

# **GUIDELINES ON THE MANAGEMENT OF PATIENTS WITH MULTI-DRUG RESISTANT TUBERCULOSIS IN HONG KONG**

A consensus statement of  
the Tuberculosis Control Coordinating Committee of  
the Hong Kong Department of Health and  
the Tuberculosis Subcommittee of  
the Coordinating Committee in Internal Medicine of  
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**March 2005**

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March 2005

ACKNOWLEDGEMENT

***This statement is prepared by a Working Group consisting of the above authors on behalf of the Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Tuberculosis Subcommittee of the Coordinating Committee in Internal Medicine of the Hong Kong Hospital Authority. The authors would like to thank the members of the two Committee/ Subcommittee. The members are: Dr. HS Chan, Dr. KS Chan, Dr. JWM Chan, Dr. K Choo, Dr. CM Chu, Dr. SS Ho, Dr. DSC Hui, Dr. FY Kong, Dr. CW Lam, Dr. HM Ma, Dr. LKY So, Dr. CY Tam, Dr. KWT Tsang, Dr. ML Wong, Dr. WKS Yee, Dr. WC Yu, Dr RWH Yung.***

*[Extracted from Annual Report (Suppl) 2005, TB & Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health, Hong Kong]*

## Introduction

Multi-drug resistant tuberculosis (MDR-TB), defined as tuberculosis caused by tubercle bacilli showing in vitro resistance to at least both isoniazid and rifampicin, is of increasing concern in tuberculosis control programmes all over the world [1]. Use of DOTS has been shown to reduce the transmission of tuberculosis and the incidence of drug resistant diseases. As regards drug-resistant TB in particular MDR-TB, they are more difficult to treat with significantly lower treatment success rates, treatment costs are much higher, and they may remain infectious for longer period of time. For the control of MDR-TB, “DOTS-PLUS” strategy is recommended. This strategy incorporates continuous drug resistance surveillance, culture and drug susceptibility testing for TB patients, and tailoring of individual drug regimen with the use of first and second line drugs.

At present, the rate of TB notification in Hong Kong is still high as compared with other western developed countries, at a level slightly below 100 per 100,000. The rate of MDR-TB, as noted in the Government Chest Service’s annual report, has shown a decreasing trend with a rate of around 1% in recent years [2]. It is necessary to remain vigilant and continue to update our knowledge and measures for the control of drug-resistant TB.

The Tuberculosis Control Coordinating Committee has published guidelines on the management of both clinical and public health aspects of patients with TB [3-6]. As patients with MDR-TB may first approach and seek for care from general medical doctors working in public non-chest hospitals or in private health care facilities, a specific set of guidelines for MDR-TB is considered desirable. Recommendation is provided on diagnosis, reporting, general principles in treatment, contact screening, infection control and preventive measures in relation to MDR-TB for reference by general medical doctors. Most of the basic principles in the management of a case of uncomplicated TB are also applicable for drug resistant cases. On top of these basic principles, the guidelines in this paper should be referred to when managing a multi-drug resistant case, although each case should be managed according to each individual circumstance.

## Recommendations

The treatment of MDR-TB involves second-line (reserve) drugs which are much more expensive, generally less efficacious, and have more potential adverse effects than the first line drugs. Clinical expertise and good laboratory support are essential for the successful management of patients with MDR-TB. It is therefore recommended that treatment of MDR-TB be managed by or in close consultation with TB specialists.

### 1) Diagnosis

It has been recommended that drug susceptibility testing of pretreatment positive culture isolates should be done for all TB patients [1]. In this regard, diagnosis of drug-resistant TB can be made and the treatment regimen can be modified with the availability of the susceptibility test results.

However, early diagnosis of drug resistant TB, particularly MDR-TB, is highly desirable. A high index of suspicion is required. A history of incomplete treatment for tuberculosis, close contact with MDR-TB patients and migration from an area endemic for drug resistance are some of the useful clues. Other risk factors for MDR-TB such as HIV infection, drug addiction and alcoholism should also be sought in the history.

For re-treatment cases, the number of episodes of previous treatment, treatment non-adherence, and the treatment details for each episode of treatment should be enquired.

The Public Health Laboratory Centre (PHLC) of Department of Health may be contacted for consideration of drug susceptibility tests for first line as well as second-line anti-tuberculosis drugs. Under appropriate circumstances, PHLC may also be contacted for consideration of either rapid drug sensitivity tests with BACTEC or performing drug susceptibility tests concomitantly with identification tests.

