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A REVIEW ON TUBERCULOSIS AND ITS DIAGNOSIS

Prof. Sharma Shubham* and Diwan Deeksha

Department of Pharmacy, Shri G S Institute of Technology and Science, Indore (M.P.).

Corresponding Author: Prof. Sharma Shubham
Department of Pharmacy, Shri G S Institute of Technology and Science, Indore (M.P.).
Email id:

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ABSTRACT

Tuberculosis (TB), often thought of a disease from the past, is still rampant in major portions of the world. With 1.5 million deaths annually, it is the most important cause of death due to an infectious disease worldwide with India being the highest TB burden country in the world. Tuberculosis (TB) is a ubiquitous medical problem causing high mortality and morbidity rates which also affects people mentally and socially, especially in countries undergoing development. The contagious, pestilent disease is caused by Mycobacterium tuberculosis (MT) that has always been a challenging pathogen over the centuries, because of its severe pathophysiological implications. It has been hypothesized that the genus Mycobacterium originated more than 150 million years ago and still is considered an implacable enemy. TB has always been associated with a high mortality rate over the centuries, and also nowadays, it is estimated to be responsible for 1.4 million TB deaths. Due to its contagious nature, complex immunological response, chronic progression and the need for long-term treatment, TB has always been a major health burden. In more recent years, the appearance of multi-drug resistant forms have resulted from the bacterial persistent mutations along with the current TB-HIV epidemic and related medical consequences. Therefore, the prevention and treatment of tuberculosis have been proven to be an arduous task over the period of time.

KEYWORDS: Tuberculosis (TB), Mycobacterium tuberculosis (MT).

INTRODUCTION

Tuberculosis (TB) is a nocuous infection which most often occurs in the lungs and respiratory system, and interferes with the breathing process, caused by a bacterium called *Mycobacterium tuberculosis*. It spreads from person to person when an infected person coughs, sneezes, laughs, or spits. Tiny droplets of fluid from the lungs are carried in the air and can infect the people in vicinity. Although it can affect many parts of the body, the infection is most common in lungs.

One third of the world's population are living with TB, hence it is one of the world's leading causes of death along with HIV Infection. The World Health Organization (WHO) estimates that 3.2 million women became sick with TB in 2018. Out of ten million new cases of tuberculosis in 2018, around 862,000 occurred in people living with HIV. The risk of developing TB is estimated to be 19 times greater for people living with HIV than for those who are HIV-negative.

Approximately 8.8 million people got affected and around 1.4 million deaths were caused globally in 2010, including a half-million women and at least 64,000 children. It is intricately linked with human immunodeficiency virus (HIV), as well as non-communicable diseases and ill-health determinants such as diabetes mellitus, smoking, alcoholism, and malnutrition. The Stop TB Strategy, founded on the Directly Observed Treatment, Short-Course (DOTS) strategy, provides the framework for the global response against tuberculosis and has been implemented in virtually all countries. As a result, 46 million tuberculosis patients have been cured and 6.8 million were treated, including those of 2, 50, 000 children and up to 1.7 million women of childbearing age. However, more than one-third of estimated tuberculosis cases are still not identified by existing services and systems. As a result, the global detection of estimated tuberculosis cases has been stagnating at 60%–65% between 2006 and 2010. Unfortunately, despite causing nearly 10 million cumulative orphans due to parental deaths in 2009, tuberculosis prevention, diagnosis, and treatment services are still not acknowledged nor widely implemented by maternal and child healthcare stakeholders and implementers.

M.Tuberculosis is an aerobic, non-motile, non-spore-forming rod that is highly resistant to drying, acid, and alcohol. It is generally transmitted from person to person via droplet nuclei containing the organism and is spread mostly by coughing when others inhale the same. A

person with active but untreated TB infects approximately 10–15 other people per year. The probability of transmission increases with the number of infectious droplets expelled by the affected, the time of exposure, and the virulence of the bacteria. The risk of developing active TB is greatest in patients with altered host cellular immunity, children and elderly, malnutrition, cancer, immunosuppressive therapy, HIV infection, chronic or end-stage renal disease, and diabetes.

