



CHALLENGES TO CONTROL TUBERCULOSIS

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Article Received on 10/06/2019

Article Revised on 01/07/2019

Article Accepted on 21/07/2019

ABSTRACT

Tuberculosis (TB) is an infectious bacterial disease characterized by the growth of nodules or tubercles in the tissues, especially the lungs. It is caused by *Mycobacterium tuberculosis*. If not treated properly TB disease can be fatal. The disease is spread from one person to another through droplets containing the bacteria which are released into the air when the TB patient coughs, sneezes or talks. New techniques like Xpert MTB/RIF assay are present to diagnose the strains of Bacteria. Vaccines like *Bacillus Calmette Guerin* (BCG) and rBCG30 induce immunity and cross protection against TB. The disease can be treated with drugs like Isoniazid, Rifampicin, Streptomycin and Ethambutol. In choosing a suitable drug regimen, underlying comorbidity, as well as the potential for drug interactions must be considered.

INTRODUCTION

Tuberculosis (TB) is an infectious bacterial disease characterised by the growth of nodules or tubercles in the tissues, especially the lungs. It is one of the most ancient diseases of mankind. The bacillus causing tuberculosis is *Mycobacterium TB* (M.TB). It was discovered by Robert Koch. The principle cause of human TB is M.TB. Other members of mycobacterium tuberculosis complex which can cause tuberculosis in human is *M.bovis*. Humans become infected with the disease when consuming unpasteurised milk and milk products and meat from an infected animal.^[1,2] The disease is spread from one person to another through droplets containing the bacteria which are released into the air when the TB patient coughs, sneezes or talks.

In spite of new TB diagnostic methods and treatment strategies yet millions of people are still being infected and also dying from the disease. Although the causative agent M.TB was identified yet a definitive understanding about the pathogenesis of the disease is still to be understood.^[3,4] The pathogen can affect individuals of any age group but immunocompromised individuals who have HIV infection are at increased risk. TB infection in healthy individuals does not show any symptoms as their immune system walls off the causative agent. Infection with TB results in either asymptomatic latent tuberculosis infection or active TB disease.

World wide scenario

TB is one of the leading cause of death caused due to single infectious agent. It was estimated that 1.3 million deaths with tuberculosis and an additional of 30,000

deaths due to TB in HIV positive people. In the year 2017 Globally 10.0 million people developed TB disease these were cases in all countries with 72% in Africa, 27% in India, 9% in China, 8% in Indonesia, 6% in Philippines, 5% in Pakistan, 4% in Nigeria, 4% in Bangladesh and 3% in South Africa. The above countries along with 22 other countries in WHO listed regions accounted for 87% of the world cases with 3% in the European region and 3% in America.^[5] According to WHO every second, one individual in the world is newly infected with TB bacilli. TB co-infection with HIV weakens the immune system.

Directly observed treatment short course (DOTS) is the internationally recommended strategy for controlling TB. It consists of five components, namely sustained political and financial commitment, diagnosis of the symptoms by quality ensured sputum smear microscopy, standardised short course anti-TB treatment, regular supply of high quality anti-TB drugs, and standardised recording and reporting to monitor the overall program performance.^[6] All the five components of DOTS were not properly implemented in sub-Saharan Africa, but there were places where DOTS program was very effective.^[7] The main drawback of DOTS programme is it did not take any account of drug resistant TB, when resistance already existed to first line drugs like Isoniazid and Rifampicin. The DOTS program reverted to a short course of Pyrazinamide and Ethambutol. These were at doses insufficient to treat active TB but in doses large enough to boost resistance. So this circumstance in the DOTS programme cause a worsening of MDR-TB situation.

From the global prospective, South East Asia Region (SEAR) is a home to 25% of the global population. It suffers with both communicable and non-communicable disease due to poor health infrastructure. In the year 2000 'DOTS plus' programme has been developed by WHO and their partners, with an account of the usage of 2nd line anti TB drugs where significant level of MDR TB is present. One of the difficulties that arose in the DOTS plus pilot projects was the need of second line anti TB drugs which were expensive and difficult to obtain. Arrangements were made with the pharmaceutical industries for preferential rates for the second line anti TB drugs used for implementing DOTS plus. With the ending of the pilot phase there was evidence that management of MDR TB was both feasible and effective.