It has been described that about 96% of rifampicin resistant isolates have a mutated *rpoB* gene, and the mutations are concentrated on a short, less than 100-bp stretch of the gene [7]. Thus, genetic testing for rifampicin resistance

would be useful and its positive predictive value for MDR-TB can be high. Hence, when available and in case of high index of suspicion, rapid genetic testing for rifampicin resistance may be recommended [1].

## 2) Reporting of MDR-TB cases

Timely notification of TB cases, drug susceptible and drug resistance cases alike, is crucial to the effective control and prevention of the disease. It is also important for public health surveillance and for initiation of contact screening. In addition to the usual TB notification registry, a MDR-TB registry has been set up within the TB & Chest Service since May 1995 and the procedures have been updated in 2004 (MDR\_Flow\_protocol0503) to include reporting of MDR-TB cases from sources outside TB & Chest Service. Whenever a currently active and previously unreported case of MDR-TB is diagnosed, health care workers are requested to *notify* the case to Wanchai Chest Clinic using the MDR-TB notification form (MDR\_Noti\_Form0503). In order to track progress of patients with MDR-TB, a set of special programme record forms have been designed (TB-PFMDR-X(1)/10-2004 and TB-PFMDR-X(2)/10-2004). These forms are to be filled in every 6 months after the completion of the usual set of programme record forms (PFA, B1, B2, C and D) from 2.5 year to 5 year from date of starting treatment (DOS). The forms can be downloaded from the DH TB website ([http://www.info.gov.hk/tb\\_chest](http://www.info.gov.hk/tb_chest)). [NB: PFA at pretreatment, PFB1 & PFB2 at 6m, PFBC at 12m, PFBD at 24m, and PFMDR-X at 30m, 36m, 42m, 48m, 54m, and 60m]

## 3) Treatment

There are several general principles:

### *Regimen*

For MDR-TB patients with known susceptibility pattern, the regimen should comprise 5 to 6 drugs to which the organism is or is likely to be susceptible for the initial 6 months, and then 3 to 4 drugs subsequently. Some would recommend the inclusion of an injectable agent and a quinolone in the core regimen. Daily regime should be used, except for the injectables especially when they are used

during the continuation phase. Drugs showing in vitro resistance are avoided with possible exception of the use of isoniazid in cases with low-level isoniazid-resistance. The possibility of cross-resistance between drugs should be noted [8-9].

Apart from first-line anti-tuberculosis drugs, available drugs for treatment of MDR-TB include the fluoroquinolones (e.g. ofloxacin, levofloxacin, ciprofloxacin), aminoglycosides (e.g. kanamycin, amikacin), prothionamide/ ethionamide, cycloserine, para-aminosalicylic acid, and clofazimine. [Tables 1-3] Drugs that have not been used to treat the patient before are preferred.

There is controversy on the best approach in managing MDR-TB patients before drug susceptibility results for the second line drugs become available. Some experts advocate empirical use of second line drugs while others may wait till definitive drug susceptibility results are available to avoid misuse of ineffective drugs which may lead to emergence of further resistance. The relative merits and de-merits of either practice has never been systematically studied. Each case should be judged depending on the individual circumstances. For example, patients with poor general condition or extensive diseases should be commenced on treatment as early as possible. The opinion of TB experts should be sought under these circumstances. If it is considered necessary to treat a suspected MDR-TB patient before second-line drug susceptibility test results are available, it is advisable to give both the essential first-line drugs plus at least three second-line drugs that have not been used previously.

The total duration of therapy for MDR-TB has not been clearly established; most will recommend a total duration of 18 months at least, or 18 months after culture being converted negative. However, local experience suggests that, with combination drug treatment and the inclusion of quinolones to which the bacilli are still susceptible, the total duration may be shortened to 12 to 15 months, or one year after sputum culture conversion [10]. The longer duration may be required for patients with diabetes mellitus, silicosis, slow sputum culture conversion, extensive drug resistance or extensive disease. Again the opinion of TB experts should be sought.

A single drug should never be added to a failing regimen, because doing so may select for organisms that are resistant to the newly added drug (*Addition Phenomenon*). Combination of two or three drugs to which the organism is or is

likely to be susceptible should be added.

Caution is to be exercised in the use of second-line drugs as they are often associated with significant adverse effects. Bactericidal drugs are preferred to bacteriostatic drugs. Cycloserine should be used only with caution and when its benefit is perceived to outweigh its adverse effects.

### *Drug supervision*

Therapy of all patients with MDR-TB should be delivered by DOT (directly observed treatment) as far as practicable. Failure to comply with treatment is the main cause of emergence of drug resistant organisms. Therefore every effort should be made to ensure that patients complete the full course of treatment.