Tuberculosis infection starts when the mycobacteria reach the pulmonary alveoli, where they invade and multiply within the alveolar macrophages. Inhaled mycobacteria are phagocytized by the alveolar macrophages, which interact with the T lymphocytes, which results in differentiation of macrophages into epithelioid histiocytes. Epithelioid histiocytes and lymphocytes aggregate into small clusters, resulting in granulomas. In the granuloma, CD4 T lymphocytes (effector T cell) secrete cytokines, such as interferon-γ, which activate macrophages to destroy the bacteria with which they are infected. CD8 T lymphocytes (cytotoxic T cell) can also directly kill infected cells. Bacteria are not always eliminated from the granuloma, but can become dormant, resulting in a latent infection. Another feature of human TB granulomas is the development of necrosis in the center of the tubercles.

Ghon focus is the primary site of infection in the lungs. It either enlarges as disease progresses or, much more commonly, undergoes healing. Healing results in a visible scar that is usually dense and contains foci of calcification. During the early stage of infection, organisms are commonly spreaded through lymphatic channels to regional hilar and mediastinal lymph nodes and through the bloodstream to distant sites in the body. Ranke complex is the combination of the Ghon focus and affected lymph nodes. The initial infection is usually clinically silent. In approximately 5% of infected individuals, immunity is inadequate and clinically active disease develops within 1 year of infection, a condition known as progressive primary infection. However, TB remains clinically and microbiologically latent for many years for most infected individuals.

In approximately 5% of the infected population, endogenous reactivation of latent infection develops many years after the initial infection (post primary TB). The reactivation TB tends to involve predominantly the apical and posterior segments of the upper lobes and the superior segments of the lower lobes. This location is likely due to a combination of relatively higher oxygen tension and impaired lymphatic drainage in these regions. As distinct from primary infection site, in which healing is the rule, reactivation TB tends to progress. The main abnormalities are progressive extension of inflammation and necrosis, frequently with development of communication with the airways and cavity formation. The endobronchial spread of necrotic material from a cavity may result in TB infection in the same or in other lobes. Haematogenous dissemination may result in miliary TB.

Childhood Tuberculosis

It is estimated that children younger than 15 years contribute 15%–20% of the global tuberculosis burden. Few countries have reported data on childhood tuberculosis, and the reported case notification rates range between 3% and 25%. The data reported on childhood tuberculosis cases among the 22 countries with a high burden of tuberculosis accounted for 82% of the notified cases in 2010, in which only half of the countries' reported tuberculosis cases were stratified by age and sex. A national facility-based survey in Malawi in 1998 showed that childhood tuberculosis accounted for 12% of all the cases notified and for 37% of the overall smear-negative and extra pulmonary tuberculosis burden. The global extent of multi drug-resistant (MDR) tuberculosis and extensively drug-resistant (XDR) tuberculosis among children is unknown.

A World Health Organization (WHO) drug-resistance surveillance study from 34 countries and territories showed that the frequency of MDR tuberculosis peaked for the 0–14-year age group in countries outside Central and Eastern Europe. A post-mortem study in Zambia showed that one-fifth of children who died from respiratory illnesses had tuberculosis, of whom 60% were HIV positive. Similarly, tuberculosis caused 22% of deaths among Mexican children with perinatal HIV infection who were receiving antiretroviral therapy (ART). In a hospital based study conducted among 52 HIV-infected infants with culture-confirmed tuberculosis in South Africa, a third of them died.

The DOTS strategy, based on sputum microscopy, has been the mainstay of tuberculosis control activities, including childhood tuberculosis in many countries with a high burden of tuberculosis. The Stop TB Strategy now emphasizes the equitable access to tuberculosis prevention, diagnosis, and care for all cases of tuberculosis in adults and children, and guidelines are available for national tuberculosis control programs to effectively address childhood tuberculosis, including in children living with HIV.

