Medicon Medical Sciences
Volume 3 Issue 6 December 2022
Review Article

Diagnosis and Treatment of Tuberculosis: A Review

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Received: November 14, 2022; **Published:** November 27, 2022

DOI: 10.55162/MCMS.03.084

Abstract

The organism known as Mycobacterium tuberculosis, which was responsible for the development of tuberculosis was contagious through the air. Despite substantial efforts, tuberculosis continued to cause threat to the general public. The initial stage of tuberculosis called Latent tuberculosis could be prevented and controlled if being diagnosis early. Over the Years, Medical scientist, researchers and scholars have focused on the diagnosis and treatment of tuberculosis which has been the principal focused to prevent its spread. The disease have affected many countries including Saudi Arabia. Consequently, the implementation of comprehensive tuberculosis program that takes into account the management of latent tuberculosis infection illnesses among healthcare workers who have been reported to be at a higher risk for active tuberculosis than the general population would be important in curtaining the spread of the diseases. Therefore, the present research review the current diagnosis, treatment, prevention along with the negative medical and financial impact that the disease have on both the individuals and healthcare system. In addition to that, some suggestion and recommendation was provided as how the disease may be halted.

Keywords: manifestations TB; Symptoms; TB in children; TB in old people; Advances in the imaging diagnosis of TB; Microbiology.Molecular; serology for antibody/antigen detection; cellular immunodiagnosis; skin test; immunodiagnosis for IGRA; and Treatment

Introduction

The organism known as Mycobacterium tuberculosis (MTB), which is responsible for the development of tuberculosis, is contagious through the air [1]. It causes pulmonary tuberculosis when it infects the lungs, which is the most common site of infection. On the other hand, it is also capable of infecting other organs, which might lead to extrapulmonary tuberculosis (EPTB). People of all ages and from all walks of life are susceptible to contracting tuberculosis, which is one of the world's most widespread infectious diseases [2]. It is essential to take into consideration the fact that after a period of two years following infection with Mycobacterium TB, 10% of otherwise healthy individuals will get tuberculosis (TB) [3]. Those who are infected with the human immunodeficiency virus also have a significantly increased risk of contracting the disease [4].

Tuberculosis (TB) continues to be a significant threat to public health all over the world, particularly in nations that are considered to be less developed, in spite of this, significant efforts have been made to prevent and control the disease's transmission [5]. In this context, the six countries with the highest prevalence of tuberculosis are India, Indonesia, China, Nigeria, and Pakistan [10]. South Africa is also included in this list. The six countries accounted for sixty percent of the world's newly reported cases of the disease. India and China alone accounted for fifty percent of the daily cases of TB recorded globally.

According to several reports, the most prevalent form of illness in the northern region of Iran is pulmonary tuberculosis [7]. Turkey is another country in the Middle East with a high incidence rate [8]. In 2014, there were a total of 58252 documented cases, and Turkey was responsible for 22 percent of those cases, making it the country with the highest incidence rate. In addition, the worldwide TB report from 2016 included a ranking of the gulf nations based on the incidence rate of tuberculosis in their respective populations. First place went to Kuwait with a rate of 200 cases per million residents, followed by Saudi Arabia with a rate of 89 cases per million, and the United Arab Emirates with the lowest rate of 6.8 cases per million. 19 With barely three instances per 100,000 people, the United States has one of the lowest rates of any industrialized nation, making it one of the nations with the lowest rates overall. As a result of this low frequency, which may be ascribed to the modern healthcare system in the country, the United States is among the least impacted countries [11].

The development of tuberculosis through time (TB)

The fragile equilibrium that existed between humans and the tubercle bacillus was upset as environmental factors, such as population density, began to shift over the course of hundreds of years and millennia. Two schools of thought attempt to explain the TB pandemic and its eventual decline. During the 1700s and 1800s, tuberculosis was the leading cause of death in Western Europe and the United States. After another 100-200 years, Christianity spread throughout Eastern Europe, Asia, Africa, and South America. Over the course of two centuries, the disease spread throughout Western Europe. During this outbreak, nearly every person in Western Europe contracted M. tuberculosis, and one in every four died as a direct result of the disease. Researchers from the British military identified no cases of tuberculosis in Africa before the arrival of Europeans. According to the sensitivity of the microorganisms to the medicine, one patient with TB laryngitis was extremely infectious. It is highly unusual for a micro pandemic of tuberculosis to occur in places with poor ventilation less than a century after Koch discovers the tubercle bacillus.

