# GUIDELINES ON THE MANAGEMENT OF MULTIDRUG-RESISTANT AND EXTENSIVELY DRUG-RESISTANT TUBERCULOSIS IN HONG KONG

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Summary points:

1. Multidrug-resistant tuberculosis (MDR-TB) is defined as disease caused by bacillary strains showing resistance to at least both isoniazid and rifampicin *in vitro*. Extensively drug-resistant TB (XDR-TB) is MDR-TB with additional resistance to any fluoroquinolone and at least one of the second-line injectable drugs: kanamycin, amikacin and capreomycin.
2. MDR-TB and XDR-TB present an increasing threat to global tuberculosis control.
3. A multidrug-resistant tuberculosis registry has been set up within the Tuberculosis and Chest Service of Department of Health.
4. Health care workers are requested to notify MDR-TB and XDR-TB cases to the Tuberculosis and Chest Service using a standard notification form for these diseases.
5. MDR-TB is more difficult to treat when compared to drug-susceptible disease, thus resulting in a significantly lower treatment success rate. XDR-TB is even more difficult to treat.
6. The regimen used to treat MDR-TB should comprise 5 to 6 drugs to which the organism is or likely to be susceptible for the initial 6 months, and then 3 to 4 drugs subsequently. Extended regimens, consisting of multiple second-line and even third-line anti-TB drugs, given for prolonged periods are needed to treat XDR-TB.
7. A single drug should never be added to a failing regimen.
8. Surgical resection of a major pulmonary focus may be a useful adjunct for selected cases with sufficiently localised disease not responding well to drug treatment.
9. Periodic follow up screening may be indicated for MDR-TB and XDR-TB contacts with normal chest radiograph findings on initial screening.
10. Measures to prevent nosocomial spread of MDR-TB and XDR-TB include an effective triage system, isolation of infectious patients, minimisation of patients' duration of stay in the health care settings, advice on personal hygiene, and the use of face masks.

## Background

Tuberculosis (TB) is still an infectious disease of public health importance today globally and locally. Of particular concern is the occurrence of multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB). MDR-TB is TB with bacillary resistance to at least isoniazid and rifampicin. XDR-TB is defined as MDR-TB with additional bacillary resistance to any fluoroquinolone and at least one of the second-line injectable drugs: kanamycin, amikacin and capreomycin. Data from the World Health Organisation (WHO)/ International Union Against Tuberculosis And Lung Diseases (IUATLD) Global Project on Drug Resistance Surveillance have identified several hot spots for MDR-TB and XDR-TB.[1] Inner Mongolia and Heilongjiang in China have a relatively high MDR-TB rate among new cases, while in Hong Kong and United States the MDR-TB rates are on a decline. WHO estimated that around 490,000 MDR-TB and 40,000 XDR-TB cases emerge every year. Drug resistance develops through selection pressure. Most commonly the development of multidrug-resistance occurs when there is a large bacillary population, when an inadequate drug regimen is prescribed, or when there is a combined failure of both the patient and provider to ensure that an adequate regimen is taken.[2] With appropriate combination chemotherapy that is reliably taken, clinically significant resistance will not develop.[3] Use of directly observed treatment, short course (DOTS) has been shown to reduce the transmission of TB and the incidence of drug-resistant disease. Efficiently-run TB control programmes based on DOTS policy is essential for preventing the emergence of MDR-TB and XDR-TB.

MDR-TB is more difficult to treat when compared to drug-susceptible disease, thus resulting in a significantly lower treatment success rate. Treatment cost is also much higher, and patients with MDR-TB may remain infectious for a longer period of time. For the control of MDR-TB, “DOTS-PLUS” strategy is recommended.[4] This strategy incorporates continuous drug-resistance surveillance, culture and drug susceptibility testing for TB patients, and tailoring of individual drug regimen through the use of first and second-line drugs.

At present, the rate of TB notification in Hong Kong is still high in comparison with other developed countries, viz around 80 per 100,000.[5] The rate of MDR-TB ranges from 0.3 to 0.6 per 100,000 populations for the years 1997 to 2006. In general, around 10% of MDR-TB cases are XDR-TB. Overall, MDR-TB and XDR-TB cases comprise around 1% and 0.1% of the total bacteriologically-positive TB notifications respectively. Nevertheless, it is necessary for doctors to remain vigilant, and continue to update knowledge and measures for the control of drug-resistant TB.