For patients who have problems with drug adherence, the reasons for defaulting treatment should be carefully explored. All efforts should be made to seek cooperation from treatment defaulters for treatment. The management of treatment defaulters can be problematic. Team approach is the strategy. Counseling by specially trained TB workers and medical social workers form an integral part of management of these patients. Early referral to government chest clinics or HA MDR-TB Centres would be desirable.

### *Surgery*

For selected cases of MDR-TB with sufficiently localized disease that are not responding well to treatment with an adequate chemotherapeutic regimen, surgical resection of a major pulmonary focus may be a useful adjunct to anti-tuberculosis treatment. The remaining lung tissue should be relatively devoid of TB and there should be sufficient drug activity to diminish the Mycobacterial burden to facilitate healing of the bronchial stump [9]. The opinion of thoracic surgeons should be sought under these circumstances.

### *Monitoring*

Close monitoring of progress during anti-TB treatment is required, in particular the general condition, body weight, chest radiograph and bacteriological status. Sputum specimens should be sent monthly for AFB smear and culture examination, as well as drug susceptibility tests, until they are converted negative

for three consecutive months. Sputum tests may be monitored at longer intervals thereafter, say, every three months, depending on the clinical situation. Renal function should be checked periodically particularly if an aminoglycoside is given. Liver function should be monitored regularly in patients with risk factors for hepatitis. The patient should also be regularly assessed for other potential adverse reactions from the drugs given.

Caution should be exercised in the interpretation of chest radiograph when initial radiographic improvement is observed. Sometimes this may only indicate temporary improvement due to response of the drug-susceptible part of the bacilli population in the lesion, leaving behind the selected resistant part to grow subsequently and deteriorate again. The opinion of TB experts should be sought if response to anti-TB treatment is unsatisfactory.

### *Admission*

Admission of patients with MDR-TB to special care centres (to HA MDR-TB Centres including Grantham Hospital or Kowloon Hospital for newly diagnosed cases; or to the respective chest hospitals if they are their old cases) is recommended particularly during the initial period. This will facilitate detail assessment, stabilization and optimisation of drug regime, re-enforcement of health education, and enhancement of treatment adherence during subsequent outpatient follow up after discharge. Arrangement for hospital admission can be made by direct referral to the specialist outpatient clinics of the relevant chest hospitals or through government chest clinics.

### *General measures*

The patient should be provided health education on measures to prevent the spread of the disease, e.g., good personal hygiene (avoid spitting and sneezing in public area), and avoid going to overcrowded areas. The patient should be advised to put on surgical masks if there is a need to go to crowded public areas including public transport vehicles.

#### 4) Contact screening

Good public health measures are indispensable for the prevention of emergence



and transmission of drug resistant organisms. Contact screening, together with notification, surveillance, health education and infection control are the most important public health measures undertaken by DH. The general principles for screening of close contacts also apply to those of MDR-TB cases [2,11]. In addition, for MDR-TB contacts with normal CXR findings on initial screening, periodic screening say every 6 to 12 months may be indicated, depending on the infectiousness of the index case as assessed from the updated findings on chest radiograph and sputum status. The contacts should also be educated on symptoms suspicious of tuberculosis and advised to return for consultation if such symptoms develop. The health staff of chest clinics may be contacted for arranging contact screening if the latter has not been undertaken by general medical doctors.

If a contact is found to have developed active pulmonary tuberculosis, it is important to correlate with the drug susceptibility pattern of the index case. Special public health measures may have to be taken if transmission of MDR-TB among contacts is suspected. To achieve effective public health control of the infection, close communication should be maintained with the relevant parties including Department of Health. Restriction fragment length polymorphism (RFLP, or DNA fingerprinting) may be considered.

#### 5) Infection control measures

Measures should be taken to prevent nosocomial spread of MDR-TB in clinics, hospitals and other health care settings. These include an effective triage system, minimization of the MDR-TB patients' duration of stay in the health care settings, advice on personal hygiene and the use of face masks, etc [12,13].

#### 6) Other issues

Special management may be necessary for chronic MDR-TB cases not responding well to treatment, and the failure-failure cases. Compassionate re-housing may have to be considered. It would be useful to discuss with the patient and his/her household members on observation of personal hygiene, maintenance of good indoor ventilation, as well as other measures including special arrangement of the home setting and layout of rooms. The use of

incentives and enablers may be desirable through liaison with medical social workers. Incentives like those in the form of special diet allowance should be used with close monitoring and follow-up remedial actions to ensure that they are used effectively. The DH staff may be contacted if the above arrangement is considered necessary.