The stop TB partnership was set up in 2001, following the Amsterdam conference in 2000, but this time to be achieved by the year 2005. Three of its working components are DOTS expansion, TB/HIV and DOTS plus. Its aim was to provide a road map towards a TB free world.

In Global plan to stop TB 2006-2015, a range of targets like development of improved diagnostics and drugs have been implemented. In 2009 the stop TB partnership produced a report, which showed that significant progress has been made in many areas but in other areas screening HIV positive people for TB was found to be of less progress. It was also noted that the provision of funding for TB per year has become difficult.

Another global plan: WHO in the year 2016 planned to end TB and initiated the WHO END TB strategy and the global plan to end TB 2016-2020. Meetings were held and documents with set targets have been written. It was said that there needed to be a radical change in how TB was viewed. The strategy aims to end the global TB epidemic with targets to reduce TB deaths by 95% and to cut new cases by 90% between 2015 and 2035. It also ensures that no family is burdened with huge expenses due to TB. It sets interim milestones for 2020, 2025 and 2030.^[8] The resolution calls on government to implement the strategy with commitment and financing. It reinforces a focus on serving populations who are highly vulnerable to infection and poor health care access such as migrants with a note of tackling the problem of MDR TB and promoting collaboration across international borders.

HIV and TB

People living with HIV positive are 20 to 40 times more likely to develop active TB.^[9] It is a leading cause of death in HIV positive people, as it is the commonest HIV-associated opportunistic disease in the world.^[10] The level of immune suppression determines clinical presentation of TB. Co-infection of HIV and TB also results in rapid development of MDR-TB.^[11,12]

Irrespective of the HIV status of the patient TB requires a minimum of 6 months of treatment with 4 drugs in the intensive phase and 2 drugs in the continuation phase.^[13] Treatment consists of Isoniazid(INH), Rifampicin(RIF), Ethambutol(EMB) and Pyrazinamide(PYZ) for 2 months followed by INH and RIF for 4 months given either daily or intermittently. The anti retroviral (ART) agents are nucleoside reverse transcriptase inhibitors(NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors(PIs), integrase inhibitors, chemokine receptors antagonists and entry (fusion) inhibitors. Regimens recommended for HIV/TB patients include a combination of 2NRTIs with Efavirenz or Nevirapine. The NRTI combinations used commonly are Zidovudine with Lamivudine, Stavudine with Lamivudine, Tenofovir with Lamivudine, Abacavir with Lamivudine or Didanosine with Lamivudine.^[13]

Multi drug resistant tuberculosis

Drug resistant tuberculosis is one of the major obstacles encountered in the control of TB world wide. Inappropriate use of rifampicin for decades has generated an increase in rifampicin resistant TB cases (RR-TB). But if this drug is not used then the treatment of TB could be for upto 21-24 months. 90% of RR -TB cases are also carriers of Isoniazid resistant strains. Hence these patients make the multi-drug resistant TB group. The challenge is more compounded by the spread of extensively drug-resistant TB (XDR-TB) where the bacterial strain is resistant even to flouroquinolones like Levofloxacin, Moxifloxacin and second line injectable drugs like Amikacin, Capreomicin and Kanamycin. Studies have shown that globally 3.9% of untreated cases of TB and 21% of previously treated cases have RR/MDR-TB leading to 250,000 death in the year 2015.^[14] TB cases must be tested with rapid molecular detection using Gene Xpert which is a real time PCR. It greatly increases the sensitivity of sputum smear and also detects Rifampicin resistance in less than 2hours.^[15,16] Highly potent drugs like Linezolid, Bedaquiline and Delamanid along with other drugs like carbopenems (Imipenem, Meropenem, Ertapenem and Clofazamine) are used for curing many cases of XDR-TB patients,^[17,18]

CONCLUSIONS

There are miles to go to make this world TB free. WHO with its 'STOP TB' strategy has given a vision to eliminate TB by 2050.^[19] To accurately estimate the burden of all kinds of TB, it is necessary to strengthen the surveillance programs. It is necessary to regulate the rational use of first and second line anti-TB drugs. They should not be sold as over the counter drugs. Working association between physicians, private sectors and other non-profitable organizations should be strengthened and given awareness about the diagnosis, management and control of TB. Better diagnostic tests for quick screening should be developed. Programs for developing new drugs and vaccines against TB should be encouraged.

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