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Review Article

**A REVIEW ON ADVERSE DRUG REACTIONS IN DRUG
RESISTANCES TUBERCULOSIS AND ITS MANAGEMENT**Vishnu priya. B. P^{1*}, Dr Prasobh G.R², Mr. E. Sam Jeeva Kumar³, Ms. Anjana U.J⁴, Ms.
Binisha S.K⁵, Ms. Arathy Sreenivasan⁶, Ms. Simchu R.B⁷¹Sree Krishna college of pharmacy and research centre, Parassala. Thiruvanthapuram Dist,
Kerala.**Article Received:** March 2023**Accepted:** April 2023**Published:** May 2023**Abstract:**

Tuberculosis is a contagious disease caused by mycobacterium tuberculosis, leading to increased mortality and morbidity. Although many new diagnostic tests and treatments have emerged for TB, there is still a big question as to why it is not ending. The disease roots easily due to many confounding factors such as patient noncompliance, development of ADR during treatment and the evolution of drug resistance. The drugs used in treatment have a higher proportion of side effects. The majority patients required treatment modification due to ADRs. The proper identification, reporting, management, or prevention can increase compliance and positive outcomes of therapy.

Keywords: *Tuberculosis, Tuberculosis Treatment, Tuberculosis drugs, ADR management, Drug-resistant Tuberculosis.*

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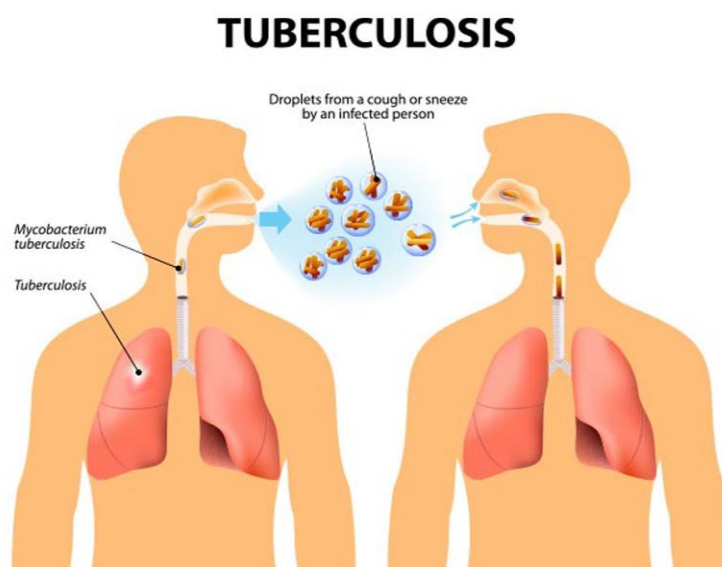
INTRODUCTION:

Tuberculosis (TB) is a chronic bacterial infection caused by *Mycobacterium tuberculosis* complex, most commonly by *Mycobacterium tuberculosis*, and is usually characterized pathologically by the formation of granulomas. The most common site of infection is the lung, but other organs may be involved including the kidney, spine, and brain, skin, etc. Compliance is crucial for curing TB. Adverse effects often negatively affect the compliance, because they frequently require a change of treatment, which may have negative consequences for treatment outcome. One of the adverse effects affecting TB treatment outcome is anti-TB drug induced hepatotoxicity. Hepatotoxicity is usually presented and diagnosed with jaundice or a high concentration of liver function marker proteins like aspartate aminotransferase (AST)/alanine aminotransferase (ALT), alkaline phosphatase (APT), or total bilirubin. Treatment should be interrupted and, generally, a modified or alternative regimen should be used for those with ALT elevation more than three times the upper limit of normal (ULN) in the presence of hepatitis symptoms and/or jaundice, or five times the ULN in the absence of symptoms. An increase in serum ALT is more specific for hepatocellular injury than an increase in AST which can also signify abnormalities in muscle, heart, or kidney. The cornerstone of TB management is a 6-month course of using anti-TB drugs where isoniazid, rifampicin, pyrazinamide, and ethambutol are taken for 2 months in the intensive phase followed by a fourth month use of isoniazid and rifampicin in the continuous phase of managing protocols of the disease. Among the first-

line anti-TB drugs, isoniazid, rifampicin, and pyrazinamide are known to cause hepatotoxicity, but pyrazinamide attribute to a higher percentage for the drug induced liver toxicity compared to the other drugs. The treatment regimen of tuberculosis can be tailored on patient's needs, mycobacterial tuberculosis resistance pattern, and location of the disease. Even though the first-line anti-TB drugs are effective, their liver toxicity may lead to drug interruption; which can in turn be the cause for the development of Multidrug Resistant Tuberculosis (MDR-TB). The simultaneous use of a number of drugs for a prolonged period of time, for the treatment of TB, further complicates the drug-induced toxicity problem.