## Conclusions

Treatment success rate for MDR-TB is relatively low. It should be much more cost effective to prevent its emergence in the first place. The routine use of DOTS in the treatment of all cases of TB cannot be overemphasized. Currently, a number of new drugs as well as new vaccines for TB are under different phases of research and development. Fluoroquinolones are currently among the most valuable drugs in the medical treatment of MDR-TB. As Hong Kong has a relatively high TB prevalence, careful use of fluoroquinolones is highly desirable, not only in the context of TB, but also in other medical conditions including community acquired pneumonia. Otherwise, the loss of this important group of compounds will have adverse consequences on our battle against TB.

To control MDR-TB, specific surveillance programmes like the MDR-TB registry, drug resistance surveillance and treatment outcome monitoring are indispensable. They should provide useful information for close monitoring, evaluation, and planning of targeted control measures. Today TB is still an infectious disease of public health importance globally and locally. The control of TB is a long term work. Continuous multisectoral cooperation is necessary.

**Table 1 Adverse reactions to antituberculosis drugs**

Drug	Reactions		
	Common	Uncommon	Rare
Isoniazid		Hepatitis Cutaneous hypersensitivity Peripheral neuropathy	Giddiness Convulsion Optic neuritis Mental symptoms Haemolytic anaemia Aplastic anaemia Lupoid reactions Arthralgia Gynaecomastia
Rifampicin		Hepatitis Cutaneous hypersensitivity Gastrointestinal reactions Thrombocytopenic purpura Febrile reactions "Flu syndrome"	Shortness of breath Shock Haemolytic anaemia Acute renal failure
Pyrazinamide	Anorexia Nausea Flushing	Hepatitis Vomiting Arthralgia Cutaneous reaction	Sideroblastic anaemia
Ethambutol		Retrobulbar neuritis Arthralgia	Cutaneous reaction Peripheral neuropathy
Streptomycin	Cutaneous hypersensitivity Giddiness Numbness Tinnitus	Vertigo Ataxia Deafness	Renal damage Aplastic anaemia
Thiacetazone	Gastrointestinal reactions Cutaneous hypersensitivity Vertigo Conjunctivitis	Hepatitis Erythema multiforme Exfoliative dermatitis Haemolytic anaemia	Agranulocytosis

Amikacin Kanamycin Capreomycin	{ Ototoxicity: hearing damage, vestibular disturbance Nephrotoxicity: deranged renal function test	Clinical renal failure	
Ofloxacin Levofloxacin Ciprofloxacin	{ Gastrointestinal reactions Insomnia	Anxiety Dizziness Headache Tremor	Convulsion
Ethionamide Prothionamide	{ Gastrointestinal reactions	Hepatitis Cutaneous reactions Peripheral neuropathy	Convulsion Mental symptoms Impotence Gynaecomastia
Cycloserine	Dizziness Headache Depression Memory loss	Psychosis Convulsion	Sideroblastic anaemia
Clofazimine	Nausea Giddiness Discoloration of skin (dose-related) and urine Dryness of skin	Eye irritation Diarrhoea with high doses	Taste disorder
Para-aminosalicylic acid	Gastrointestinal reactions	Hepatitis Drug fever	Hypothyroidism Haematological reactions

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**Table 2 Usual dosages of conventional antituberculosis 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 * <sup>@</sup>	5	–	300 mg <sup>#</sup>	10-15 three times/week	–	–
Rifampicin *	10	<50	450 mg	10-12 three times/week	–	600 mg
		≥50	600 mg			
Streptomycin *	12-15	<50	500-750 mg	12-15	<50	500-750 mg
		≥50	750 mg		≥50	750-1000mg
Pyrazinamide	25-30	<50	1.0-1.5 g	30-40 three times/week	<50	2.0 g
		≥50	1.5-2.0 g		≥50	2.5 g
Ethambutol	15	–		30 three times/week	–	–
Thiacetazone *	2.5	–	150 mg	–	–	–
Rifater		per 10 kg	1 tablet			
		>50 kg	5 tablets			

\* Some authorities recommend higher dosages 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.

**Table 3 Usual dosages of second-line antituberculosis drugs in the treatment of MDR-TB**

Drug	Daily dosage			
	Adults and children (mg/kg)	Adults		
		Weight (kg)	Dosage	
Amikacin	15		750 mg	} three to five times/week
Kanamycin	15		750 mg	
Capreomycin	15		750 mg	
Ofloxacin			600-800 mg	
Levofloxacin			500-600 mg	
Ciprofloxacin			750-1500 mg	
Ethionamide	} 15	<50	500-750 mg	
Prothionamide		(adults)	≥50	750-1000 mg
Cycloserine	} 15	<50	500-750 mg	
		(adults)	≥50	750-1000 mg
Clofazimine			50-100 mg	
Para-aminosalicylic acid	2 g/10 kg		10-12 g	

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