisation (WHO) issued a policy statement commenting that there is insufficient data and low quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high TB and/or HIV burden.[6] IGRAs and TST cannot accurately predict the risk of infected individuals developing active TB disease. Neither IGRAs nor the TST should be used for the diagnosis of active TB disease. IGRAs are more costly and technically complex to do than the TST. Given comparable performance but increased cost, replacing TST by IGRAs as a public health intervention in resource-constrained settings is not recommended. However, the WHO's policy statement is not intended to apply to high-income countries or to supercede their national guidelines.

The TB Reference Laboratory of DH performs anti-TB drug susceptibility tests for the great majority of health care facilities in the public sector, including TB&CS of DH and chest medical units of HA. Identification and drug susceptibility tests to the four first-line anti-TB drugs (isoniazid, rifampicin, ethambutol and streptomycin) are regularly performed for all pretreatment culture isolates which are positive for MTB. Drug susceptibility tests to second-line anti-TB drugs are also performed if there is multidrug-resistance (resistant to at least isoniazid and rifampicin), or with other clinical indications. The drug susceptibility test results provide a useful guide to the clinical management of the patient, and also allow epidemiological surveillance of drug resistance rates and evaluation of the local TB control programme. Hence, sputum or other relevant specimens should be sent for bacteriological

examination including drug susceptibility tests as far as possible.

Newer generations of molecular amplification tools have been increasingly utilized to facilitate the rapid diagnosis of TB and detection of drug resistance. The use of Xpert MTB/RIF test has recently been endorsed by WHO.[7,8,9] It has been recommended as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB. On the other hand, it may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. However, local epidemiological profiles, service constraints and cost-effectiveness considerations will need to be taken into account in the actual deployment of these evolving molecular tools in a service setting.

Notification

Cases diagnosed as active pulmonary TB should be notified promptly to DH, particularly once the case is put on treatment.[1] If the patient happens to be a health care worker or working in other relevant occupations with increased risk of exposure to TB, notification to the Labour Department is required under the Occupational Safety and Health Ordinance.[10] De-notification is necessary if the case eventually turns out to be non-TB, atypical mycobacterial infections, or other diagnoses. De-notification forms can be downloaded from the TB website (http://www.info.gov.hk/tb_chest).

Treatment

"Short course chemotherapy" is the current standard treatment for active pulmonary TB. The regimen consists of a two-month initial phase comprising four drugs, namely, isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) (or streptomycin (S)), plus a four-month continuation phase of two drugs, namely, isoniazid and rifampicin, making a total duration of six months.[11,12] The drugs can be given either daily or three times weekly at the appropriate dosages (Table 1, Appendices 1 and 2). The drugs should, as far as possible, be taken together in one single dose each time and not in split doses in order to achieve optimal therapeutic efficacy. Combined drug preparations (or fixed-dose combinations, e.g. rifater, rifinah) are useful alternatives but have to be given daily. While they help to avoid monotherapy with a single drug, they do not allow flexible dosage adjustment of the individual components of the regimen. TB patients are generally managed as an outpatient for ambulatory care unless there are other indications for hospital admission.

Table 1. Standard regimen for anti-tuberculosis treatment

Initial phase (2 months)	Isoniazid (H) + Rifampicin (R) + Pyrazinamide (Z) + Ethambutol (E) [or Streptomycin (S)]
Continuation phase (4 months)	Isoniazid (H) + Rifampicin (R)

In the recent WHO TB treatment guidelines,[13] systematic reviews were quoted, showing differences in risks of acquired drug resistance and treatment failure between patients given daily dosing and intermittent dosing regimens. Thus, updated recommendations on the dosing frequency for new TB patients were made (Table 2). In addition, WHO recommended that in settings where the level of isoniazid resistance among new TB cases is high and isoniazid susceptibility testing is not done (or results are not available) before the continuation phase begins, ethambutol may be continued during the continuation phase together with isoniazid and rifampicin (i.e., 2 months of HRZE + 4 months of HRE). However, further research has yet to be done to define the level of isoniazid resistance that would warrant the addition of ethambutol (or other drugs) to the continuation phase of treatment under such conditions.