TUBERCULOSIS:**Definition:**

Tuberculosis (commonly known as TB) is an infection caused by the bacterium *Mycobacterium tuberculosis*, which commonly affects the lungs (pulmonary TB) but can also affect the central nervous system, lymphatic system, circulatory system (military TB), genitourinary system, bones and joints. [1] Most infections show no symptoms, in which case it is known as latent tuberculosis. Around 10% of latent infections progress to active diseases which, if left untreated, kill about half of those affected. Typical symptoms of active TB are chronic cough with blood-containing mucus, fever, night sweats, and weight loss. It was historically referred to as consumption due to the weight loss associated with the disease. Infection of other organs can cause a wide range of symptoms.



Epidemiology:

Assuming lifelong infection, approximately 2 billion people are infected with *M. tuberculosis*. [2] TB is one of the most common causes of death from an infectious disease in the world. Globally there were an estimated 9.4 million new cases of TB in 2009, which represent an increase of 1.1 million cases compared with 2000. [3] In the United States a total of 11,181 cases of TB were reported in 2010 and the incidence rate was 3.6 per 10000 population which represent the lowest recorded rate since national reporting began in 1953. In 2010 four countries accounted for more than half of TB cases in foreign born persons; Mexico (23%), Philippines (11%), India (8.6%), Vietnam (7.7%). [4] In 2020, 86% of new TB cases occurred in the 30 high TB cases: India, China, Indonesia, the Philippines, Pakistan, Nigeria, Bangladesh and south Africa. According to WHO, in 2020 9.9 individuals become ill with TB and 1.5 million died. [5] The prevalence of all forms of TB for all ages in India was 312 per lakh population for the year 2021 and the highest prevalence for all forms of TB was 746 per lakh in Delhi and the lowest was 137 per lakh population in Gujarat. Kerala's TB incidence is estimated to be 67 cases per 100,000, less than half the 138 per 100,000 pan-India, as per 2017 RNTCP figures. Since 2009, when Kerala began active case-finding, the TB notification rate in the state's public sector has been falling by about 3% every year. The WHO has recently launched a new global TB strategy for the "post-2015 era" aimed at "ending the global TB epidemic" by 2035. This strategy is based on the three pillars that emphasize patient centered TB care and prevention, bold policies and supportive system, and intensified research and innovation. Continued commitment to and strengthening of TB control programs is essential to TB control programs is essential to the goal of TB elimination.

Etiology:

TB is caused by *M. tuberculosis*, an aerobic bacillus that resists decolorization by acid alcohol after staining with basic fuchsin. For this reaction, the organism often is referred to as an acid-fast bacillus (AFB). It is also different from other organism in that it replicates slowly once every 24 hours instead of every 20 to 40 minutes as with other organisms. The bacillus thrives in environments where the oxygen tension is relatively high, such as the apices of the lungs, the renal parenchyma, and the growing ends of bones. [6,7]

Clinical Manifestation:

Although our body can harbor the bacteria that cause tuberculosis, your immune system usually can prevent you from becoming sick.

- Latent TB: - You have a TB infection, but the bacteria in your body are inactive and cause no symptoms. Latent TB, also called inactive TB or TB inactive, isn't contagious. Latent TB can turn into active TB, so treatment is important.
- Active TB: - Also called TB disease, this condition makes you sick and, in most cases, can spread to others. It can occur weeks or years after infection with the TB bacteria.

Sign and Symptoms:

Symptoms of TB disease depends on where in the body the TB bacteria are growing. TB bacteria usually grow in the lungs (pulmonary TB). TB disease in the lungs may cause Symptoms such as,

- Coughing for three or more weeks
- Coughing up blood or mucous
- Chest pain, or pain with breathing or coughing
- Unintentional weight loss
- Fever
- Fatigue
- Night sweats
- Chills
- Loss of appetite

Diagnosis:

The most widely used screening method for tuberculosis infection is the tuberculin skin test (Mantoux method), which uses purified protein derivative (PPD). The Mantoux method of PPD administration, which is the most reliable technique, consists of the intracutaneous injection of PPD containing 5 tuberculin units. The test is read 48 to 72 hours after injection by measuring the diameter of the zone of induration. Some patients may exhibit a positive test after an initial negative test, and this is referred to as a booster effect. Daily sputum collection over 3 consecutive days is recommended. [8]

Laboratory test of tuberculosis:

The PPD skin test (Mantoux method) is a limited diagnosis tool used for the detection of infection with *M. tuberculosis* and necessary for the diagnosis of clinical disease. When a mycobacterial infection occurs, a delayed hyper sensitivity reaction to the tubercle bacilli us or to its components develops in the host. This reaction usually develops within 2 to 8 weeks after initial infection. The abbreviation PPD refers to the purified protein derivative of *M.*

tuberculosis, which is prepared from a culture of tubercle bacilli. The solutions are available as 1,5 or 250 tuberculin units (TU) per 0.1ml, although the 5-TU preparation (formerly referred to as intermediate strength PPD) is most common in united states. The 250 TU/0.1 ml PPD has limited usefulness in the diagnosis of tuberculosis infection and not recommended by the centers for diseases control and prevention (CDC) be the preparation are not standardized, making accurate interpretation difficult. It has however, occasionally been used to assess immunologic status. [9]

Clinical diagnosis:

The clinical diagnosis of TB disease is based on the symptoms and signs in the patient together with chest radiography, microscopy of sputum (for acid-fast bacilli) followed by culture and tuberculin skin testing. Blood-based immunological tests, introduced in the last few years, will play an increasingly important role in TB diagnosis. These tests can distinguish between TB infection and previous BCG vaccination. [10]

Microbiological:

Microbiological investigations are undertaken to assess the infectious state of the patient, and distinguish between infection with mycobacteria causing TB and other mycobacteria. They also determine the drug-susceptibility patterns of the infecting organisms, to ensure that the drugs prescribed will be effective in treating the individual patient. Investigations comprise microscopy, culture, drug-susceptibility testing and strain typing. Direct microscopy of sputum is the simplest and quickest method of detecting the infectious patient, by looking for acid-fast bacilli. A minimum of three sputum samples, one of which should be early morning, should be collected from patients with suspected respiratory TB. Direct microscopy is not as useful in non-pulmonary disease, any specimens taken should be sent for culture. If conventional culture methods are used, such as the Lowenstein–Jensen medium, growth may take up to 6 weeks. Modern liquid cultures can produce results more quickly. Polymerase chain reaction (PCR)-based tests can also detect *M. tuberculosis* complex in clinical specimens. A rapid

test is available for assessing rifampicin resistance in individuals thought to have drug-resistant TB. A positive result indicates the need to assess susceptibility to other first line anti-TB drugs. Drug-susceptibility testing still needs to be done on isolates grown on culture media. [10]

Tuberculin testing:

Tuberculin testing is used to detect LTBI. Only the Mantoux test is now used but it should be carried out by health care professionals trained and experienced in its use. The standard Mantoux test consists of an intradermal injection of 2 TU of Statens Serum Institute (SSI) tuberculin RT23 in 0.1mL solution for injection. In this test, 0.1 mL of the appropriate solution is injected intradermally, usually on the forearm, so that a bleb of around 7mm is produced. The results are read 48–72h later, although a valid reading can be obtained up to 96h later. The transverse diameter of the area of induration is measured with a ruler and the result recorded in millimetres. The interpretation of the test will depend on the clinical circumstances, including a past history of TB or exposure to TB. A diameter of induration of less than 6mm is negative, that is, there is no significant hypersensitivity to tuberculin protein. In the absence of specific risk factors for TB, induration of between 6 and 15mm diameter may be due to previous TB infection, or BCG vaccination or exposure to non-tuberculous mycobacteria. An induration of more than 15mm is strongly suggestive of TB infection or disease. [10]

Chest radiography:

The chest radiograph is a non-specific diagnostic tool, as TB may present as virtually any abnormality on chest radiography. This is why microbiological evidence of confirmation should be sought. Pulmonary TB may appear as bronchopneumonia with confluent shadowing, without cavitation. Cavitation may be seen; the incidence can vary between 10% and 30%. Uncharacteristic radiological patterns may occur in the presence of HIV infection. In children local lymph nodes may also show lesions. In post-primary tuberculosis the number of lesions seen may be greater and they be bilateral. [10]



Pathophysiology:

Aerosolization:

This story of tuberculosis pathophysiology caused by *M. tuberculosis* will begin where it will end: with the transmission of infectious bacteria. The tuberculosis transmission cascade breaks down into several steps and criteria. The first criteria in the transmission is that there must be a source of the bacteria - the index case. That source must generate infectious particles - that is, have primary or active tuberculosis. *M. tuberculosis* can then infect healthy individuals via mucous membrane, damaged dermal layers, the digestive system, and most commonly, the respiratory tract. As stated, the source is a person with active tuberculosis of the lungs or larynx able to aerosolize *M. tuberculosis*. The source generates these aerosolization's via forceful expiratory actions such as coughing, sneezing, shouting, or singing tuberculosis is then able to survive airborne. Susceptible individuals inhale the aerosolized *M. tuberculosis*. Some of these droplets that are smaller than 5 μm and contain 1–3 bacilli can reach the alveolar sacs upon inhalation. The size of the infectious particles, however, varies from 0.65 to > 7 μm . Upon reaching the alveolar sacs, the bacteria take up residence there. [11]