Manifestations Tuberculosis

Consumption and phthisis are two of the many names that have been given to pulmonary tuberculosis. Both of these names refer to the significant weight loss and the coughing up of blood that are symptoms of the later stages of the disease. Pott's disease, also known as spinal tuberculosis, was named after an English physician who practiced in the 18th century. This bone disease is characterized by spinal deformity and other bone defects. Hippocrates believed that there was a significant similarity between this bone disease and pulmonary tuberculosis, as well as possibly a common origin. Scrofula, also known as cervical lymphadenitis, was a prevalent ailment that affected people during the medieval ages. The disease was characterized by an enlargement of the lymph nodes in the neck. Because of the urban legend that it could be cured by the mere touch of a king or queen who was currently in power, it was also known as "The King's Evil." In the 1860s, the researcher Villemin, who was mentioned earlier, demonstrated that scrofula and pulmonary

tuberculosis shared the same root cause [12]. It is also possible for tuberculosis to manifest itself in the central nervous system, in which case meningitis is the most common form of the disease. Additionally, tuberculosis can manifest itself in the urogenital tract, the digestive system, and the skin in the form known as lupus vulgaris. The prevalence of tuberculosis in its many extrapulmonary forms varies greatly from one nation to the next. [13].

Since most milk products are now pasteurized, the most common way that tuberculosis infections are contracted in modern times is through the pulmonary route of exposure. This is particularly true in wealthy countries. In research conducted in 1978, before the onset of the AIDS epidemic, it was found that 85 percent of newly diagnosed cases of tuberculosis were pulmonary [14]. Therefore, the many manifestations of the disease that were described earlier are almost always the result of the spread of the bacilli from the lungs that have been affected. In many instances, tuberculosis adheres to a basic pattern that was outlined by Wallgren, who separated the development of the disease and its eventual resolution into four stages [15]. When *M. tuberculosis* from inhaled aerosols becomes implanted in alveoli, the first stage is the dissemination of the bacteria via lymphatic circulation to regional lymph nodes in the lung, forming what is known as the primary or Ghon complex. This can take place anywhere from 3 to 8 weeks after infection. This stage can be dated by the passage of time. At this point, the reaction changes to one that is tuberculin-sensitive. Hematogenous circulation of bacteria to many organs, including other parts of the lung, characterizes the second stage, which lasts for about three months; at this time, the acute form of the disease, which can sometimes be fatal, can occur in the form of tuberculosis meningitis or miliary (disseminated) tuberculosis in some people. Both of these forms of the disease can cause tuberculosis. Inflammation of the pleural surfaces, also known as pleurisy, can occur during the third stage, which can last anywhere from three to seven months and cause excruciating chest pain. However, this stage can be postponed for up to two years. It is hypothesized that this disease is brought on either by the hematogenous spread of bacteria or by the release of bacteria into the pleural space from sub-pleural concentrations of bacteria in the lung. Both of these hypotheses are currently under investigation. It is believed that the free bacteria or their components engage with sensitized CD4 T cells, which subsequently attract other CD4 T lymphocytes, causing them to multiply, and then produce inflammatory cytokines [16]. It may take up to three years for the disease to reach its last stage, known as resolution of the primary complex, in which it will no longer advance. Some people will experience chronic back pain at this stage of the disease, which is often a symptom of extra-pulmonary lesions that develop more slowly than those in the lungs, such as those in the bones and joints. However, the majority of people who are infected with tuberculosis do not develop symptoms of the disease's progression. One-third of HIV-negative people who are exposed to tuberculosis end up getting infected, and of these people, between three and five percent acquire TB within the first year. Infected people have a 3-5% increased risk of developing tuberculosis later in their lifetimes. It is hypothesized that the majority of adult cases of tuberculosis in people who do not have HIV are due to the reactivation of an earlier infection [17]. People who are HIV-positive and have been infected with *M. tuberculosis* have a one-half probability of developing reactivation tuberculosis (also known as post-primary TB) at some point in their lives. These people, along with those who are immune-compromised, have an increased risk of becoming newly infected with *M. tuberculosis* and, in many instances, show a more rapid progression to active disease [18]. Whether it is the result of HIV activation or new infection, tuberculosis in adults almost always affects the lungs and is associated with varying degrees of lung involvement and damage, most notably necrosis, cavitation, and bleeding. Adult TB can also occur in patients who have not been infected with HIV [13].

