

## 1. INTRODUCTION

Tuberculosis (TB) is an ancient disease that is caused by the infection of *Mycobacterium tuberculosis*. It is been estimated by World Health Organization (WHO) that one-third of the world's population is infected with TB. In the past TB is a disease, a cause of death, where as the death rate has come down in the last forty years in the developed countries.<sup>1</sup> TB has been one of the common opportunistic infection in patients who have been infected with Human Immunodeficiency virus (HIV). There is an increase of susceptibility to primary and reactivation TB in HIV infected patients. The infection of TB alone has shown greater infectivity than HIV-associated TB.<sup>2</sup>

### 1.1 HISTORY AND BACKGROUND

TB is a disease caused by the bacteria *Mycobacterium tuberculosis* that affects lungs through respiration, but sometimes they can move to other parts of the body or any organ.

The spine of Egyptian mummies, in British museum has shown, TB decay which shows that TB was present in humans since ancient times. A clear detection of the organism *M. tuberculosis* was in the remains of bison which was 18,000 years old.<sup>3</sup>

It remains unclear, the origination of TB whether from cattle to human or diverged from some other ancestor infecting a different species. But it is clear that the infection has not directly descended from *M. bovis* which is been evolved recently.<sup>4,5</sup>

The bacteria *Mycobacterium tuberculosis* is an anaerobic, non-motile bacillus bacterium.<sup>6</sup> This pathogen has high lipid content which is responsible for many of its clinical characteristics. It is a slow dividing bacterium, which divides every 16 to 20 h, whereas most of the other bacteria divide at a rate of less than one hour<sup>7</sup> (e.g. Strains of *Escherichia coli* which is found to be the fastest growing bacteria can divide every 20 min approximately). *M. tuberculosis* is an organism which has a cell wall but lacks the phospholipids outer membrane is classified as a gram- positive bacterium. But these organism doses not retain the dye of gram-positive due to the mycolic acid and the high lipid content of the cell wall.<sup>8</sup> *M. tuberculosis* is an organism which can withstand weak disinfectants and can remain dry for more than a week. However, this bacterium can grow only in a host cell by nature; it can also be cultured *in vitro*.<sup>9</sup>

The samples obtained from expectorants like sputum can be stained using histological stains; and the bacterium can be identified under a regular microscope. It is called as Acid Fast Bacillus (AFB) as it is treated with acidic solution before staining.<sup>10</sup> The Ziehl- Neelsen stain is the most common acid fast staining technique where the AFBs show bright red stains in blue back ground. The AFB can be stained even by an auramine-rhodamine stain under fluorescence microscope.

Four other stains of TB causing *Mycobacterium* have been found; *M. bovis*, *M. africanum*, *M. canetti*, *M. microti*. Among these *M. bovis* is a common organism which is found in milk but has been almost eliminated by the introduction of pasteurized milk in developed countries.<sup>11,12</sup> *M. africanum* is not widespread but found only in parts of Africa. *M. canetti* is also not widespread and found only in few parts of Africa. *M. microti* is an organism which causes TB in immunodeficient people, although it is possible that the occurrence of this has been under estimated.

There are other known *Mycobacterium* species which includes *M. leprae*, *M. marinum*, *M. avium*, *M. kansasii*. In this *M. avium* and *M. kansasii* have not reported TB nor-leprosy but seem to cause pulmonary disease similar to TB.

A granuloma is formed by the aggregation of Macrophages, T-lymphocytes, B-lymphocytes and fibroblasts with lymphocytes that surround the infection and hence TB is classified under granulomatous inflammatory conditions. The granuloma which is formed, not only functions to prevent the *Mycobacterium* distribution but it also provides an environment which helps to communicate the cells for immune system. The infecting bacteria are destroyed by the activation of macrophages by the enzymes that are secreted by T-lymphocytes like cytokines (interferon gamma) within the granuloma. Perforin and granulysin may also be secreted by cytotoxic T-cells that kill infected cells directly.