Macrophage phagocytosis:

Once *M. tuberculosis* has become resident in the alveolar sacs, the bacilli will encounter alveolar macrophages, also known as dust cells in this relative anatomical capacity, along with monocytes and dendritic cells. The alveolar macrophages are the dominant cell type in tuberculosis, and are considered to have limited bactericidal activity due to operating in surfactant. *M. tuberculosis* will bind with dust cells via mannose receptors, scavenger receptors,

complement receptors (CR1, CR3, CR4), Fc receptors, and surfactant protein receptors (SPR). The mannose receptor is a pathogen recognition receptor that is responsible for regulating trafficking, antigen presentation, macrophage differentiation, and inflammation. The mannose receptor is the most abundant receptor of human monocyte-derived macrophages. Once the *M. tuberculosis* has bound to the mannose receptor, the mannose receptor recruits Grb2, which activates the Rac/Pak/Cdc-42 pathway of *M. tuberculosis* uptake. The Rac/Pak/Cdc-42 pathway is related to the uptake of *M. tuberculosis* and recruits Src homology 2 (SH2) domain containing protein tyrosine phosphatase 1 (SHP-1). SHP-1 limits the activity of phosphatidylinositol 3-phosphate (PI3P), a trafficking phospholipid, and thereby limits the phagosome and the lysosome fusion. PI3P is also eliminated from the phagosome by a secreted lipid phosphatase, secretory acid phosphatase (SapM), produced by *M. tuberculosis*. [Moreover, PI3P is a docking molecule that interacts with proteins on the lysosome. Therefore, PI3P is a regulatory lipid essential in the merger of the phagosome and the lysosome that is eliminated in phagosomes containing live *M. tuberculosis*.

M. tuberculosis also induces the macrophage to express and secrete vascular endothelial growth factor (VEGF) into the extracellular spaces. Multiple isoforms of VEGF are critical components in several granuloma processes related to the pathogenesis of mycobacterium. These processes include angiogenesis, monocyte accumulation, macrophage recruitment, and inflammation. As stated, VEGF is responsible for the recruitment of blood vessels and vascular permeability through a physiological process known as angiogenesis. [The purpose of angiogenesis into the

eventual tuberculosis granuloma is not entirely clear. Still, there exist both immunological and pathological reasons. Immunologically, the eventual blood vessels will serve as an expedient way for immune cells to reach the granuloma and attempt to fight the infection. Pathologically, the eventual blood vessels will serve as a highway for the bacteria to reach systemic circulation and disseminate to other parts of the body. Regardless of defining the purpose of angiogenesis, the vasculature is chaotic, lacks pericytes, has an incomplete basement membrane, and is hyperpermeable. Additional to angiogenesis, VEGF Receptor (VEGFR) has been associated with lymph angiogenesis and mycobacterial specific T cells. The next role of VEGF is as a macrophage chemokine that contributes to the progression of tuberculosis through monocyte and macrophage recruitment in a non-angiogenic manner. This recruitment enhances the bacterial infection by providing new host cells and contributes to cell death signalling related to granuloma repopulation. Inflammation is the third hallmark of the VEGF contribution to mycobacterial infection and granuloma formation. This inflammation is excessive for protection and contributes to the symptomatology and lung pathology of the disease. Interestingly, VEGF inhibition has been shown to reduce granulomatous inflammation, and co-treatment with corticosteroids reduces tuberculosis patient mortality by 17%. [11]

Phagolysosome blockage and replication:

M. tuberculosis replicates intracellularly within the macrophages after preventing the fusion of the phagosome and the lysosome. *M. tuberculosis* has a very unique form of cell division known as asymmetric cell division. Asymmetric cell division means that the bacilli grow preferentially from one pole, and by doing so produce a fast-growing daughter cell and a slow-growing daughter cell. The slow-growing daughter cell differs in many ways from the fast-growing daughter and must assemble a growth pole de novo. These differences are most striking in that the differences between the daughter cells affects both growth rate and antibiotic resistance, a possible reason for the prolific and persistent nature of this bacteria in humans. During this part of the latent infection, the macrophage and *M. tuberculosis*, either together or individually, will migrate from the alveolar space into the lung parenchyma. Once in the lung parenchyma/interstitial, the immune system will begin to form a granuloma around the invader, in this instance also referred to as a tuberculoma. As the granuloma forms with the simultaneous recruitment of monocytes and immune cells, the bacteria enter the logarithmic phase of growth and must be contained.