Symptoms and signs

Popularizing the traditional symptoms and signs of pulmonary tuberculosis (box): cough, sputum, hemoptysis, breathlessness, weight loss, anorexia, fever, malaise, wasting, and terminal cachexia all figure in various combinations, not only in the descriptions of the heroes, heroines, and villains, but also among the artists, poets, and musicians themselves. 3 To be clear, TB is not characterized by any of these symptoms in particular. Patients diagnosed with pulmonary tuberculosis who exhibit a whole range of symptoms and indications are becoming increasingly rare in wealthy nations. On the other hand, healthcare care professionals in underdeveloped nations regularly encounter patients who fit this description. In industrialized countries, lung cancer has emerged as a more common factor in the development of some or all of these symptoms. As the prevalence of cigarette smoking rises in developing countries, this is likely to also become the situation there [13].

Tuberculosis in children

Tuberculosis in children is notoriously challenging to diagnose due to the paucibacillary nature of the disease. The percentage of children in developed as well as developing nations who have a bacteriologically confirmed infection rarely surpasses 30-40%. As a result, the diagnosis of tuberculosis in children living in settings with limited access to medical resources is largely reliant on a combination of factors, including a history of contact with a known tuberculosis patient, clinical signs and symptoms, and specialized examinations, such as chest radiography and the TST when they are available [19] Edwards and his colleagues observed a total of 91 tuberculosis cases in children younger than 15 years, of which approximately half were HIV-infected. They discovered the following frequency of symptoms and signs in HIV-seronegative children: weight loss in 69% of cases, fever in 100% of cases, cough in 83% of cases, night sweat in 43% of cases, fatigue in 21% of cases, tuberculosis contact in 60% of cases, malnutrition in 57% of cases, lymph A number of different point-scoring systems, diagnostic classifications, and diagnostic algorithms have been established as a result of these discoveries in order to help the development of an objective diagnostic judgment. The researchers Marais et al. tested such an approach and discovered that the combination of a persistent non-remitting cough that lasted for more than two weeks, documented deterioration of health (in the preceding three months), and fatigue provided reasonable diagnostic accuracy in HIV-uninfected children (sensitivity 62.6%; specificity 89.8%; positive predictive value 83.6%). The performance was worse in HIV-infected youngsters than in the low-risk group, which presents a significant problem in settings with limited resources that are experiencing high rates of HIV epidemics. Despite this, the positive predictive value is only assessed to be 24% in a patient population that has a prevalence of tuberculosis that is as high as 5%. This is due to the fact that the set of sensitivity and specificity that was used [20].

Tuberculosis old people

In areas with a low frequency of the disease, tuberculosis primarily affects older people and accounts for a disproportionately high number of cases of clinical manifestation in immunecompromised patients and individuals. Because of this, there are a significant number of instances of tuberculosis in older people that have “atypical” clinical presentation(s). Patients above the age of 65 are at a higher risk of developing extrapulmonary TB, which may sometimes involve Diabetes. According to the findings of a meta-analysis, the proportion of older patients with bacteriologically proven pulmonary tuberculosis was higher than the proportion of younger patients with the disease.

