MANAGEMENT OF A PATIENT SUFFERING FROM UNCOMPLICATED PULMONARY TUBERCULOSIS

Tuberculosis and Chest Service

(Prepared in 2018)

Internal guidelines of
the Tuberculosis & Chest Service of
the Department of Health of
the Government of the Hong Kong SAR

MANAGEMENT OF A PATIENT SUFFERING FROM UNCOMPLICATED PULMONARY TUBERCULOSIS

SS Huang, WS Law, CK Chan

Summary points:

1. The objectives in managing a TB patient are: to identify and cure the individual patient, to contain the spread of the infection, and to prevent the development of drug-resistant TB.
2. A full medical history with physical examination is essential in the diagnosis of TB. Chest radiograph and sputum bacteriological examination are useful 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. Newer tools including molecular detection and amplification tests can shorten the time for diagnosis of TB and detection of drug resistance. 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. Apart from clinical management, public health measures are also essential. These include notification, contact tracing, infection control measures and health education.
5. Directly observed treatment (DOT) refers to treatment administered under direct supervision.
6. The standard treatment is the 6-month regimen for the treatment of drug susceptible pulmonary tuberculosis. Drug prescription should be made after assessment of contraindications and necessary precautions. Biochemical and clinical monitoring are performed where appropriate.

Introduction

The incidence of tuberculosis (TB) has been declining in Hong Kong in the past few decades. A total of 4,346 TB cases were notified to the Department of Health (DH) of Hong Kong in 2016. The corresponding notification rate was 59.2 per 100,000, which represented a more than 90% drop compared to the rate of 697.2 in 1952.[1] Ambulatory chemotherapy has been the mainstay of anti-TB treatment. While the majority of TB notification originates from hospital units under the Hospital Authority (HA), over 80% of the notified TB cases are managed in the chest clinics of the Tuberculosis & Chest Service (TB&CS) under the administration of the DH. Ambulatory treatment entails bringing the continuum of care closer to patients and communities, as well as enables patients to reduce the costs associated with reduced time at work or home,[2] and is an important TB management strategy recommended by the World Health Organization (WHO).[3] Ambulatory treatment may also reduce the risk of nosocomial TB transmission to hospital staff and among patients. This chapter provides an updated summary and general view of ambulatory care of a patient with uncomplicated pulmonary TB, as well as its public health management.[4]

Management Goals

The main objectives in managing a TB patient are (1) to establish an early diagnosis and prompt initiation of anti-TB treatment to bring about cure of the individual patient, (2) to contain the spread of the infection, and (3) to prevent the development of drug-resistant TB.[5] In this regard, the health care provider has a responsibility to monitor every TB patient for treatment progress until treatment completion.

(A) History and Physical Examination

As TB is endemic in Hong Kong, and it can mimic other respiratory diseases, a high index of suspicion should be maintained, especially for patients presenting with symptoms like persistent cough for over 3 to 4 weeks, hemoptysis, 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 a previous history of TB, coexisting medical illnesses that have been reported to be associated with an increased risk of TB (in particular diabetes mellitus, silicosis, chronic renal disease, collagen vascular diseases, HIV disease, etc), occupational history, contact history, smoking habit, as well as drug history (e.g. anti-tumor necrosis factor (TNF) agents, corticosteroids or other immunocompromising drugs). For patients with a history of TB contact and where the index case has a positive culture of *Mycobacterium tuberculosis* (MTB), the anti-TB drug susceptibility pattern of the latter may help 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 not uncommonly yields negative findings. Some features may be worth mentioning, however, 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.

(B) Investigations

1. Chest Radiograph

The chest radiograph is a relatively simple and sensitive test. Typical radiographic changes, like apical lesions (especially if situated posteriorly), 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 co-infected 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.[6,7]

2. Microbiological Tests

Sputum examination for acid fast bacilli (AFB) is essential for the diagnosis of pulmonary TB.[8] Diagnostic sputum samples, preferably collected in two consecutive mornings, are sent for direct smear and culture examination. If direct smear results 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 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.[9,10,11]

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 detection of bacillary drug resistance, though at a higher cost. However, some positive results of nucleic acid amplification tests may need to be interpreted with care, 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, fiberoptic bronchoscopy, and percutaneous transthoracic fine needle aspiration biopsy. 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 a situation, careful clinical evaluation of treatment response is called for to confirm the clinical diagnosis and exclude other possibilities.