The Tuberculosis Control Coordinating Committee has published guidelines on the

management of patients with TB regarding both clinical and public health aspects.[6, 7, 8, 9] The treatment of MDR-TB involves the use of second-line drugs which are much more expensive, generally less efficacious, and have potentially more adverse effects than the first-line drugs. Suboptimal management of MDR-TB may result in further drug resistance. Clinical expertise and good laboratory support are essential for the successful management of patients with MDR-TB. It is therefore recommended that MDR-TB be managed solely by, or in close consultation with TB specialists. In this paper, general recommendation is provided regarding diagnosis, reporting, principles of treatment, contact screening, infection control and preventive measures in MDR-TB. It should be stressed that each case should be managed according to the individual circumstances, with the help of the necessary expertise.

## Diagnosis of Multidrug-resistant Tuberculosis and Extensively Drug-resistant Tuberculosis

It has been recommended that drug susceptibility testing of all pretreatment positive culture isolates should be done.[1] When the results of drug susceptibility testing are available, diagnosis of drug-resistant TB can be made readily, and the treatment regimen may be modified accordingly as needed.

In addition, early diagnosis of drug-resistant TB, particularly MDR-TB and XDR-TB, is highly desirable. Delay in the diagnosis of these diseases may result in progressive lung destruction, higher bacillary load, and continuing disease transmission. To enable early diagnosis, a high index of suspicion is required. A history of incomplete treatment for TB, close contact with MDR-TB patients, HIV infection, drug addiction, alcoholism, and migration from an area endemic for drug resistance are some useful clues. In our locality, a recent study showed that Chinese non-permanent residents, living on financial assistance, history of frequent travel and young age are additional risk factors.[10] For retreatment cases, the number and details of previous treatment lots as well as documentation of non-adherence should be obtained. A careful investigation of prior anti-TB treatment may help in identifying the likely pattern of drug resistance.

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

Furthermore, most rifampicin-resistant isolates have been reported to have a mutated *rpo*B

gene, and the mutations are concentrated on a short, less than 100-bp stretch of the gene.[11] In Hong Kong, a study found that the rate of resistant rifampicin strain that harbours *rpo* gene mutation was 93%.[12] On the other hand, the prevalence of MDR-TB in Hong Kong is not high. Clinical risk factors for MDR-TB should be considered before ordering rapid genetic tests for rifampicin resistance. In selected patients with known risk factors for MDR-TB, especially those with a known history of poor adherence in previous treatment, genetic testing for rifampicin resistance in M. tuberculosis can be useful, and the positive predictive value of the test in this subgroup of patients can be high.

**Reporting of Multidrug-resistant Tuberculosis Cases**

Timely notification of TB cases, drug-susceptible and drug-resistant 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&CS since May 1995 and the procedures have been updated in 2007 (MDR_Flow_protocol0709) (Appendix 1) to include reporting of MDR-TB (including XDR-TB) cases from sources outside TB&CS. Whenever a currently active and previously unreported case of MDR-TB (or XDR-TB) is diagnosed, health care workers are requested to notify the case to Wanchai Chest Clinic using the MDR-TB notification form (MDR_Noti_Form0709) (Appendix 2). In order to track progress of patients with MDR-TB and XDR-TB, a set of special programme forms have been designed (TB-PFMDR-X(1)/10-2004 and TB-PFMDR-X(2)/10-2004) (Appendix 3). 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) (Appendix 3) 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). [NB: PFA at pretreatment, PFB1 & PFB2 at 6 month, PFBC at 12m, PFBD at 24m, and PFMDR-X at 30m, 36m, 42m, 48m, 54m, and 60m.]

**Treatment**

For MDR-TB patients with known susceptibility pattern, the treatment regimen should comprise 5 to 6 drugs to which the organism is or is likely to be susceptible for the initial 6 months, followed by 3 to 4 drugs subsequently. The inclusion of an injectable agent (an aminoglycoside or capreomycin) for the initial 6 months and a fluoroquinolone all through are generally recommended.[13] Daily regime should be used, except perhaps for the injectables. Drugs showing *in vitro* resistance are generally excluded, with the possible exception of use of isoniazid in cases of low level resistance. The possibility of cross-resistance between drugs should be noted.[3,14]

Apart from first-line anti-TB drugs, available drugs for treatment of MDR-TB/XDR-TB include the fluoroquinolones (e.g. ofloxacin, levofloxacin, ciprofloxacin), aminoglycosides (e.g. kanamycin, amikacin), prothionamide/ ethionamide, cycloserine, para-aminosalicylic acid, capreomycin, and even clofazimine. These drugs vary in terms of anti-TB activity, convenience of administration, potential toxicity and cross-resistance. Drugs that have not been used to treat the patient before are preferred, and so are bactericidal drugs rather than bacteriostatic drugs.