In older individuals, the incidence of fever, sweating, and hemoptysis is reduced, whereas the incidence of dyspnea is increased. The TST-positive rate, serum total protein level, and white blood cell counts were all lower in senior patients compared to younger patients, according to the laboratory data. In addition, elderly individuals had a lower incidence of cavity formation, but the severity of lesions in the upper lung was comparable between the two age groups. Lesions in the lower zone of the lung that are accompanied by basal effusion or thickening are the chest X-ray finding that occurs most frequently in tuberculosis patients who are elderly or immunecompromised. When it comes to senior patients, tuberculosis can often show clinically in an uncommon manner, which can sometimes lead to a delay in diagnosis, which can then be further compounded by underlying conditions [21].

Differences	
Children	***Adult and Old Age***
Lesions in the lower zone of the lung is not common	Lesions in the lower zone of the lung
No reduction in Fever, sweating and hemoptysis	There is reduction in Fever, sweating and hemoptysis
Higher TST-positive rate, serum total protein level, white blood cell counts	Lower TST-positive rate, serum total protein level, white blood cell counts
Higher incidence of cavity formation	Lower incidence of cavity formation
No delay in Testing	There is sometimes delay in diagnosis
No any underlying conditions	There may be present of underlying conditions

Table 1: Differences between Signs and Symptoms of Tuberculosis in Children and Old people.

Fever
Frequent Cough
Fatigue
weight loss
Night sweat
Malnutrition
Lymph
severity of lesions in the upper lung

Table 2: Similarity between Signs and Symptoms of Tuberculosis in Children and Old people.

Advances in the imaging diagnosis of TB

There is not a single radiological abnormality that may be used to diagnose pulmonary tuberculosis that is considered to be pathognomonic. Despite this, TB is characterized by a number of distinct characteristics. Recent research has focused on reviewing traditional radiographic abnormalities. They include characteristics of "primary" tuberculosis, such as unilateral hilar lymph node enlargement, parenchymal air-space consolidation, and/or pleural effusion, or characteristics of "reactivation" tuberculosis, such as focal or patchy heterogeneous consolidation involving the apical and posterior segments of the upper lobes and the superior segments of the lower lobes, poorly defined nodules, and linear opacities [20, 21]. Evidence from genotype fingerprinting studies confirms that the radiographic feature in tuberculosis following recent and remote infections is very similar. Furthermore, the integrity of the immune system predicts the appearance of the patterns of active tuberculosis on chest imaging, with immune-compromised individuals (such as those with advanced HIV infection) having the appearance of "primary" tuberculosis on chest imaging [22].

The traditional chest X-ray is still the approach that is most widely used for screening individuals with pulmonary tuberculosis, diagnosing the disease, and monitoring the patient's response to treatment. However, chest computed tomography (CT), particularly high-resolution chest CT, is more sensitive than conventional chest X-rays when it comes to identifying early parenchymal lesions or mediastinal lymph node enlargements and determining disease activity in tuberculosis patients Cavitation and parenchymal abnormalities, as well as centrilobular nodules and the treein-bud pattern, are some of the radiographic findings that can be seen on CT scans that are diagnostic of active tuberculosis. Serial pulmonary [[18]F]-2-fluoro-deoxy-D-glucose positron emission tomography has been proven in recent studies to be a viable non-invasive technique for monitoring disease activity and responses to anti-tuberculosis treatment. This study was very recently completed. This technique may help the care of patients with MDR and XDR TB in some conditions, and it may even prove to be cost-effective, despite its high cost [22].

Microbiology diagnosis

Significant efforts have been undertaken on a global scale to advance the creation of new diagnostic technologies and to broaden their application. However, the detection of tuberculosis cases still relies on sputum smear and culture, radiography, and clinical symptomatology. At the moment, 57% of tuberculosis patients around the world are given a bacteriological diagnosis. For this reason, it is vital to make efforts to increase the quality of the procedures that are already in use, and there have really been certain achievements in this area [21].