## **1.2 TYPES OF TUBERCULOSIS**

Lung is the main organ infected by *Mycobacterium*. Depending upon the tissue response and age, the infection is mainly divided into two main types:

- i) Primary TB
- ii) Secondary TB

### **i) Primary TB**

The person who is been infected by TB for the first time or an unimmunized person is been infected in a primary infection or otherwise called as a childhood TB. It is also called as Ghon's

complex which commonly involves the tissues for the first infection are lungs or hilar lymph nodes. It was also reported that primary complex also affects other tissues like tonsils and cervical nodes.

## **ii) Secondary TB**

The infection occurs from post previous infections or reinfection, or chronic TB. It may have occurred from;

- a. Endogenous cause, such as reactivation or latent primary complex.
- b. Exogenous cause, where an infection is from fresh bacilli again. This occurs most commonly in lung in the regions of apex. The other tissues which can be infected are tonsils, pharynx, small intestine and skin.

## **1.3 PROGNOSIS**

TB disease occurs when the TB infection i.e the TB bacilli overcomes the immune system and starts multiplying. In around 4% of the cases, the disease occurs soon after infection, mostly in primary TB cases. A hidden infection occurs in these cases where no symptoms are shown. In around 20% of such cases these latent bacilli may produce TB after many years. The patients with HIV infection, the risk of reactivation increases

due to immunosuppressant. The DNA fingerprints of *M. tuberculosis* have shown that around 12 to 80% of the populations are susceptible of reinfection than reactivation.

#### **1.4 PATHOPHYSIOLOGY OF TUBERCULOSIS<sup>13</sup>**

TB infection infects a person when he is exposed to an environment contaminated with feasible tubercle bacilli. They enter the respiratory system through inhalation, expelled by an infected person by any means i.e. coughing, sneezing, shouting etc. they enter the respiratory bronchioles and alveoli usually towards the apex of the lungs.

The cell mediated T-Lymphocytes induce an antigen-antibody interaction, when these microorganisms multiply to the obligatory extent. At the site of infection due to the accumulation of macrophages, the tubercles are formed, which may lead to the control of the infection or survival in the foci. These survived infections in the foci may be released and circulated through the lymph and blood which infects the other parts of the body and reticulo endothelial system like liver, spleen etc.

## 1.5 SPREAD OF TUBERCULOSIS

TB is spread by various routes in the body as given below:

- a. Local spread:** In this the bacilli is carried to surrounding tissues by macrophages
- b. Lymphatic spread:** The bacillus usually passes into the lymphoid follicles of pharynx, regional lymph nodes, bronchi and the intestine resulting in regional tuberculous lymphadenitis which is typically a infection in children. It is primarily a lymphoid tissue infection.
- c. Haematogenous spread:** This is an infection which spreads in the body through blood may be due to caseous material escaping through the ruptured wall of the vein or as a result of the tuberculous bacillaemia drains into the venous system. This causes military tuberculosis in different organs of the body like lungs, liver, kidney etc.
- d. By natural passages:**
  - By trans bronchial into the lungs segments
  - Tuberculous peritonitis through peritoneal cavity
  - Tuberculous pleurisy through lungs into pleura
  - Tuberculous laryngitis through infected sputum into larynx

- Ileocaecal tuberculosis by swallowing of infected sputum

There is no evidence that TB is an hereditary disease. It is an infection which can infect all people. The people with high risk are the people who are directly exposed to the infection like poor and homeless, living with an infected individual, alcoholics and intravenous drug users, healthcare workers etc. Chest X-rays, sputum analysis and skin test are some of the test that is used for the diagnosis of TB.<sup>14</sup>

### **1.6 KEY CONCEPTS IN THE TREATMENT OF TB**

Treatment of TB is a great challenge as the bacterium is slow growing intracellular organism. It has to be treated with a combination of drugs in such a way to prevent the appearance of resistance. The other major therapeutic challenge is the ability of these organisms to remain latent but viable of causing disease and the risk of adverse reaction is also a major consideration in this therapy. So before treating three basic concepts that have to be considered

- Treatment should have multiple drugs to which the organism is susceptible.
- The drug has to be taken regularly
- The therapy has to be continued for a sufficient time.

Traditionally there were some antibiotics that are used for the treatment of TB which are also called first line drugs such as Isoniazide, Rifampicine.