Pathologically, the anatomical translocation to the lung parenchyma is associated with inflammation of the lungs. As stated, the bacilli replicate intracellularly, and this expansion will eventually cause the destruction of the macrophage via apoptosis, pyroptosis, necroptosis, ferroptosis, and extracellular trap-associated destruction. Apoptosis is an initial defence mechanism against the invading bacteria, and strongly virulent strains inhibit the apoptotic process. As a whole, however, apoptosis and pyroptosis restrict *M. tuberculosis* growth, whereas necroptosis and ferroptosis are beneficial to the bacteria's survival and success. [11]

T-helper response:

The dendritic cells and the monocytes from earlier in the story will have migrated to local and regional lymph nodes to activate T-cells by way of major histocompatibility complex (MHC) class II proteins and IL-12. This cluster of differentiation 4 (CD4+) response occurs after the first three weeks of infection, during which time *M. tuberculosis* will have extensively proliferated its population and potentially spread to other organs. The CD4+ T-cell response is why HIV patients are more susceptible to being unable to control tuberculosis infection, as HIV patients have a reduced CD4+ T-cell count. These antigen-specific T-cells will initiate the TH1 response, which, as stated begins about three weeks after infection. TH1 cells mediate the cell-mediated immune response. This response involves activating endothelium, proliferating effector T cell populations, and most relevant to granulomas, using interferon gamma (IFN γ) and cluster of differentiation 40 (CD40) ligand to activate macrophages. Natural killer cells recruited to the lesion will also release IFN γ . Cell-mediated immunity has three primary effects. The first is a type IV hypersensitivity reaction - pathophysiological, this reaction is the cause of the positive Mendel-Mantoux test with the purified protein derivative tuberculin glycerol extract. The second primary effect is the release of IFN γ that is the further activation of macrophages with augmented bactericidal properties so as to combat better the invader.

Granuloma formation:

A granuloma, as an analogy, is a bacterial jail that intends to imprison a bacterium inside a wall of immune cells. The IFN γ from the TH1 response will allow the maturation of the phagolysosome in the macrophages, cause the macrophage to produce nitric oxide via nitric oxide synthase, and induce autophagy. The activated macrophage, now being unable to eliminate the pathogen, will release TNF alpha (TNF α). TNF α induces differentiation of monocytes

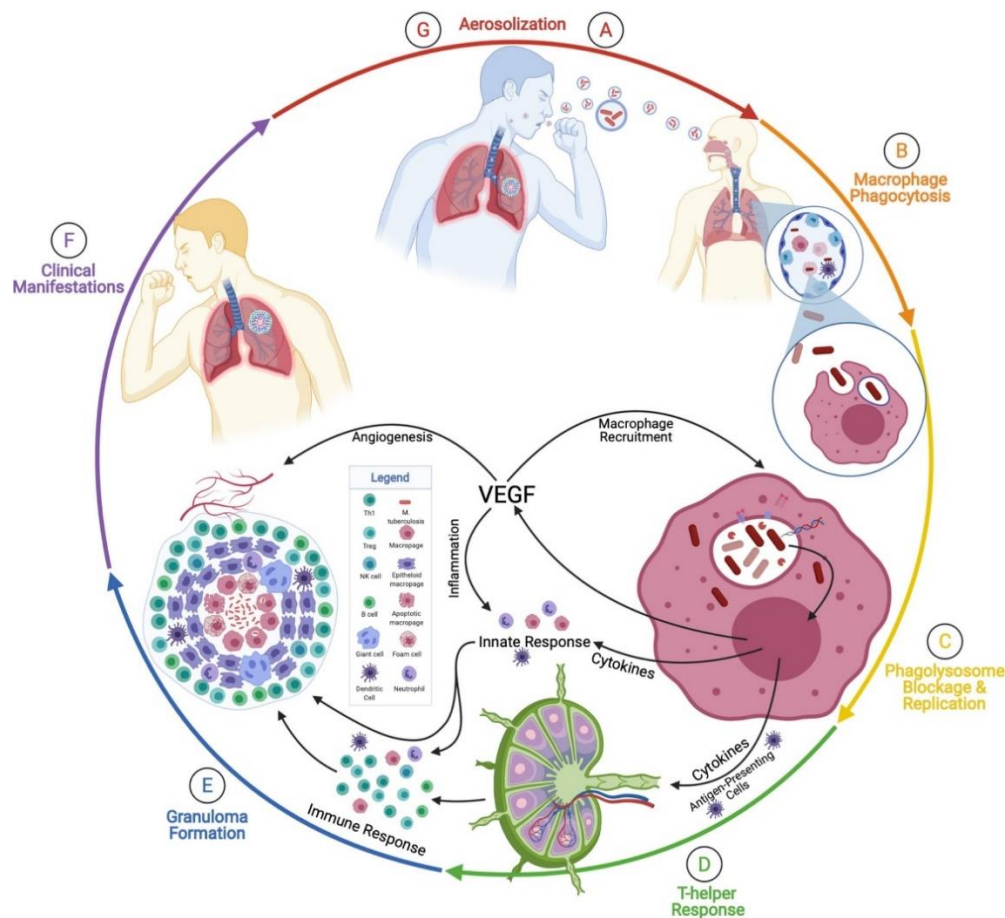
into epithelioid histiocyte cells that form caseating granulomas to contain *M. tuberculosis*. Some of these epithelioid histiocyte cells fuse to form giant cells. The TNF α continues a feedback chain by recruiting more monocytes to replace the newly differentiated monocytes. The granuloma itself is formed from both macrophages and lymphocytes surrounding and containing *M. tuberculosis*. Cells involved in the granuloma include TH1, regulatory T cells (Treg), natural killer (NK) cells, B cells, Giant cells, dendritic cells, neutrophils, macrophage, foam cells, and epithelioid macrophage (Fig. 1E). The hypoxic environment within the granuloma temporarily restricts the growth *M. tuberculosis*, but may also further promote angiogenesis into the tuberculoma.

