Current Management of Pulmonary Tuberculosis

Dr. Poon-chuen Wong
MBBS, FRCPE, FHKAM, FHKCP, FCCP
Consultant Physician, Tuberculosis and Chest Unit, Grantham Hospital, Hong Kong

Introduction

Tuberculosis (TB) has been a fatal infectious disease of humans for centuries, though potentially treatable in recent decades. Worldwide, the TB-infected population is huge. It was estimated that one third of the world’s population were infected with Mycobacterium tuberculosis (MTB). Every year, the disease develops in over 8 million and claims the lives of about 3 million people. The problem of TB is further complicated by an upsurge of cases with multidrug-resistant (MDR-)* and extensively drug-resistant (XDR-)# bacilli in recent years. TB affects the respiratory system mainly with pulmonary tuberculosis (PTB), either on its own or together with TB of other sites, accounting for more than 85% of all TB cases notified in Hong Kong.

(* MDR: meaning resistant to the two most powerful anti-TB drugs, isoniazid and rifampicin, at least;
# XDR: meaning MDR plus resistant to any fluoroquinolone and at least one of the three injectable second-line drugs, amikacin, kanamycin or capreomycin.)

Many factors contribute to the continuous prevalence of this infectious disease. They include:

1. the existence of a stage of latent TB infection that occurs in many asymptomatic subjects in high prevalence countries,
2. the breaking down of latent infection into progressive disease when immunity of host wanes,
3. the late presentation of many infectious, open PTB patients,
4. the long duration of treatment that is required for PTB,
5. the lack of good TB control programmes in many countries,
6. the increasing prevalence of other immunocompromising conditions like HIV infection, use of immunosuppressive drugs or even an ageing population itself and
7. the trend of globalisation and increased population movement between states and continents.

Successful control of TB relies on the existence of good TB control programme and initiative in all parts of the world especially the underprivileged and developing areas. Affordable and reasonably accurate laboratory testing, early detection and treatment of smear positive cases, effective and continuously available chemotherapy, experienced and dedicated healthcare team together with surveillance and monitoring mechanisms are mandatory to such programmes. The ultimate outcome of our battle against TB will depend on the concerted effort of all countries in running and maintaining a good TB control programme of their own. World Health Organization (WHO) and International Union Against Tuberculosis and Lung Diseases (IUATLD) are committed to this work of fighting TB through collaboration of countries with different socio-economic, cultural and religious background.

In the frontline, we, clinicians, should familiarise ourselves with updates in the diagnosis and treatment of the disease in order to assist in the “fighting TB” battle.

Diagnosis of PTB

Microbiology

Sputum microscopy and conventional solid medium culture are still the cornerstones in the diagnosis of PTB nowadays. They are cheap and widely available. Sputum direct smearing for acid fast bacilli, using the Ziehl-Neelsen or auramine staining, has the disadvantage of a low yield (positive in about 30% of all active PTB cases) but detects cases of open PTB to allow early treatment and reduces infectivity. Sputum culture for MTB on conventional solid medium (Lowenstein Jensen medium) can diagnose 50-60% of all active PTB cases. Its limitation is a long turn-around-time (TAT) of 3-8 weeks and an additional 4-6 weeks for drug susceptibility result. Rapid culture systems (in liquid media) by detecting CO2 production or O2 consumption (the BACTEC and MGIT systems) are more sensitive and has a slightly shorter TAT of about 2 weeks compared with conventional solid medium culture. The technology and cost needed to operate these broth-based culture systems, however, limit their availability in poor countries.