There is controversy on the best approach in managing MDR-TB patients before drug susceptibility results for the second-line drugs become available. Each case should be judged on individual grounds. Recourse to the empirical use of several second-line drugs is often necessary while waiting for the definitive results. If it is considered necessary to treat a suspected MDR-TB patient before drug susceptibility test results are available, it may be advisable to employ an expanded regimen and give both the essential first-line drugs plus at least three second-line drugs that have not been used previously. A single drug should never be added to a failing regimen, because doing so may select organisms in the bacterial population that are resistant to the newly added drug (addition phenomenon). A combination of two or three drugs to which the organism is or is likely to be susceptible should be added.

Admission of patients with MDR-TB to special care centres including Grantham Hospital or Kowloon Hospital for newly diagnosed cases, or to the respective chest hospitals for old cases, is recommended particularly during the initial period. This will facilitate detailed assessment, stabilization and optimization of drug regime, reinforcement of health education and treatment adherence during subsequent outpatient follow up after discharge. Arrangement for hospital admission can be made through government chest clinics, or direct telephone/ facsimile contact of the hospital units.

All patients with MDR-TB should be given directly observed treatment (DOT), as far as practicable. Failure to comply with treatment is the main cause of poor treatment outcome and emergence of drug-resistant organisms. Therefore, every effort should be made to ensure that patients complete the full course of regular treatment.

For patients who have problems with drug adherence, the reasons for defaulting treatment should be carefully explored and addressed promptly. All efforts should be made to seek co-operation from treatment defaulters. 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.

Close monitoring of progress during anti-TB treatment is mandatory, in particular the general condition, body weight, chest radiograph and bacteriological status. Sputum specimens should be sent monthly for acid fast bacilli (AFB) smear and culture examination, until they are converted negative for three consecutive months, and then the persistent negative status is further confirmed with sputum culture examination every three months until the cessation of therapy. Sputum culture conversion in the early months of treatment correlates with a higher probability of cure in MDR-TB patients.[15]

Caution should be exercised in the interpretation of chest radiograph when initial radiographic improvement is observed. Sometimes this may be a temporary phenomenon due to control of the drug-susceptible bacterial subpopulation when a suboptimal regimen is employed.

Caution is to be exercised in the use of second-line drugs as they are often associated with significant adverse effects. Renal function should be checked regularly when 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. Cycloserine should only be used with caution and when its benefit is perceived to outweigh its potential adverse effects. Linezolid may be a useful drug for cases with extensive drug resistance, but it is relatively toxic and must be used with caution.[16]

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 fluoroquinolones 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.[17] A longer duration may however be required for patients with diabetes mellitus, silicosis, slow sputum culture conversion, extensive drug resistance or extensive radiographic disease.

The treatment of XDR-TB is even more difficult, as there are fewer remaining classes of drugs to which the tubercle bacilli are susceptible. Extended regimens, consisting of multiple second-line and even third-line anti-TB drugs, given for prolonged periods are needed to treat XDR-TB. Only around 40% of XDR-TB cases can be cured. XDR-TB cases should be solely managed by TB specialists as for the MDR-TB cases.

**Surgery**

For selected cases of MDR-TB with predominantly localised disease that is not responding well to treatment with an “adequate” chemotherapy regimen, surgical resection of a major pulmonary focus may be a useful adjunct. The remaining lung tissue should be relatively devoid of disease and there should be sufficient drug activity to diminish the mycobacterial burden to facilitate healing of the bronchial stump.[3] The opinion and expertise of thoracic surgeons should be sought under these circumstances. In recent years, there has also been a revival of interest in the use of artificial pneumothroax.[18]

**Contact Examination**

Good public health measures are mandatory 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.[19] In addition, for MDR-TB contacts with normal chest radiograph findings on initial screening, periodic screening afterwards, 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 bacteriological status. The contacts should also be educated on symptoms suspicious of TB 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 TB, 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 or XDR-TB among contacts is suspected. To achieve effective public health control of the infection, close communication should be maintained with the relevant parties including DH. Restriction fragment length polymorphism (RFLP) analysis (DNA fingerprinting) may be considered.