Clinical manifestations:

There are two types of tuberculosis regarding clinical relevance primary tuberculosis and secondary tuberculosis. Primary tuberculosis is a novel infection; that is, the first time someone has acquired *M. tuberculosis*. This (primary) is the infection that results when the immune system cannot control the initial infection, and is usually the case seen in immunocompromised persons. This stage is where the infected individual can generate infectious aerosolization of *M. tuberculosis* and infect the next susceptible individual.

Suppose the immune system and granuloma contain *M. tuberculosis* but do not eliminate the bacteria. In the case, the disease is said to be latent and can progress to secondary tuberculosis at a later stage. Suppose the immune system and granuloma contain *M. tuberculosis* but do not eliminate the bacteria. In that case, the disease is said to be latent and can progress to secondary tuberculosis at a later stage. During the latent stage of tuberculosis, the bacteria form protective biofilms within the necrotic tissue. Subsequent immunosuppression allows the *M. tuberculosis* within the granuloma to reactivate and can result in pulmonary disease, extra-pulmonary disease, or miliary tuberculosis. Pulmonary disease is

the most common outcome following LTBI and includes the goon complex radiographic finding and cough, haemolyses, weight loss, night sweats, anorexia, and fever. Extra-pulmonary disease disseminates to the lymph nodes, genitourinary system, gastrointestinal system, pleura, and skeletal systems (with the latter resulting in tuberculosis spondylitis). Miliary tuberculosis is a disease where the granuloma has spread systemically and tuberculomas are resident throughout the body. Secondary tuberculosis can also be the end of the story, as the tuberculoma can liquefy and drain upon bacterial reactivation (cavitation), and the bacilli are aerosolized via the airways. To conclude, infection with *M. tuberculosis*, and the pathophysiology of the disease known as tuberculosis, can result in Suppose the immune system and granuloma contain *M. tuberculosis* but do not eliminate the bacteria. In that case, the disease is said to be latent and can progress to secondary tuberculosis at a later stage. During the latent stage of tuberculosis, the bacteria form protective biofilms within the necrotic tissue. Subsequent immunosuppression allows the *M. tuberculosis* within the granuloma to reactivate and can result in pulmonary disease, extra-pulmonary disease, or miliary tuberculosis. Pulmonary disease is the most common outcome following LTBI and includes the goon complex radiographic finding and cough, haemolysis, weight loss, night sweats, anorexia, and fever. Extra-pulmonary disease disseminates to the lymph nodes, genitourinary system, gastrointestinal system, pleura, and skeletal systems (with the latter resulting in tuberculosis spondylitis). Miliary tuberculosis is a disease where the granuloma has spread systemically and tuberculomas are resident throughout the body. Secondary tuberculosis can also be the end of the story, as the tuberculoma can liquefy and drain upon bacterial reactivation (cavitation), and the bacilli are aerosolized via the airways. To conclude, infection with *M. tuberculosis*, and the pathophysiology of the disease known as tuberculosis, can result in primary or secondary manifestations for clinical outcomes. [11]



Treatment:

Drug treatment is the cornerstone of TB management. A minimum of two drugs, and generally three or four drugs, must be used simultaneously. Drug treatment is continued for at least 6 months and up to 2 to 3 years for some cases of multidrug-resistant TB (MDR-TB). Measures to assure adherence, such as directly observed therapy, are important. Patients with active disease should be isolated to prevent spread of the disease. Public health departments are responsible for preventing the spread of TB, finding where TB has already spread using contact investigation. Debilitated patients may require therapy for other medical conditions, including substance abuse and HIV infection, and some may need nutritional support. Surgery may be needed to remove destroyed lung tissue, space-occupying lesions, and some extrapulmonary lesions. [8]

BCG Vaccine:

Many countries use BCG vaccine as part of TB control programs, especially for infants. The efficacy of BCG for meningitis TB protection in children is higher (greater than 80%). However, the protective efficacy

for pulmonary TB prevention in adolescents and adults is variable (from 0-8%). The effectiveness of BCG is much lower in areas where mycobacteria are less prevalent. [1]

First Line Anti-TB Drugs:

(Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin)

The most commonly used standard chemotherapeutic regimen for treatment of TB consists of first line drugs such as isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (EMB) for an initial 2-month phase followed by a continuation phase with INH and RIF for 4 months. Streptomycin is a bactericidal antibiotic that affects polypeptide synthesis but is no longer considered as a first line drug because of high rates of resistance. [12,13]

Second Line Anti-TB Drugs:

(Amikacin, Kanamycin, Para amino salicylic acid, Cycloserine, Ethionamide, Capreomycin, Ciprofloxacin)

The second line drugs are often used for treatment of TB in special conditions such as extensively drug-

resistant tuberculosis (XDR-TB) or multidrug-resistant tuberculosis (MDR-TB). The second-line drugs differ from first-line ones as they may be less effective than the first-line drugs (e.g., p-amino salicylic acid); or may have toxic side-effects (e.g., cycloserine); or may be unavailable in many developing countries (e.g., fluoroquinolones). [13,14]

DOTS (Directly Observed Treatment, Short-Course):

Drug resistance is more relevant in TB and is contributed by the poor management of chemotherapy, which makes the treatment more complex, increases its length and side effects. [15] Multidrug-resistance (MDR) is mainly concerned with the resistance of M. tuberculosis strains to both isoniazid and rifampicin, regardless of the sensitivity/resistance to other drugs. MDR-TB is alarming due to the high risk of death associated with it while resistance to either drug may be managed with other first-line drugs or second-line drugs under DOTS Plus. Extensively drug-resistant TB (XDRTB) strains have been recently reported by various Centres for Disease Control (CDC) with resistance to at least three out of the six classes of second-line drugs (aminoglycosides, polypeptides, fluoroquinolones, thioamides, cycloserine, and p-amino salicylic acid). Almost 20% of MDR-TB cases were classified as XDR-TB in some regions, raising concerns over a future epidemic of virtually untreatable TB. DOTS is the most effective strategy available for controlling TB. [16] It plays a major role in global plans of WHO to stop TB on the basis of five main principles that include

1. Political commitment to control TB (establishing a centralized and prioritized system of TB monitoring, recording and training).
2. Case detection by sputum smear microscopy examination.
3. Anti-TB drugs to be given under the direct observation of the health care provider/community DOT provider.
4. Regular, uninterrupted supply of anti-TB drugs.
5. Systematic recording and reporting system that allows assessment of treatment results of each

and every patient during the whole TB control programme. ⁽¹⁷⁾

DOTS is a managed chemotherapy and has a success rate exceeding 95% and prevents the emergence of further multidrug resistant strains of tuberculosis. In 1998, WHO extended the DOTS programme especially for the management, diagnosis and treatment of MDR-TB in the name of DOTS-Plus. The main focus of DOTS-Plus implementation is to carry out the drug-susceptibility testing and to check the availability of second-line agents in addition to all other requirements of DOTS. For DOTS-Plus to be successful, special attention is needed for the quality assured laboratory capacity (smear, culture and drug sensitivity testing), treatment design, adherence to difficult to-take regimens for long periods, side-effect management, drug procurement, recording and reporting and human and financial resource constraints. Therefore DOTS-Plus is much more complex and expensive than DOTS and requires much greater commitment from countries wishing to implement it. World Health Organization recommended that the regimen based on 2 months of rifampicin 2HRZE/6HE (where H(Isoniazid), R (Rifampin), Z (Pyrazinamide), E (Ethambutol) should be discontinued and be changed to the full 6 months-based regimen of rifampicin 2HRZE/4HR to reduce the number of relapses and failures. Drug Susceptibility Testing (DST) is one of the main objectives of WHO to start the therapy for all previously treated patients. ⁽¹⁸⁾ Drug Resistance Surveillance (DRS) data is helpful in identifying and halting the spread of MDR-TB. WHO currently recommends a regimen consisting of amikacin (AMK), ethionamide (ETH), fluoroquinolone (such as moxifloxacin, MXF) and PZA for the treatment of MR-TB. The main focus of Centres for Disease Control (CDC) is to control the extensively drug resistant TB (XDR-TB), which is a kind of MDR-TB with additional resistance to fluoroquinolones and to at least one of the injectable second-line drugs such as capreomycin, kanamycin, and amikacin. CDC recommends the basic regimens for the treatment of TB which might be helpful to prevent the MDR/XDR-TB. [19]