Table 2. Dosing frequency for new TB patients[13]

Dosing frequency during initial phase	Dosing frequency during continuation phase	Remarks
Daily	Daily	Optimal
Daily	3 times per week	Acceptable alternative for any new TB patient receiving directly observed treatment (DOT)
3 times per week	3 times per week	Acceptable alternative provided that the patient is receiving directly observed treatment and is not living with HIV or living in an HIV-prevalence setting

Contraindications to the use of the anti-TB drugs should be noted prior to commencement of therapy, in particular: history of major diseases such as liver and renal diseases, visual problem, hearing problem, drug allergy, and concomitant treatment with other medications. Young females are counselled on pregnancy-related issues, especially the reduced efficacy of oral contraceptives due to interaction with rifampicin, and alternative contraceptive methods may have to be recommended. Pretreatment blood tests for liver function, renal function, HBsAg[14] and HIV antibody (after counselling and obtaining patient's consent) are performed. Baseline vision tests for visual acuity and colour perception (e.g., using Snellen chart and Ishihara chart) are also performed if ethambutol is to be started.[15] Studies show that it would be desirable to closely monitor liver function for HBsAg carriers during anti-TB treatment.[14] Health education is given on the nature of the disease, personal hygiene, avoidance of smoking and alcohol, necessity for full adherence with drug treatment, and the possible pharmacological and side effects of the anti-TB drugs (e.g., discoloration of urine, faeces, tear and other body fluids). This is supplemented by written educational materials. Self-reporting of side effects is also advised. The importance of health education on drug-induced hepatotoxicity and ocular toxicity have been emphasised in the relevant sets of local guidelines.[14,15,16] The establishment of good rapport with the patient from the very beginning is essential for the success of the treatment programme.

Public health measures

The health nurses will enquire the patient about his/ her close contacts (usually the household members), and contact screening will be conducted where appropriate. Casual contacts are, in general, not targeted for screening because of the low cost-effectiveness, although this has to be assessed on a case-by-case basis. Contact tracing normally follows the "stone-in-the-pond principle". Under this principle, contact tracing will be limited first to the innermost circle with the highest degree of close contact, and if more cases are found, consideration may be given to screen successively the outer circles with lesser degree of contact. However, examination of contacts should be considered mainly as an adjunctive measure in the overall TB control programme as only a relatively small proportion of TB cases can be found through this route. A more effective approach would be to emphasise on health education and early awareness of suspicious symptoms.

The sputum smear status is a general guide to the infectiousness of the TB patient. Those patients with severe cough, cavitary disease, and positive sputum smear are likely to be highly infectious. Prompt initiation of treatment is crucial as infectiousness rapidly decreases with effective treatment. Health education, personal hygiene measures, maintenance of good indoor ventilation and screening of close contacts are useful adjunctive measures to reduce the risk of transmission. Sick leave may be granted for the period during which infectivity is considered significant on a case-by-case basis. In general, infectivity is reduced significantly after two weeks of effective anti-TB treatment. Particular concern should be paid to infectious patients who are in frequent contacts with susceptible people, such as teachers, staff of homes for the elderly, medical personnel working for debilitated patients, and elderly home infectious residents where more stringent measures may be necessary.

DOTS and other monitoring measures

In the chest clinics, anti-TB medication is given under direct observation by the health nurses to ensure full adherence. Directly observed treatment, short course (DOTS), with five principal elements and implemented through holistic care, is strongly recommended by the WHO as one of the most important TB control measures, and is crucial for the success of the treatment programme. Directly observed treatment (DOT) is one of the five principal elements of DOTS. DOT by a health care worker also facilitates closer clinical monitoring of adverse drug effects.