Maternal Tuberculosis

Globally, more tuberculosis cases are reported in men than women, and several factors, including biological, clinical, epidemiological, and social, have been considered to explain the sex differential. There are conflicting reports about access to health services as the reason for the sex differential, although more women with tuberculosis were detected by active case-finding strategies than by self-reporting in public sector facilities. Increasingly, more women with tuberculosis are notified than men in high HIV prevalence settings, particularly in the southern part of Africa. For example, the male-to-female ratio of notified tuberculosis cases for

smear-positive pulmonary tuberculosis dropped from 1.4 in 2000 to 1.0 in 2010 in both Swaziland and South Africa, reflecting the increased burden of tuberculosis among women, primarily due to the feminization of the HIV epidemic. There is conflicting global evidence about the risk of MDR tuberculosis by sex. Although there was more risk of being affected by MDR tuberculosis among female patients in South Africa, the risk was higher among male tuberculosis patients in countries of the former Soviet Union. The incidence of genital tuberculosis as a cause of overall infertility ranges between 1% and 16% and causes about 40% of the infertility due to problems with the fallopian tubes. It results in a low (10%–20%) chance of conception, even after successful diagnosis and treatment. Genital tuberculosis also causes menstrual cycle problems, including secondary amenorrhea and oligo menorrhea, in up to 40% of these patients.

Tuberculosis in Pregnancy: Reports show that pregnant women with untreated tuberculosis, including those living with HIV, have poor obstetric and perinatal outcomes. Pulmonary tuberculosis was associated with an approximate 2-fold increase in premature birth, neonates that are low birth weight and small for gestational age, and a 6-fold increase in perinatal deaths. With the exception of tuberculosis lymphadenitis, extra pulmonary tuberculosis has adverse outcomes for pregnancy including increased antenatal hospitalization and neonatal complications.

Diagnosis

A definitive diagnosis of TB can only be made by culturing M. tuberculosis organisms from a specimen which is taken from a patient's body. However, TB can be a difficult disease to diagnose, mainly because of the difficulty in culturing this slow-growing organism in the laboratory. A complete evaluation for TB must include a medical history, a chest radiograph, a physical examination, and microbiologic smears and cultures. It may also include a tuberculin skin test and a serologic test. The treatment of latent TB infection to prevent progression to active disease has been an essential component of public health efforts to eliminate TB. Currently, latent infection is diagnosed in a non-immunized person by a tuberculin skin test (TST), which yields a delayed-hypersensitivity-type response to purified protein derivatives of M. tuberculosis. However, the TST, which has been used for years for the diagnosis of latent TB infection, has many limitations, including false positive test results in individuals who were vaccinated with bacilli Calmette-Guérin (BCG) and in individuals who have infections not related to M. tuberculosis. Discovery of the role of T lymphocytes and interferon-γ in the immune process has led to the development of an in vitro assay for cell-mediated immune reactivity to M. tuberculosis. Recently, this whole-blood interferon-γ assay has been introduced for the diagnosis of latent TB infection and has shown a higher diagnostic accuracy than the TST. These new TB tests are being developed with the hope of cheap, fast, and more accurate TB testing. These new tests use polymerase chain reaction detection of bacterial DNA and whole-blood interferon-γ assay. Individuals with a positive TST or whole-blood interferon-γ assay, especially HIV-infected persons or those who have chest radiographic or CT findings consistent with TB, should be considered for treatment of a latent infection.

Currently available diagnostics can be classified as those that:

Direct Detection Methods

1. *Microscopy*

Sputum smear microscopy still remains the basis for diagnosis of TB in developing countries. The most regular practice is acid-fast staining using carbol fuschin and fluorochrome, dye-auramine/rhodamine.