**Infection Control Measures**

The patient should be provided health education on measures to prevent the spread of the disease. For examples, these include (1) good personal hygiene (like no spitting, and covering mouth and nose during coughing and sneezing in public area), (2) avoid going to overcrowded areas, and (3) put on surgical masks if there is a need to go to crowded public areas including public transport vehicles.

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, isolation of infectious MDR-TB patients in a negative pressure room until assessed to be non-infectious, 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.

**Other Issues**

In its Global MDR-TB & XDR-TB Response Plan (2007-2008), the World Health Organization (WHO) warned that XDR-TB raised the possibility that the current TB epidemic of mostly drug susceptible TB would be replaced with a form of TB with severely restricted treatment options.[20] In Hong Kong, the overall treatment success rates for MDR-TB and XDR-TB have been estimated to be 63% and 38% respectively. Special management is necessary for chronic MDR-TB/XDRTB cases not responding well to treatment, and those who failed treatment (failure-failure cases). These patients can remain infectious and pose a public health risk. WHO advises MDR-TB patients not to travel by air until proven by adequate laboratory confirmation (i.e. culture) to be non-infectious.[21] An RFLP study in PHLC has shown some case clustering and within household transmission of XDR-TB. Some form of isolation may be necessary. This can be in the form of voluntary isolation in a singleton flat in a remote area, or as inpatient for sanatorial care. The patient and his/ her household members should be advised and emphasized repeatedly on observation of personal hygiene, putting on a face mask when necessary, 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 special diet allowance should be used with close monitoring to ensure that they are used optimally. Compassionate re-housing may have to be considered.

The Prevention and Control of Disease Ordinance (PCDO)(Cap.599) has been newly enacted on 14 July 2008. It aims to provide for the prevention and control of infectious diseases and to enable our compliance with the requirement of the International Health Regulations (2005) promulgated by the World Health Organization. Provisions for prevention of cross-boundary spread of infectious diseases are included. Under its subsidiary legislation, the Prevention and Control of Disease Regulation (PCDR)(Cap.599A), XDR-TB is included as a specified disease such that health officers are empowered to prohibit XDR-TB from leaving Hong Kong unless written permission is given. Under the legal framework, sometimes compulsory coercive actions have to be exercised to protect public health. These include measures such as detaining an XDR-TB patient at the airport before he intends to travel by air, or detaining TB patients for isolation or medical examination in hospital. In fact, compulsive measures for TB patients have been in practice in United States[22] and United Kingdom[23]

since 1990. However the use of such legal power must be viewed as a last resort, and justified only after all voluntary measures to isolate such a patient have failed, and the isolation order should be of a limited duration and subject to review.[24]

**Conclusions**

MDR-TB and XDR-TB presents an increasing threat to global TB control. Treatment success rate for these diseases is relatively low. In addition, the cheapest MDR-TB treatment regimen is 100 times more expensive than the best first line regimen. It should be much more cost effective to prevent emergence of MDR-TB and XDR-TB in the first place, through implementation of the DOTS strategy. Effective implementation of the DOTS strategy saves lives through decreased TB transmission, decreased risk of emergence of drug resistance, and decreased risk for individual patient of treatment failure, TB relapse, and death. The routine use of DOTS in the treatment of all cases of TB cannot be overemphasised.

Many crucial issues in MDR-TB and XDR-TB management remain unresolved. The existing data on MDR-TB and XDR-TB treatment come mainly from retrospective cohort analyses.[14] Randomised or controlled clinical trials have not been performed to answer questions concerning best treatment regimens and optimal treatment protocols for patients with various patterns of drug resistance. There is a need for further clinical research on MDR-TB and XDR-TB treatment. There is also the need for new anti-TB drugs to be developed and tested. Currently, a number of new drugs as well as new vaccines for TB are under different phases of research and development.[25, 26, 27] Fluoroquinolones are currently among the most valuable drugs in the medical treatment of MDR-TB because of their bactericidal and sterilising activities and excellent oral bioavailability.[17,28] 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 to prevent escalation of fluoroquinolone resistance. Clearly the loss of this important group of compounds will have adverse consequences on our battle against TB.

To control MDR-TB and XDR-TB, specific surveillance programmes like the MDR-TB registry, drug resistance surveillance and treatment outcome monitoring are indispensable. These are all in place in Hong Kong and 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 demands long term work. Continuous multi-sectoral co-operation/ collaboration is necessary.

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