Sputum smear examination by microscopy

The recent recognition of the benefits of fluorescent microscopy for increasing sensitivity over that of ordinary light microscopy without any compromise in specificity is one of the recent achievements in conventional TB microscopy. Fluorescence microscopy, which is utilized to a large extent in nations that are blessed with an abundance of resources, has been proven to be more sensitive than traditional microscopy, despite the fact that there is a concern that it may lose its specificity, particularly in environments that

are typical of the developing world. In spite of this, a recent analysis of the relevant literature revealed that it may perhaps be useful in the second scenario as well. This might be increased even further by affixing a more powerful light source, which is referred to as an ultra-bright light-emitting diode (Lumin TM, Life Energy, and Germany). Another comprehensive study of sputum processing methods used in sputum smear testing discovered that centrifugation paired with any of many chemical procedures (including bleach) is more sensitive, and overnight sedimentation preceded by chemical processing is more sensitive and specific. Both of these findings were consistent with the prior review's findings. Operational studies are required in order to identify the appropriate proportion of benefits derived from enhanced sensitivity to expenses associated with increased complexity and the possibility of increased exposure to biohazards [23].

The examination must be performed three times in order to increase the sensitivity of sputum smear tests; however, this notion has been challenged so that the third examination adds very little to the first two examinations, at least in laboratories that have adequate quality control. This is something that is incorporated into the International Standards of Tuberculosis Care that are used in everyday practice.

Any method that can be used to induce sputum production in a patient who is unable to generate sputum should be tried. This is notably helpful to ensure a high sensitivity of sputum smear testing in resource-poor situations where methods as extreme as stomach washing or fibro-optic bronchoscopy cannot be employed. This is very beneficial. It was demonstrated that induction performed successfully in developing nations with only a marginal increase in expenditures. Recently, a novel gadget for inducing sputum that is being referred to as the 'lung flute' has been invented and maybe be something that is worth experimenting with [23].

Microbiology diagnosis molecular methods

Nucleic acid amplification techniques

The nucleic acid amplification tests (NAAT) that are unique to *M. tuberculosis* and that are done on the bronchopulmonary material are the molecular tests that are utilized in the laboratory the most commonly for the diagnosis of pulmonary tuberculosis. The results of the NAAT can be made accessible to the doctor within one day of collecting sputum or bronchoalveolar lavage (BAL) fluid, and these results have the potential to have significant implications for the care of a patient. Sadly, NAAT amplification goals are not standardized, and the diagnostic accuracy of the tests varies greatly from one lab to the next.

In recent years, the clinical utility of in-house and/or commercial NAAT testing done on respiratory specimens for the purpose of diagnosing pulmonary tuberculosis has been subjected to a number of meta-analyses and has been examined in depth on multiple occasions [24].

The sensitivity of NAAT to detect *M. tuberculosis* nucleic acid on these specimens is better than 95% in persons who have AFB sputum smears that are positive. The presumptive diagnosis of tuberculosis can therefore be promptly verified when AFB is discovered on sputum or BAL smears. A negative result from the NAAT in this circumstance clearly suggests the existence of a non-tuberculous Mycobacteria (NTM) species in the sample being tested. There are extremely few cases where this is not the case. The estimated sensitivity of NAAT for the diagnosis of active tuberculosis in individuals with negative AFB sputum smears, on the other hand, is highly heterogeneous (especially when in-house assays are compared), and it is not consistently accurate enough to be routinely recommended for tuberculosis diagnosis. [Citation needed] [Citation needed] [Citation needed] [Citation needed] [Citation needed] [Citation needed Higher diagnostic accuracy is typically associated with the use of nested NAAT methods as well as the IS6110 gene as the amplification target [24].

An earlier meta-analysis and a more recent independent investigation also found that the specificity of NAAT for the diagnosis of active tuberculosis was 97% and 98%, respectively, among persons who had negative sputum smear results. When done on a respiratory material, a positive result in an M. tuberculosis-specific NAAT is consequently strongly suggestive of pulmonary tuberculosis. However, based on our years of experience, we've found that the percentage of patients with smearnegative tuberculosis who have a positive sputum or BAL NAAT result is far lower than 50%. Individuals who have a previous medical history of tuberculosis and patients who

have been diagnosed with bronchogenic carcinoma are more likely to have false positive results [24].