It is relatively fast, inexpensive and specific for TB in high incidence areas. Although highly specific, smear microscopy is insensitive – it detects roughly 50% of all the active cases of TB. The higher load of bacilli (10,000 bacilli/ml) that need to be present leads to a varying sensitivity from 20% to 80% depending on various factors such as quality of the specimen and the training and motivation of laboratory personnel. Sensitivity can be as low as 20% in children and HIV-infected people.[As per the current Revised National Tuberculosis Control Programme (RNTCP) guidelines, the patient should visit the clinic at least twice to submit a spot – early morning or spot-spot specimen. At least two ml specimen should be collected which should be mucopurulent. Sputum specimens should be examined within two days of collection. Studies have documented that the first sputum specimen detected 85.8% of TB cases with the second smear adding on to another 11.9%.Relying on sputum microscopy alone may be dangerous from the public health point of view as 17% of smear-negative cases are known to transmit the disease. Routine microscopy cannot differentiate between live and dead bacilli and hence cannot be used as a follow-up diagnostic test. It can neither be used to predict MDR nor the presence of non-tuberculosis mycobacteria. Despite the multitude of disadvantages, in the absence of better alternatives, it is a useful tool in the basic laboratories common in developing countries. RNTCP has revised the diagnostic algorithm to allow for nucleic acid amplification detection based on cartridge based technologies (CBNAAT) for cases who are smear positive with presumptive MDR-TB/ or living in high MDR-TB areas (>5% and >20% among new and retreatment cases respectively). It also allows simultaneous testing of second specimen by the above-mentioned cartridge based technology for smear negative cases with radiological abnormalities and even those solely based on high clinical suspicion in spite of negative CXR and smear.

2. *Fluorescent microscopy with light-emitting diodes*

Conventional fluorescence microscopy (FM) using the quartz-halogen lamps or high-pressure mercury vapour lamps was expensive, vulnerable and required expert handling. Light-emitting diodes (LED s) are more robust, sustainable and user-friendly, thus allowing advantages of FM at peripheral health-care systems. Royal blue colour LED lamps used in these newer generation fluorescent microscopes have an extremely long life expectancy (10,000 h vs. 200 for a conventional mercury lamp). Furthermore, they do not produce ultraviolet (UV) light, do not require darkened rooms and significantly decrease the instrument's power consumption, allowing longer lasting battery life and thus decreasing the cost incurred, unlike older lamps. FM increases the sensitivity of smear microscopy as it allows a much larger area of the smear to be seen, resulting in more rapid examination of the specimen (up to four times faster), allowing sixty slides to be screened per day as opposed to 25 using the Ziehl–Neelsen (ZN) method. Being WHO recommended in 2009, the RNTCP has adopted LED microscopy to replace ZN method in its designated microscopy centres (DMCs) across India.

Instability of fluorescent stains under field conditions and instability of the stained smears for blinded rechecking have been reported. Proper training of laboratory personnel is imperative as detection and interpretation of results may be affected. Unlike Ziehl Neelsen, international guidance on quality assurance for FM does not currently exist and is under development. The sensitivity, specificity, cost-effectiveness and cost-benefit of this approach have not yet been adequately established.

3. *Sodium hypochlorite (bleach) microscopy*

The digestion of sputum with house-hold bleach before sputum smear preparation and microscopy has been reported to be an effective, simple method to improve the yield of smear microscopy even in high HIV prevalence settings. Progress on the development of a bleach microscopy method has been complicated by the wide heterogeneity and lack of standardisation in methods described. A standardised bleach method, the Mathare sodium hypochlorite (MaSH) method, has recently been developed and evaluated in Medecins Sans Frontieres sponsored studies in Mathare, Nairobi. The addition of standardised sodium hypochlorite solution to sputum followed by overnight sedimentation resulted in a 15% increase in TB cases detected. The MaSH method is now being evaluated by the WHO's Tropical Disease Research initiative under operational conditions in large multi-country studies.

4. *Front-loaded microscopy*

Microscopy services usually require the patients to make repeated visits to the healthcare facility leading to increased drop-out patient rates. The WHO definition (2009) of a smear-positive case allows patients to be diagnosed as TB on a single smear. In front-loaded microscopy, the first two specimens are collected and examined on the same day a patient present to the clinic. Patients with negative smears are asked to return with a morning specimen the next day, depending on whether routine services are based on two or three specimens being examined. Thus, TB patients can be offered treatment on the first day they present.