3. Screening for TB Infection

Both tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) are immunological tests designed primarily for the diagnosis of infection. 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 WHO has issued a policy statement stating 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.[12] 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 in low- and middle-income countries. However, the WHO's policy statement is not intended to apply to high-income countries or to supersede their national guidelines.

4. Drug Susceptibility Tests

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 or medical units of HA. Identification and drug susceptibility tests to the first-line anti-TB drugs (namely isoniazid, rifampicin, ethambutol as well as streptomycin although the latter is seldom used nowadays for treatment of TB) 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 rifampicin resistance or 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

and/or other relevant specimens should be sent for bacteriological examination including drug susceptibility tests as far as possible.

5. Nucleic Acid Amplification Tests

Newer generations of molecular amplification tools have been increasingly utilised to facilitate the rapid diagnosis of TB and detection of drug resistance. The use of Xpert MTB/RIF test has been endorsed by WHO for early detection of rifampicin resistance (as a proxy for MDR-TB).[13,14,15] It has been recommended as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB. As MDR-TB cases may not be readily excluded by absence of risk factors (such as a history of previous treatment for TB or close contact with MDR-TB patients), screening for rifampicin resistance for all smear positive cases is crucial to detect any presence of rifampicin resistance or MDR and to avoid progressive acquisition of further drug resistance during anti-TB treatment.

(C) Management

1. Notification of TB

Once a diagnosis of active TB is made, the case should be notified to DH, a statutory requirement according to the Prevention and Control of Disease Ordinance (Cap. 599). 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".[16]

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.[17]

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).

2. Contact Tracing and Screening

The health nurses will enquire the patient about his/ her close contacts (usually the household members and/or other close contacts according to the actual circumstances), 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 secondary 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.

3. Infection Control Measures

The sputum smear status is a general guide to the infectiousness of the TB patient. Those patients with severe cough, cavitary pulmonary disease, and positive sputum smear, as well as those with laryngeal TB, are likely to be more infectious. Prompt initiation of treatment is crucial as infectiousness rapidly decreases with effective treatment.[18]

Health education, advice on respiratory 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, however, should be paid to infectious patients (including teachers, staff of homes for the elderly, medical personnel working for debilitated patients, and elderly home infectious residents) who are in frequent contacts with susceptible people. More stringent measures and granting of prolonged sick leave may be necessary.

4. Directly Observed Therapy

The most important reason for failure of anti-tuberculosis treatment is poor adherence. Studies have shown that there is no good way to predict adherence to drug therapy. In the chest clinics, anti-TB medication is given under direct supervision by the health nurses to ensure full adherence through "Directly observed treatment (DOT)". Supervised treatment is crucial for the success of the treatment programme.[19] DOT by a health care worker also facilitates closer clinical monitoring of adverse drug effects.

(D) <u>Treatment</u>

The standard 6-month treatment regimen of 2HRZE/4HR consists of a two-month intensive phase comprising four drugs, namely, isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) (or rarely streptomycin (S)), plus a four-month continuation phase of two drugs, namely, isoniazid and rifampicin, making a total duration of six months for patients with usual, uncomplicated drug-susceptible pulmonary TB.[20,21] (Table 1). 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. As most transmission occurs before diagnosis, and the risk of a TB patient infecting other people drops significantly after the first few to 14 days of effective treatment, TB patients are generally managed as an outpatient for ambulatory care unless there are other indications for hospital admission, in line with WHO recommendation.

