Update on Evidence Based Practices

Diagnosis of tuberculosis – From yesteryear to recent days

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Introduction

Tuberculosis (TB) is still a priority public health concern around the globe. According to the World Health Organization (WHO), the estimated number of incident cases of TB was 10.4 million in 2015. Of them, only 6.1 million were notified to the national TB programme while around 4 million remain undiagnosed or without any treatment (1). Though early detection is important in preventing the transmission of TB, it continues to be a major challenge for most countries in the world including Sri Lanka. Around 8000-9000 TB cases are reported each year and in 2016, 8660 incident (new and relapse) cases were reported to the National Pro-gramme for TB control and Chest Diseases (NPTCCD). The estimated incidence for Sri Lanka for 2015 was 65 per 100,000 population, which equals approximately 13,500 cases (1). With these estimates, it is likely that 4500 cases remain in the society undetected and without treatment.

In 2015, treatment success rate for all forms of TB was 84.1%, and Sri Lanka is moving forward to achieve the treatment success rate of 90% by 2017, which is the set target in the revised national strategic plan for TB control in Sri Lanka for 2015-2020 (2). High death rate is one of the major challenges for achieving this target, while complications due to late case detection are one of the main reasons for high death rates in Sri Lanka. Therefore, early diagnosis of TB cases will contribute to achieve high treatment success as well as control of further spread of the disease.

Sputum microscopy

There are several WHO accepted methods for diagnosis of TB (3). Of these, sputum microscopy remains the most simple, rapid and cost effective method of diagnosis of pulmonary TB since the discovery of *Mycobacterium tuberculosis* in late 18th century. The Ninth Report of the WHO expert committee issued in 1974 promoted sputum microscopy on people with symptoms suggestive of TB and those at high risk (4). It is still the most commonly used initial diagnostic test in the developing countries for TB diagnosis.

Whenever a patient is suspected of having TB, sputum smear stained with Ziehl-Neelsen is examined microscopically for detection of acid fast bacilli. Three sputum samples are required for establishing the diagnosis and one of the samples preferably has to be an early morning sample. There are certain limitations in the performance of this procedure. The sensitivity of sputum microscopy depends on the quality of the sample and is low when the microbial load is less than 10,000 organisms per ml of sputum (5).

Fluorescent microscopy

Fluorescent microscopy was introduced in 1930 as an improved method of microscopy for TB diagnosis. Fluorochrome dyes are used for staining of smears, and the sensitivity of fluorescent microscopy was 10% higher than the conventional microscopy (5). The limitations were low specificity, high cost of mercury vapour light sources and the need for regular maintenance (6). A dark room is also required for the performance of this method (5).

Light emitting diode microscopy

Light emitting diode (LED) microscope offers the same functions of a conventional fluorescence microscope but with much less cost. It has been especially developed to be used in resource limited settings. In 2009, WHO recommended replacing the conventional fluorescent microscopy with LED microscopes as an alternative for sputum smear microscopy in a phased out manner (6).

Chest X ray

Chest X ray (CXR) is one of the primary tools used in screening for TB since ancient times. It was used to screen military recruits for TB during the First World War, and later for three decades for screening of civilian populations (3). Though its value is limited in the diagnosis of TB due to its low specificity, it is useful as a diagnostic aid when pulmonary TB cannot be confirmed bacteriologically (7). WHO in its year 2008 publication on guidelines for TB control programmes, recommended the usage of chest radiography for TB diagnosis directly after a negative bacteriological test (7).