During the initial phase of chemotherapy, follow up consultation can be arranged monthly to assess progress, and to reinforce patient adherence. For patients at risk of drug-induced hepatitis, including HBsAg carriers, those with pre-existing liver diseases, the alcoholics, the very old, and the malnourished, it would be desirable to monitor liver function tests once every two weeks during the initial two months of treatment, or more frequently as clinically indicated.[14] In the absence of any risk factors, routine biochemical monitoring may not be necessary, but liver function test should be performed if clinical features suspicious of hepatitis arise, such as fever, nausea, vomiting, anorexia and jaundice.

There is controversy about the role of regular follow up visual testing for patients put on ethambutol. This may, however, be considered if ethambutol is to be prescribed to some patients at a higher risk of oculotoxicity, especially when a high dose (e.g., 25 mg/kg/day) is used, treatment is prolonged,[15] or for those with impaired renal function.[16]

A chest radiograph is usually taken at the second or third month to assess progress. If the pretreatment bacteriology is positive, sputum examination after the second month will be done to assess whether there is conversion to negativity. If the bacteriology then is still positive, a further sputum examination after the third month is indicated. Prolongation of the treatment duration has been recommended by some authorities in case the sputum shows slow bacteriological conversion and cavitary disease is present.[2]

Treatment defaulters will be approached by the health nurses through various means, including telephone calls, visits, and mail. Adherence is positively enhanced through health education and an assisting approach. The underlying reasons for defaulting should be identified and possible solutions are provided to restore adherence. Through the work of the medical social workers, incentives like nutrition allowance or other forms of social assistance may be introduced for eligible patients to enhance treatment adherence. Minimising non-adherence is vital for the overall success of the TB control programme.

At the end of six months' treatment, the patient is assessed with a repeat chest radiograph and sputum examination. After stopping treatment, further health education is delivered to the patient on issues like maintenance of a healthy lifestyle, and returning for assessment should symptoms suspicious of TB recur. Relapse of TB should be uncommon after adequate chemotherapy and regular follow up is not a necessity in general. However, for the purposes of outcome evaluation, TB patients are preferably followed up periodically for two or more years. In fact, standardised "Programme Forms" are being used for continuous evaluation of the service programme in the TB&CS since 1998 and an updated version of the Forms has been introduced since 2001 and extended for use to other health care sectors including the HA and the private sector.[17] Data collected include information on demography, past history of treatment, type of TB (pulmonary or extrapulmonary), extent of disease (if pulmonary), case category (new, relapse, treatment after default and treatment after failure), date of starting treatment (DOS), bacteriological status at certain time points, drug susceptibility test results, and treatment outcome at selected time intervals from DOS. Monitoring of treatment outcome is an essential component of the DOTS strategy advocated by WHO. Surveillance of treatment outcomes are regularly reported in the Annual Reports of TB&CS.[17]

Complicating issues

From time to time, complicating issues may be present, including extensive disease, slow bacteriological conversion, poor general condition, diagnostic dilemma, treatment failure related to poor adherence and drug resistance, concurrent medical diseases, adverse drug reactions, and relapse of TB disease, etc. Opinion from experienced physicians in this field has to be sought and hospital admission may be required. Modification of the drug regimen

may be necessary, for example, in cases with drug-induced hepatitis.[14] Transient rise of liver enzymes may occur, and it does not, by itself, represent genuine hepatotoxicity. The following cut-off levels are recommended for withholding potentially hepatotoxic anti-TB drugs in patients without symptoms: (i) alanine transaminase rising to three times the upper limit of normal or the baseline; or (ii) bilirubin level rising to two times the upper limit of normal or the baseline. A more cautious approach should be adopted in the presence of symptoms suggestive of hepatitis, in which case anti-TB drugs may have to be stopped before the availability of the test results.

Care should also be taken not to add a single drug to a failing regimen (the addition phenomenon), otherwise resistance to the newly added drug will soon develop. Re-challenging and desensitisation with anti-TB medications may be required with drug-induced hypersensitivity skin rash, but care should be taken not to induce emergence of drug-resistant organisms during this process. TB in children is more difficult to diagnose, and treatment with ethambutol should be avoided especially for those under six years old as they may not be able to report visual symptoms reliably. Thus, childhood TB should be managed by an experienced physician. On the other hand, TB in the elderly may have atypical presentations, and there is a higher incidence of side effects from drugs among this population.