As regards dosing frequency, systematic reviews were quoted in the recent 2017 updated WHO TB treatment guidelines,[19] showing patients with thrice-weekly dosing had a higher risk of treatment failure, disease relapse and acquired drug resistance in both drug-susceptible disease and when the strain susceptibility was unknown. Hence, WHO recommended that thrice-weekly dosing in the intensive phase should never be

used. For continuation phase, thrice-weekly dosing had a higher risk of treatment failure and disease relapse, but not acquired drug resistance rates compared to daily dosing. Therefore, it is essential to ensure absolute drug compliance if thrice-weekly dosing is used in the continuation phase. WHO encouraged all countries to use exclusively daily dosing throughout the treatment period.

Table 1. Standard regimen for anti-tuberculosis treatment

Intensive phase (2 months)	Isoniazid (H) + Rifampicin (R) + Pyrazinamide (Z) + Ethambutol (E)*
Continuation phase (4 months)	Isoniazid (H) + Rifampicin (R)

*Streptomycin has been used in the past as an alternative to ethambutol; it is seldom used nowadays due to increasing prevalence of resistance to the drug in many parts of the world and its potential side effects.

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,[22] HIV antibody (after counselling and obtaining patient's consent) and if indicated, blood sugar or HbA1c are performed. Baseline vision tests for visual acuity and colour perception (e.g., using Snellen chart and Ishihara chart) are also performed if ethambutol or other potential ocular toxic drug is to be started.[23] Studies show that it would be desirable to closely monitor liver function for HBsAg carriers during anti-TB treatment.[22] 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 (e.g., discoloration of urine, faeces, tear and other body fluids) and side effects of the anti-TB drugs. 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.[4,22,23,24] The establishment of good rapport with the patient from the very beginning is essential for the success of the treatment programme.

Follow-up and Monitoring

During the initial phase of chemotherapy, follow up consultation can be arranged monthly to assess progress, and to reinforce patient adherence for patients without experiencing adverse effects from anti-TB treatment. 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.[22] Blood sugar or HbA1c would be checked at baseline for evaluation of diabetic control in patients with diabetes mellitus (DM). If DM control is unsatisfactory (HbA1c>7%), referral letter to the responsible caring unit should be given to facilitate better DM control. 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 is used, treatment is prolonged[23] or for those with impaired renal function.

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.

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. Minimizing non-adherence is vital for the overall success of the TB control program. For the occasional infectious TB patient (both drug-susceptible and drug-resistant) who poses a significant public health risk and who fail to cooperate and where all other measures for encouraging the patient to adhere to treatment have failed, coercive measures including issuance of isolation order may be undertaken to safeguard the health of the public.

At the end of six months' treatment, the patient is assessed with a follow-up 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. Standardised "Programme Forms" have been used for continuous evaluation of the service programme in the TB&CS since 1998 and extended for use to other health care sectors including the HA and the private sector. An updated version of the Programme Forms was recently introduced in January 2018. Data collected include information on demographics, 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 TB control programme. Surveillance of treatment outcomes are regularly reported in the Annual Reports of TB&CS.[1]

Practical Aspects of Treatment

From time to time, complicating issues may 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.[22] Transient rise of liver enzymes may occur, and it may not, by itself, represent genuine hepatotoxicity. Locally, the recommendation is to withhold potentially hepatotoxic anti-TB drugs in patients without hepatitis symptoms when the ALT rises ≥ 3 times upper limit of normal (ULN) or when the bilirubin level rises to ≥ 2 times ULN. In the case of clinical suspicion of significant hepatitis reactions, the anti-TB drugs may have to be stopped even before the availability of the biochemical 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 desensitization 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. 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 (including pulmonary TB associated with medical diseases or in special settings) can be found in various local and international publications and guidelines, and the TB website (www.info.gov.hk/tb_chest).[5,19]

Special Issue: Ambulatory Treatment versus Hospitalization

TB is an old disease. The introduction of sanatorium care in the mid-19th century provided the first real step in the battle against this dreadful disease. With the advent of anti-TB medications in the late 1940s, TB patients could be treated as out-patients.[25] An ambulatory care model for TB has been adopted in Hong Kong in the past few decades. To facilitate easy access to TB treatment and to facilitate DOT on an out-patient basis, TB&CS now operates chest clinics throughout the territory. Clinic-based ambulatory treatment embodies a holistic patient-centred approach to supporting treatment adherence. Apart from reducing the cost associated with hospitalizations, ambulatory treatment also decreases the risk of nosocomial transmission to health care workers and other vulnerable patients. The latter may be of particular relevance given reports of outbreaks of MDR-TB in the hospital setting in recent years.[26,27] On the other hand, the risk of infection for contacts of patients treated at home was found to be no greater than for contacts of patients treated as in-patients, as exposure mostly occurs before diagnosis and appropriately treated patients rapidly become non-infectious.[28]