Nucleic Acid Amplification (NAA) methods for detection of segments of MTB-DNA or RNA, such as Polymerase chain reaction (PCR-MTB), were widely investigated and used for the diagnosis of TB in recent years. These tests have higher sensitivity than sputum smear and approach the sensitivity of culture. They are rapid (TAT: 1-2 day) but costly. Refinements to NAA tests allow detection of drug resistance by finding resistant mutations, like rpo-B gene, readily. With its inherent high specificity, NAA test is particularly helpful in diagnosing paucibacillary extrapulmonary TB, like TB meningitis, peritonitis and pericarditis. By the same token, it also helps differentiating MTB from other atypical mycobacteria with the various commercially available DNA probes that are specific for the common species of Mycobacterium.
Another method investigated recently for rapid diagnosis and drug susceptibility testing of TB is called the microscopic observation drug susceptibility (MODS) assay. The technique is a relatively simple approach which uses little new technology. A sample is decontaminated and aliquotted into wells containing 7H9 broth with or without anti-TB drugs on a 96-well plate. The plate is examined under inverted microscope daily after inoculation for the characteristic cording appearance of growing MTB. A preliminary study showed encouraging results with MODS giving a sensitivity of 97.8% as compared with 89% for broth-based culture and 84% for culture on solid medium. The medium time to culture positivity was 7, 22 and 26 days for the three techniques respectively.

Radiology
Many patients with active PTB are still diagnosed on radiological grounds as a result of initial negative bacteriology. Patients with "typical TB changes" on chest radiographs (such as upper lobe predominant, patchy consolidations, fibrocavitary lesions, miliary, granuloma or granulomata with calcification) and clinical picture highly suspicious of PTB (fever, night sweating, cough, haemoptysis, perhaps together with a strongly positive tuberculin skin test for patients in or coming from an area with high TB prevalence) are often diagnosed as suffering from active PTB and treated as such. They should be carefully monitored for response to treatment and side effects of drugs and subsequently revealed with culture results.

Computed Tomography (CT thorax) is occasionally useful in detecting subtle lesions not discernable on plain x-ray. It also can depict small airway disease pattern (tree-in-bud appearance), endobronchial or mediastinal involvement by TB. It is important to recognise that the proportion of PTB patients with underlying immunodeficiency state is increasing with time. The radiological presentations of such patients can be fairly atypical (like inconspicuous lesions or mottlings in patients with HIV co-infection or lymphopenia, lower lobe consolidations or tumour-like masses in diabetics). Under such circumstances, invasive investigations such as fibreoptic bronchoscopy, needle lung biopsy or even video-assisted thoracoscopic surgical (VATS) biopsy may be required to make a diagnosis of PTB.

Treatment of PTB
Directly observed therapy, short-course (DOTS) is the key to success for anti-tuberculosis chemotherapy nowadays. It involves the use of a multi-drug regimen with isoniazid (H), rifampicin (R) and pyrazinamide (Z) as essential drugs and a fourth drug, streptomycin (S) or ethambutol (E), was usually added in countries with high prevalence of drug resistance. These four drugs are administered together for 2 months (the intensive phase), followed by a continuation phase of 2 drugs, HR for 4 months (2HRZS or 2HRZE/4HR), in a fully supervised fashion. Medications should never be divided and taken at different times of the treatment day. Treatment success with DOTS was found to occur in over 95% of patients suffering from drug susceptible PTB. Alternative but less potent regimens for treatment of PTB include 2HRZE/6HE, 2HRZS/6S2H2Z2 and 2HRE/7HR. These alternative regimens should be considered as inferior to the standard regimen and are only employed in case of intolerance to pyrazinamide or because of financial problem from the high cost of rifampicin. Immunocompromised patients, those with coexisting silicosis or suffering from miliary, extrapulmonary or extensive pulmonary TB should receive prolonged therapy. They are preferably managed by pulmonologists with experience in treating TB.

Adverse effects of anti-TB drugs are many. Most of them are mild such as gastrointestinal and cutaneous reactions and may not require treatment cessation or modification. The most important adverse effect of anti-TB treatment is hepatotoxicity as all three key anti-TB drugs (H, R and Z) are potentially hepatotoxic. This may be further aggravated by underlying hepatitis-B virus infection, alcoholic liver disease, etc. It is recommended that liver function test should be checked at pre-treatment and be repeated any time after treatment when hepatotoxicity is suspected. Management of drug-induced hepatotoxicity could be complicated and specialists’ (pulmonologist’s and hepatologist’s) consultations are recommended.