5. *Newer microscopic technologies*

Automated microscopic technology by TBDx (Signature Mapping Medical Sciences, USA) integrates robotic loading of stained slides and automated high-resolution digital image analysis to provide a result in minutes. The system has a 200-slide capacity reducing the burden on technicians. Early studies suggested improved sensitivity over the human eye, but specificity was reduced; thus, manual review of positive slides was necessary. Performance studies are underway in Nigeria and South Africa, with further studies planned for Asia.

A second innovation to assist a microscopist is Cell Scope, a portable digital FM that provides enlarged digitalised images.

1. Indirect Method of Detection

a. *Interferon-gamma release assay*

This is an *in vitro* assay wherein T-cells sensitised with MTB on encountering mycobacterial antigen (early secretory antigenic target 6 [ESAT-6] and culture filtrate protein 10 [CFP-10] and TB7.7) release interferon-gamma (a TH1 cytokine). Advantages of this test are that the antigen used is recognised by T-cells of TB patients and not by BCG-vaccinated or healthy unvaccinated individuals. It has a very high specificity and much less likely than the TST to be confounded by exposure to environmental mycobacteria or by prior BCG vaccination. It does not boost responses that will be measured by subsequent tests as happens with TST. IGRAs do not require a second visit to the clinic to evaluate the test result, thus potentially reducing costs to the patient. Results can be available within 24 h. Disadvantages the sample drawn should be incubated within 16 h for older IGRAs and 8 h for the T-SPOT of collection which may require the use of portable incubators or establishment of systems enabling transportation to properly equipped laboratories for testing. Commercially available tests are Quanti FERON-TB Gold (QFT-G) and Quanti FERON-TB Gold in Tube (QFT-GIT) (Cellestis, Australia) and T-SPOT TB.

b. *Tuberculin skin testing*

Popularly known as Mantoux test involves injecting the purified protein derivative (PPD) of MTB intra dermally in the forearm and the resulting reaction is read after 48–72 h. It was developed by in 1890 by Koch, but the intradermal technique currently in use was described in 1912 by Charles Mantoux, a French physician who developed on the work of Koch and Clemens von Pirquetto to create his test in 1907. While using

tuberculin test, it should be remembered that, in general, it detects only presence or absence of infection, i.e., exposure to MTB or latent TB. At present, only two tuberculin have been accepted as standard tuberculin by WHO, i.e., PPD-S PPD, prepared according to the method described by Siebert, from MTB and PPD RT 23. The International Standard Tuberculin's is in the custody of the Laboratory of Biological Standards, Staten, Serum Institute, Copenhagen, Denmark.

PPD-RT 23 with Tween 80 of strength 1 TU and 2 TU is standardised tuberculin available in India supplied by BCG Vaccine Laboratory, Guindy, Chennai. Other tuberculin available in the market are not standardised. Tween 80 is added to tuberculin to prevent its adsorption on glass or plastic surface. The optimal strength of PPD is 2 TU. A positive skin test is results inna skin reaction at the point of the injection. In our country, it is used in high-risk groups, especially children, household contacts and HIV-infected patients. When 10 mm or more induration is present it is considered as positive test. However, vaccination with the BCG vaccine can also lead to a reaction at the TST site (as can repeat TST testing), which limits the test's usefulness in vaccinated children or people repeatedly tested because of high risks of exposure.

CONCLUSION

The evidence presented in this review illustrates that tuberculosis is one of the major public health concerns for women of reproductive age, pregnant women, and children. Mortality and morbidity implications are a huge toll, particularly in resource constrained settings with high tuberculosis and HIV prevalence. National policy makers, program managers, and international stakeholders (e.g. United Nations bodies, donors, and implementers) working on maternal, neonatal, and child health, especially in HIV-prevalent settings, should give due attention to and include tuberculosis prevention, diagnosis, and treatment services as part of their core functions and address the public health impacts of tuberculosis in their programs and services.

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