Despite the existence of a well-established community-based TB programme and universal health care access, an increasing proportion of TB patients are diagnosed as in-patients in Hong Kong in recent years, as reflected by the increasing proportion of TB notification originating from HA hospitals (66.9% in 2016 vs 59.8% in 2006).[1] The ageing population, increased prevalence of co-existing medical illnesses and atypical presentation may be the underlying reasons for the observed phenomenon. Studies to identify factors associated with hospitalization at the time of TB diagnosis and initiation of treatment may help local policy makers and clinicians more efficiently plan resource needs and local health program, in order that the latter has the right combination of models of care (ambulatory vs in-patient) to serve the needs of all patients and the

medical care is provided in the most appropriate setting. Given the high cost of hospitalization, the risk of nosocomial transmission of TB and the risk of acquisition of nosocomial infections, ambulatory treatment remains the preferred mode of management for the usual patients with uncomplicated pulmonary TB and without risk factors for drug resistance.

Stringent measures are necessary to prevent nosocomial transmission of TB for hospitalised patients diagnosed to have infectious TB such as sputum smear positive pulmonary TB or laryngeal TB. Because of the great difference in the background TB epidemiology between countries, the HA Task Force on Infection Control has published a local guideline on "Control of Transmission of TB in the Healthcare Settings" based on general principles, expert opinions and international recommendations. Interested readers may refer to the guideline for details of the guidance for infection control measures and respiratory isolation related to TB in the local healthcare settings[29] when necessary.

Conclusion

TB is an infectious disease which is curable with appropriate treatment. Efforts should be made to ensure all TB patients have correct and regular treatment in order to prevent the emergence of bacillary drug resistance. Community-based ambulatory treatment, being more patient-centred, helps to improve patients' treatment adherence. It also allows health care providers to have more opportunities to address social determinants and other health issues often associated with TB, and is the recommended measure for managing patients with uncomplicated pulmonary TB. It is also one of the most important TB management strategies recommended by the WHO. It is essential that chest clinics under the administration of DH expand their capacity to address all aspects of TB, including prevention, detection, infection control, community education, social support and outreach to populations at high risk. In the meantime, studies are needed in order that local policy makers and clinicians can better understand the types of patients that require hospitalization during the diagnostic and management phases of TB and thus better plan treatment programs and resource needs. An effective TB treatment program is critical for strengthening the control of TB in our local situation and for making progress towards the End TB goal as proposed by the WHO.

Prepared in 2018

Acknowledgements

We would like to thank Dr CM Tam for his contribution and kind support in the production of this paper.

References

[1] Tuberculosis and Chest Service, Department of Health, Government of Hong Kong SAR. Annual report 2016.

[2] WHO Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva: World Health Organization; 2014

[3] Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. Geneva: World Health Organization; 1999

[4] Ambulatory treatment and public health measures for a patient with uncomplicated pulmonary tuberculosis – an information paper (January 2013). Members of the Joint Committee of the Tuberculosis Control Coordinating Committee of the Hong Kong Department of Health and the Respiratory Services Working Group of the Hospital Authority. Annual Report (Suppl) 2013, TB & Chest Service, Public Health Services Branch, Centre for Health Protection, Department of Health, Hong Kong.

[5] Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of drug-susceptible tuberculosis. Nahid P, Dorman SE, Alipanah N et al. Clinical Infectious Diseases 2016; 63: e147–95.

[6] Detection of pulmonary tuberculosis in patients with a normal chest radiograph. Marciniuk DD, McNab BD, Martin WT, Hoeppner VH. Chest 1999;115:445-52.