Immunological diagnosis

Advances in serology for antibody/antigen detection

The serological reaction, also known as the detection of a specific antibody, has been the basis for the development of numerous diagnostic methods for tuberculosis over the course of a significant amount of time. In the present day, the development of such systems is extremely urgently required due to the pressure for strengthening earlier diagnosis of diseases in the paucibacillary stage. These diseases include pulmonary tuberculosis in adults with negative sputum smears, extra-pulmonary tuberculosis, childhood tuberculosis, and tuberculosis patients who have HIV co-infection. In order for the system to be used at the point of care in poor countries, it needs to have a straightforward operational design that is easy to understand. It also needs to be quick and accurate diagnostically, both in terms of sensitivity and specificity. On occasion, it is explicitly anticipated that the systems will be able to identify latent tuberculosis infection (LTBI) and track the development of tuberculosis treatment. However, in contrast to many other cases of acute bacterial and viral infections, there are several barriers to the successful application of serological reactions for diagnosing tuberculosis. These barriers include the gap between active disease and latent infection, the wide profile of the disease, which can range from one with extensive cavitary lesions to an almost inactive, minimal disease, and the distinction from NTM infection. All of these factors make it difficult to apply serological reactions successfully. These aspects of tuberculosis constitute strong forces that work against the sensitivity and specificity of the diagnostics that are anticipated to be used [25].

Advances in cellular immune-diagnosis

Both the TST and the interferon-gamma release assay (IGRA) test for the existence of mycobacteria-specific T-cell responses, although the TST does so in vivo whereas the IGRA tests for them ex vivo. They serve as an indirect marker for an active or formerly active infection. Individuals who have latent tuberculosis infection, active tuberculosis, or a history of tuberculosis cannot be differentiated using TST and IGRA tests done only on their peripheral blood.

Tuberculin skin test

Clemens v. Pirquet, an Austrian doctor, was the one who came up with the idea of using an allergy test to diagnose TB in children. This test is known as the TST. Since the beginning of the 20th century, this test has been considered to be the gold standard for making an immune-diagnosis of TB. In spite of the relatively recent development of IGRA, the TST continues to be the technique of choice for screening individuals to determine whether or not they have a positive immune response against Mycobacterium TB. Intradermal administration of a standard preparation of pure protein derivate (PPD), which is an extract of the sterile supernatant of M. tuberculosis-cultured filtrate, causes a delayed-type hypersensitivity response that manifests as induration of the local skin. TST responses in people are determined by the diameter of induration, which is assessed 48-72h after antigen injection using the 'ballpoint technique.' This method provides the highest level of test result dependability possible. According to a recent meta-analysis, the overall sensitivity of the TST for active tuberculosis is 77%. However, the sensitivity of the test can be dramatically impaired in certain populations, such as infants and toddlers as well as elderly persons, in individuals with congenital or acquired immunodeficiencies (such as those with HIV infection, patients being treated with corticosteroids or other immunosuppressive drugs, patients with chronic renal failure, malnutrition, cancer or overt TB The specificity of the TST is determined by the person being tested, namely their immunological state and whether or not they have had the BCG vaccine. Cross-reactivity of antigens may result in a positive TST response after exposure to NTM or after vaccination with M. bovis BCG. TST induration reactions that are more than 15 mm are likely attributable to tuberculosis or LTBI, regardless of whether or not the patient has been vaccinated with BCG. The TST's specificity, on the other hand, rises when the cut-off used to identify a positive induration is increased from 5 to 10 and 15 millimeters, despite the fact that the test's sensitivity drops as the cut-off increases from 5 to 10 and 15 millimeters. Several various cut-offs for a positive test response have been advised, ranging from 5 to 15 millimeters in induration. These cut-offs vary depending on the extent of exposure to an index case in contact tracing and the immunological state of the person. Recently, findings of a phase I study of a skin test that employs recombinant early

secretory antigenic target (ESAT)-6 instead of tuberculin have confirmed the safety and acceptability of such a test. These results were published in the journal Clinical Microbiology and Infectious Diseases. A skin test like this might potentially overcome some of the challenges that are presently associated with the use of the TST if it were combined with culture filtrate protein (CFP)-10 antigen to boost the diagnostic sensitivity of the test. If clinical trials demonstrate that this test is superior to the TST, then it may be possible to make it widely available for the diagnosis of LTBI in settings with limited resources, where the use of IGRA is not possible due to the high cost of the assay and the requirement of existing laboratory infrastructure [26].