Further information and recommendations about the treatment and management of tuberculosis can be found in various local and international publications and guidelines, and the TB website (www.info.gov.hk/tb_chest).[2,13,16]

Conclusions

The most important reason for failure of anti-tuberculous treatment is poor adherence. Studies have shown that there is no good way to predict adherence to drug therapy. DOTS is thus the best available tool to ensure drug adherence. The cost of DOTS is justified because it avoids the greater cost required for the management of failure cases, relapse cases, complications, late effects and even worse, drug-resistant cases. Furthermore, without an effective treatment programme, the spread of TB would lead to an even higher healthcare and economic burden. The management of a case of TB demands the combination of good professional knowledge in clinical medicine as well as adequate attention on public health measures.

Although the local TB situation has much improved in the past 50 years, it is certainly still a major public health concern. In fact, the decline of the notification rate has slowed down in the recent decades, currently staying at around 70 per 100,000 in recent years. The maintenance of a strong infrastructure for the delivery of TB control service is required to combat and prevent the resurgence of this disease. The rate of latent infection in the local population is still high, especially among senior citizens. More emphasis is now being put on treatment of latent infection for targeted groups. Many more years of work will be required before elimination of the disease may be considered as a foreseeable goal.

Appendix 1. Usual dosages of conventional anti-tuberculosis drugs

Drug	Daily dosage			Intermittent dosage		
	Adults and children (mg/kg)	Adults		Adults and children (mg/kg)	Adults	
		Weight (kg)	Dose		Weight (kg)	Dose
Isoniazid * @	5	–	300 mg #	10 (3 times/week)	–	–
Rifampicin *	10	<50	450 mg	10-12 (3 times/week)	–	600 mg
		≥50	600 mg			
Streptomycin *^						
Age ≤50	12-15	<50	500 mg (5 times/week)	12-15	<50	500-750 mg
		≥50	750 mg (5 times/ week)		≥50	750-1000 mg
Age 50-70			500 mg (5 times/week)			500-750 mg
Age ≥70			-			500-750 mg
Pyrazinamide	25-30	<50	1.0-1.5 g	30-40 (3 times/week)	<50	1.5-2.0 g
		≥50	1.5-2.0 g		≥50	2-2.5 g
Ethambutol	15	–		30 (3 times/week)	–	–
Thiacetazone *	2.5	–	150 mg	–	–	–
Rifater		per 10 kg	1 tablet			
		>50 kg	5 tablets			

* *Some authorities recommend higher dosages (per kg body weight) of isoniazid, rifampicin, streptomycin, and thiacetazone for children.*

\# *Some elderly and/or malnourished patients can only tolerate isoniazid 200 mg daily.*

@ *Pyridoxine supplement should be considered for those with malnutrition or at risk of neuropathy, e.g. pregnancy, diabetes mellitus, alcoholism, chronic renal failure, and HIV infection.*

^ *Dosage of streptomycin is adjusted according to age (Reference: American Thoracic Society. Diagnosis and treatment of disease caused by nontuberculous mycobacteria. Am J Respir Crit Care Med 1997;156:S1-25.)*

Appendix 2. Usual dosages of second-line anti-tuberculosis drugs in the treatment of multidrug-resistant tuberculosis

Drug	Daily dosage			
	Adults and children (mg/kg)	Adults		
		Weight (kg)	Dosage	
Amikacin *	15		750 mg	3 to 5 times/week
Kanamycin *	15		750 mg	
Capreomycin *	15		750 mg	
Ofloxacin			600-800 mg	
Levofloxacin			500-600 mg	
Ciprofloxacin			750-1500 mg	
Ethionamide	15 (adults)	<50	500 mg	
Prothionamide		≥50	750 mg	
Cycloserine	15 (adults)	<50	500 mg	
		≥50	750 mg	
Clofazimine			50-100 mg	
Para-aminosalicylic acid	2 g/10 kg		8-12 g	

* Dosages may be adjusted downward to 500 mg for elderly subjects.

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