Some common or important-to-remember side effects of anti-TB drugs are: pyridoxine deficiency, peripheral neuropathy and lupus-like reaction for H, thrombocytopenia, “flu syndrome” and interstitial nephritis for R, pigmentation, hyperuricaemia, arthritis or arthralgia for Z, retrolubular neuritis for E and nephrotoxicity and ototoxicity for S. Baseline testing for visual acuity and red-green colour discrimination are recommended for patients receiving ethambutol. Baseline platelet count and renal function/hearing function tests are preferred for patients receiving rifampcin and streptomycin respectively. Blood level of uric acid should be assayed for patients with a history of gout or chronic renal failure for whom pyrazinamide is to be prescribed. All tests should be repeated as indicated after commencement of therapy.

Drug interaction should also be watched out carefully as patients with PTB require a prolonged period of therapy with multiple anti-tuberculosis drugs that might interact with other co-administered agents. Common examples of drug interaction include warfarin, corticosteroids, oral contraceptives, anti-diabetic and anti-retroviral drugs with rifampicin and anti-convulsants with isoniazid and rifampicin.

Adjunctive corticosteroid or surgery is occasionally employed in the management of PTB patients. Systemic steroid can ablate severe inflammatory reaction, sometimes associated with immune reconstitution, occurring in some patients after the commencement of anti-TB treatment. The condition is commonly encountered in patients with TB lymphadenitis, TB pleuritis and in HIV-infected subjects after anti-retroviral therapy. Systemic steroid is also recommended for patients suffering from TB meningitis, tuberculoma of central nervous system or TB pericarditis.

Surgery is mainly a diagnostic tool for difficult or atypical cases of PTB. It may infrequently be required for treatment in PTB patients with severe and uncontrollable haemoptysis and in selected cases of
endobronchial, pleural, pericardial, lymph nodal or other extrapulmonary forms of TB.

MDR- and XDR-TB usually stemmed from inadequate or ineffective previous treatment thus reiterating the importance of DOTS and good TB control programme in a community. Although MDR-and XDR-TB together only account for about 1% of all TB cases in Hong Kong, the corresponding figures of our neighbouring countries or regions are relatively high. We should therefore be vigilant and watch out carefully for drug resistant TB in our daily clinical practice especially in high risk cases. Treatment for MDR- and XDR-TB is very challenging both for the patients and their physicians. It involves the use of less potent but more toxic second-line agents together with those first-line drugs that are still efficacious according to drug sensitivity result of individual patients. The reserve (second-line) drugs include the anti-TB fluoroquinlone: ofloxacin, levofloxacin or moxifloxacin, the injectable second-line drugs: amikacin, kanamycin or capreomycin, ethionamide or prothionamide, Para-amino Salicylic Acid (PAS) and cycloserine. By combining 5 to 6 of these drugs, given for an extended duration of 12-24 months, with meticulous monitoring of response to treatment and adverse effects of drug and with the help of surgeons in a few suitable cases, favourable outcome could be seen in about 70-80% of cases. Failure cases often progress to become reservoirs of transmission and pose great hazard to public health. Newer agents for treatment of drug resistant TB are slow in their development and their pre-market clinical evaluation pathway is also very long. In Hong Kong, MDR- and XDR-TB patients should always be referred to the Tuberculosis & Chest Service of the Department of Health for evaluation, management and follow up. Designated centres for management of drug resistant TB patients were also set up in certain hospitals under the Hospital Authority.

**Conclusion**

The impact of emerging infections like SARS and avian Influenza has received much attention from the public, the policymakers and the administration. Resources diverted toward research and measures taken for preparing possible outbreaks of these fancy infections have been tremendous. TB, a continuous and genuine threat to lives of millions all over the world, on the other hand, had only received a disproportionately small share of healthcare dollar in most countries. Calls for proper focusing and distribution of resources have been voiced out repeatedly by professionals and international organisations. Globally, development of new anti-tuberculosis drugs for treatment and investigational tools for diagnosis of TB is of low priority and improvement of TB control programme in poor countries is still being neglected, up to this moment.

As a result, it will still be a long way to go before we can see the fading away of tuberculosis just as what we saw with leprosy, syphilis and smallpox. So, keep updating on TB management, whether we like it or not.