The recent guidelines of 2016 highlighted the importance of chest radiography as a useful tool for triaging of TB patients and screening of TB, due to its high sensitivity in detecting pulmonary TB (7). Increased availability of radiography, digital radiography with low running cost and portable methods for field use, better image quality and low radiation risk, rapidity in documentation of results are also favourable facts for usage of chest radiography. In addition, 2016 WHO guidelines recommended the CXR as an essential tool to "end TB" including the following recommendations (7):

- CXR is a sensitive tool for screening for active TB
- An abnormal CXR is an indication for full diagnostic evaluation
- CXR is an important tool for diagnosis of childhood TB
- CXR can improve the efficiency of Xpert (MTB/ RIF) – Xpert mycobacterium tuberculosis and resistance to rifampicin
- CXR can assist diagnosis of TB among people living with HIV
- CXR helps to rule out active TB before treating latent TB infection
- CXR is an essential technology for preventive surveys

Sputum culture

Sputum culture is one of the reliable methods of TB diagnosis. It provides more definite diagnosis of TB by isolation of mycobacteria. It is more sensitive and specific than the conventional sputum microscopy. However, it takes 6-8 weeks to obtain the results and is more expensive than the sputum microscopy. Liquid cultures are more sensitive and take less time to show the results than culture methods using solid media (7). An automated liquid TB culture system and Mycobacterial Growth Indicator Tube (MGIT) have been recommended by the WHO to improve sensitivity and turnaround time in TB culture.

Molecular methods in TB diagnosis

The search for more sensitive, specific and rapid diagnostics in TB has led to the usage of molecular methods in TB diagnosis in recent years.

A few nucleic acid amplification tests (NAAT) are approved by the WHO for diagnosis of pulmonary and extra-pulmonary TB (3). NAAT is highly specific but currently shows lower sensitivity and negative predictive values than liquid cultures for all forms of TB especially for sputum negative and extra pulmonary TB (6). The conventional NAAT is not used in the NPTCCD for diagnosis of TB.

The only WHO recommended test, currently in use for rapid diagnosis of TB is the Xpert (MTB/RIF) assay which is also a nucleic acid amplification test (1). A commercially available nucleic acid amplification platform (GeneXpert instrument) and the special cartridge named Xpert (MTB/ RIF) used in this test can simultaneously detect the presence of *M. tuberculosis* and resistance to rifampicin in clinical specimens. It was initially recommended for the diagnosis of pulmonary TB and since 2013, it is used for the diagnosis of TB in children and extra pulmonary TB (1). Xpert (MTB/RIF) is more sensitive than sputum microscopy and detects TB bacilli in lower concentrations. Further, the results can be obtained within two hours.

The Xpert (MTB/ RIF) is also used to detect resistance to rifampicin, an important anti TB drug used as the first line regimen for treating TB patients. It is used as a marker for multi drug resistance as a high percentage of rifampicin resistance is associated with concurrent resistance to isoniazid (8).

At present, availability of Xpert (MTB/ RIF) is limited to the National TB reference laboratory at Welisara and nine other laboratories in the country (intermediate TB culture laboratories in the District Chest Clinic Kandy, Provincial General Hospital Ratnapura, District Chest Clinic Jaffna and Teaching Hospital Karapitiya, and microbiology laboratories of the National Hospital of Sri Lanka, Provincial General Hospitals in Anuradhapura, Badulla, Batticaloa and Kurunegala). The test is offered for:

- All the retreatment presumptive TB patients
- Other new cases, symptomatic and at risk of drug resistance
- Patients living with HIV
- New pulmonary TB patients remaining sputum positive at second month and retreatment patients positive at 3rd month
- Patients with extra-pulmonary TB especially in central nervous system
- Paediatric TB cases
- Smear negative cases with clinical/radiological evidence of TB (7)

Line probe assay is also a molecular method used for diagnosis of TB and multi-drug resistant TB (MDR TB). Line probe assay is highly sensitive and specific in detecting MDR TB in sputum positive for acid fast bacilli and can be performed within short time duration such as five hours. However, it has a limited role in sputum negative TB and is technically more demanding (9).

With the concept of "End TB", more research is being carried out in order to have better diagnostics. A next generation cartridge (Xpert Ultra) and new diagnostic platform (Gene Xpert Omni) are in the process of development and will soon be put in to practice (1).

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