Local immune-diagnosis for active tuberculosis by IGRA

Blood tests are unable to differentiate between those who have active tuberculosis and those who have latent tuberculosis infection (LTBI). This is most likely due to the fact that active tuberculosis does not have a large prevalence of effector memory T cells in this compartment. On the other hand, when TB is active, antigen-specific T lymphocytes undergo clonal expansion and become mostly localized at the site of infection. Comparison of systemic (peripheral blood) and local (BAL) T cell responses against mycobacterial antigens assayed by ELISPOT in tuberculosis suspects with negative AFB sputum smears are useful for rapidly distinguishing cases of active pulmonary tuberculosis from those with latent tuberculosis infection (LTBI) in tuberculosis suspects. Because the vast majority of patients with active pulmonary TB have negative AFB sputum smears, the local immune-diagnosis for active tuberculosis by BAL-ELISPOT has the potential to have a significant influence on the early diagnosis of tuberculosis. In a recent clinical trial, the local immune-diagnosis for mycobacteria-specific T cells by BAL-ELISPOT had a sensitivity of 91% and a specificity of 80% for the detection of sputum AFB smear-negative pulmonary tuberculosis. This was determined by comparing the sensitivity and specificity of the test to those of other diagnostic methods. When it came to the fast identification of sputum AFB smear-negative TB, the BAL-ELISPOT was shown to be much more sensitive than the M. tuberculosis-specific NAAT. A similar diagnostic accuracy of the BAL-ELISPOT for the diagnosis of AFB smear-negative pulmonary tuberculosis was recently observed in a study performed in the Republic of South Africa. Despite the fact that in this study up to one-third of test results were inconclusive due to failure of the positive and negative controls, the study found that the BAL-ELISPOT has a similar diagnostic accuracy [27].

Due to frequent exposure to *M. tuberculosis* antigens in TB-endemic countries, pulmonary immune responses to *M. tuberculosis* antigens assessed by ELISPOT may differ from those seen in tuberculosis-endemic countries. For clinicians, BAL-ELISPOT may thus be most applicable for a rapid decision to initiate anti-tuberculosis treatment in countries of low tuberculosis incidence, where bronchoscopy is routinely performed for individuals suspected to be affected by sputum.

AFB smear-negative tuberculosis and where the technology for ELISPOT is available [27].

Treatment

Tuberculosis (TB) continues to be one of the biggest infectious causes of mortality around the world, and poverty is a key contributor. Clinically, tuberculosis can manifest as “latent” TB or active TB disease; the treatment for each form of the disease is distinct. Both “early bactericidal activity” (EBA) and “sterilizing activity” can be exhibited by anti-tuberculosis medications (clearing persisters). The drug isoniazid is very good at the first task, and the drug rifampin is very good at the second task. Pyrazinamide and ethambutol are the final two components of the firstline treatment regimen for drug-susceptible tuberculosis, and each one serves a distinct purpose.