7 Normal chest radiography in pulmonary tuberculosis: implications for obtaining respiratory specimen cultures. Pepper T, Joseph P, Mwenya C, et al. Int J Tuberc Lung Dis. 2008 Apr;12(4):397-403.

[8] Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children 2016. Official American Thoracic Society / Infectious Diseases Society of America / Centers for Disease Control and Prevention.

[9] Community-acquired pneumonia and tuberculosis: differential diagnosis and the use of fluoroquinolones. Grossman RF, Hsueh PR, Gillespie SH, Blasi F. Int J Infect Dis. 2014 Jan;18:14-21.

[10] Fluoroquinolones are associated with delayed treatment and resistance in tuberculosis: a systematic review and meta-analysis. Chen TC, Lu PL, Lin CY, Lin WR, Chen YH. Int J Infect Dis. 2011 Mar;15(3): e211-6.

[11] Newer flurorquinolones for treating respiratory infection: do they mask tuberculosis? Chang KC, Leung CC, Yew WW, et al. Eur Respir J. 2010 Mar;35(3):606-13.

[12] Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries – Policy Statement. 2011. WHO/HTM/TB/2011.18.

[13] Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system – Policy Statement. 2011. WHO/HTM/ TB/2011.4.

[14] Rapid implementation of the Xpert MTB/RIF diagnostic test – Technical and operational 'How-to' practical considerations. 2011. WHO/HTM/TB/2011.2.

[15] Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level – Checklist. 2011. WHO/HTM/TB/2011.12.

[16] Guidance notes for notification of tuberculosis. Available at http://www.info.gov.hk/tb_chest. Communicable Disease Surveillance Case Definitions (Version 14.8) Revised on 17 October 2017.

[17] Notification of tuberculosis. Available at http://www.info.gov.hk/tb_chest. Revised on 31 October 2017.

[18] Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. Riley RL, Mills CC, O'Grady F, Sultan LU, Wittstadt F, ShivpuriI DN. Am Rev Respir Dis. 1962 Apr;85:511-25.

[19] Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: World Health Organization; 2017.

[20] Chemotherapy of tuberculosis in Hong Kong: a consensus statement. 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 Hospital Authority, Hong Kong. Hong Kong Med J 1998;4:315-20.

[21] Chemotherapy of tuberculosis in Hong Kong – update in 2001: a consensus statement. 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 Hospital Authority, Hong Kong. Annual Report of TB & Chest Service of Hong Kong Department of Health; 2001 (Suppl).

[22] Monitoring for hepatotoxicity during antituberculosis treatment – general recommendations. 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 Hospital Authority, Hong Kong. Annual Report of TB & Chest Service of Hong Kong Department of Health; 2002(Suppl).

[23] Preventive measures against drug-induced ocular toxicity during anti-tuberculosis treatment – internal guidelines. Annual Report of TB & Chest Service of Hong Kong Department of Health; 2002(Suppl).

[24] Tuberculosis Manual 2006. Centre for Health Protection, Department of Health, Hong Kong Government SAR.

[25] Hospital admission policy for tuberculosis in pulmonary centres in Italy: a national survey. Nutini S, Fiorentini F, Codecasa L R, et al. Int J Tuberc Lung Dis 1999; 3: 985–991.

[26] Nosocomial transmission of multidrug-resistant Mycobacterium tuberculosis. A risk to patients and health care workers. Pearson ML, Jereb JA, Frieden TR, Crawford JT, Davis BJ, Dooley SW, Jarvis WR. Ann Intern Med. 1992;117(3):191–196.

[27] Nosocomial Transmission of Extensively Drug-Resistant Tuberculosis in a Rural Hospital in South Africa. Gandhi NR, Weissman D, Moodley P et al. J Infect Dis. 2013 Jan 1;207(1):9-17.

[28] A controlled study of the infl uence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. Kamat S R, Dawson J J Y, Devadatta S, et al. Bull World Health Organ 1966; 34: 517–532.

[29] Control of Transmission of TB in healthcare settings in the HA. Hospital Authority. HA Task Force in Infection Control. Version 3.1. Updated in October 2017.