Drug-resistant TB is becoming a rising issue, which is being addressed in part by the use of repurposed pharmaceuticals (such as moxifloxacin, levofloxacin, linezolid, clofazimine, and betalactams) as well as innovative therapies (including bedaquiline, pretomanid, and delamanid). One of the challenges is selecting drugs with non-overlapping adverse drug reaction patterns. One of these issues is a prolongation of the QTc interval, which has been handled thus far. One of the most serious issues is the difficulty of entering drug sanctuaries within organisms, such as the central nervous system, bone, and pulmonary TB cavities. The area under the curve (AUC) divided by the least inhibitory concentration is the formula that can be used to characterize the pharmacodynamics of the majority of anti-tuberculosis medications (MIC). Experiments with a high level of pharmacokinetic and pharmacodynamic sophistication are pos-

sible thanks to the hollow fiber infection model (HFIM) and other animal models, particularly the mouse and the macaque. These tests may speed the selection of treatment regimens that are the most effective and shortest possible to treat even the most drug-resistant forms of tuberculosis. These discoveries may be applied to people by optimizing medication exposure in each patient via therapeutic drug monitoring and dosage individualization. This permits the discoveries from animals to be transferred to people [26].

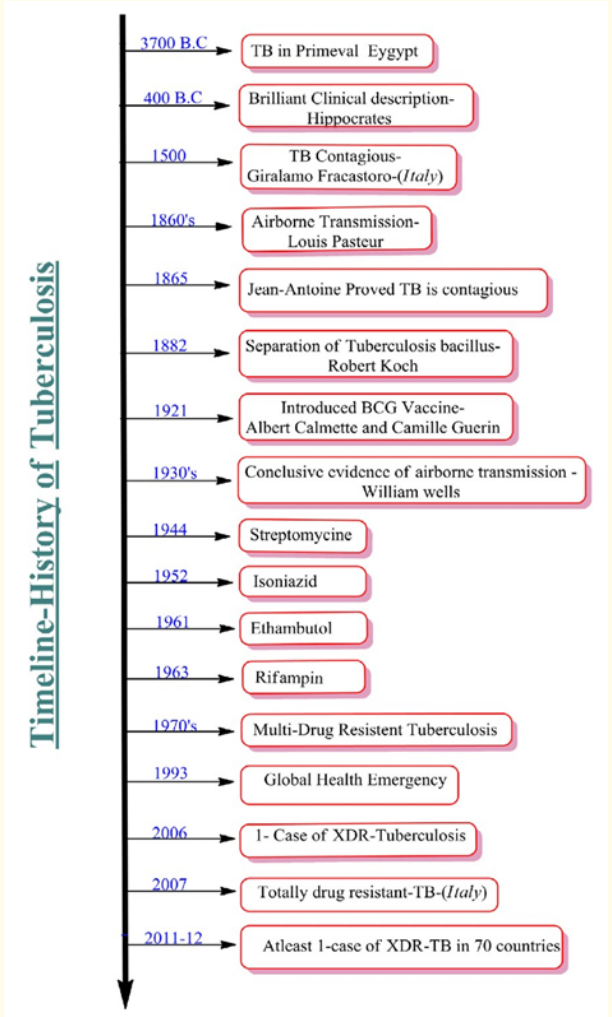

Figure 1: Timeline of TB Diagnosis (Mahesh, 2017).

Conclusion

The good combination of diagnosis and treatment is the most critical element of tuberculosis control and it will remain so until the advent of novel vaccines or drugs powerful enough to prevent development of tuberculosis perfectly. In the middle of the 20th century the treatment of tuberculosis made a revolutionary progress with the development of a series of chemotherapeutics, while only very little change was seen in the diagnostics. This caused disruption of the above combination leading to a low case detection rate in contrast with a fairly high treatment success rate as we see today worldwide. However, tuberculosis control is not possible, if the diagnosis of active cases is delayed as *M. tuberculosis* continues to be transmitted from case to contact. In addition, a false positive

diagnosis of LTBI has caused an unnecessary burden to individuals and healthcare systems. The urgent need for innovation in diagnostics is obvious.

However, it is good to see that the changes in diagnostics have started towards the end of the last century, assisted by the progress of biotechnology and the late riser's alertness to the problem. The balance between developments in the diagnosis and the treatment of tuberculosis has changed. Recent diagnostic advances overweigh the inefficient progress of new drug development against tuberculosis by far. Today, we have the technology to rapidly identify individuals with smearpositive MDR or XDR tuberculosis, but we do not have the drugs to treat these patients adequately.

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