Preferred Region	Alternative Region	Alternative Region
Initial phase Daily INH, RIF, PZA AND EMB for 56 doses (8 weeks)	Initial phase Daily INH, RIF, PZA and EMB for 14 doses (2 weeks), then twice weekly for 12 doses (6 weeks)	Initial phase thrice-weekly INH, RIF, PZA, and EMB for 24 doses (8 weeks)
Continuation phase Daily INH and RIF for 126 doses (18 weeks) or Twice-weekly INH and RIF for 36 doses (18 weeks)	Continuation phase Twice-weekly INH and RIF for 36 doses (18 weeks)	Continuation phase Thrice-weekly INH and RIF for 54 doses (18 weeks)

BASIC REGIMENS FOR THE TREATMENT OF TB:**Adverse Drug Reactions of Tuberculosis**

TB is a chronic infection caused primarily by mycobacterium tuberculosis. The lung is generally the first affected organ, as the infection is usually due to inhalation of infected droplet nuclei. Approximately 80% of the TB cases are pulmonary TB. Around 30% patients who are infected with Human Immune Deficiency Virus (HIV) will also develop active tuberculosis. Factors, such as HIV, Resistant TB, drug-drug interactions raise the complexity of problem. As per the WHO strategy, directly observed treatment short-course (DOTS) therapy for the duration of 6-8 months is one of the important components for the treatment of TB. The short-course therapy is usually performed in 2 phases: the initial phase (2 months) involves the concurrent use of at least 3 drugs to rapidly reduce the bacterial population and prevent emergence of drugs-resistant bacteria. The second, continuation phase, (4-6 months) involves fewer drugs and is used to eliminate any remaining bacteria and prevent recurrence. Worldwide, HIV infections has been identified as an important predisposing factor of immune-suppression leading of TB. It increases the reactivation rate of TB. Although this regimen is effective in treating active TB, it is associated with many ADRs and poses a significant challenge to completion of treatment. Recommended treatment regimens for TB. [20]

Importance of ADR reporting in tuberculosis:

Multiple types of drug therapy are given for TB, and even new TB patients (sensitive to first-line drugs), are receiving a treatment regimen with a combination of four drugs. There is a chance for developing ADR either for one or the combination of drugs, and that has to be identified for ensuring a sustained treatment compliance, till the completion of ATT. When treatment is given to patients with TB-associated drug resistance, multidrug resistance or rifampicin resistance, pre-extensively drug resistance TB, the number of drugs given could be higher, and it becomes imperative to identify the resulting/associated ADRs. In case any ADR takes place, the treatment management has to be done appropriately. For TB patients having HIV co-infection, the including the antiretroviral therapy, and the medication given for the associated conditions, may overlap with the ADR presented, and so it becomes very important to monitor this group of population for efficient management. In addition, also in TB patients with special medical conditions associated, like associated diabetes mellitus, liver, renal or seizure disorders, and psychosis, the treatment should be done cautiously, by closely

observing the progress and monitoring all the ADRs encountered. Furthermore, when new drugs like Bedaquiline (BDQ), Delamanid (DLM) and Pretomanid are initiated at TB programs, it is essential that the associated ADRs are captured promptly for effective management of TB ADRs associated with first-line anti-TB drugs

The ATT is expected to cause more ADRs, because it involves combination of several medicines and is used for a longer duration. One of the most common ADRs observed with the administration of ATT is gastrointestinal symptoms, such as nausea, vomiting etc. These ADRs could be symptomatically managed without the need for a change in the dosage of drugs. The hepatotoxicity is also a risk associated with ATT, and its frequency can range from 2–39% in different countries. As compared to Western population, Indian sub-population studies reported high incidence of hepatotoxicity with ATT.

Isoniazid:

Isoniazid has been shown to be well tolerated at recommended dose. However, systemic or cutaneous hypersensitivity reactions can occasionally occur during the first weeks of treatment. By daily supplementary dose of pyridoxine in vulnerable patients, the risk of peripheral neuropathy can be excluded. In the later stages of treatment, some susceptible patients can develop neurological disturbance, encompassing optic neuritis, toxic psychosis and generalized convulsions. This may require the discontinuation of isoniazid. An uncommon but potentially serious reaction is symptomatic hepatitis, which could be precluded by prompt withdrawal of treatment. Asymptomatic rise in serum concentrations of hepatic transaminases at the beginning of treatment has very low clinical significance. The same resolves spontaneously as the treatment carry on. Other rare adverse effects linked with isoniazid are lupus-like syndrome, pellagra, anemia, and arthralgias. [20]

Rifampicin:

At currently recommended doses, this drug has been shown to be well tolerated by most of the patients. Occasionally it may cause gastrointestinal reactions including abdominal pain, nausea, vomiting and pruritus with or without rash. With an intermittent drug administration, adverse effects, such as fever, influenza-like syndrome and thrombocytopenia may occur. In HIV-positive TB patients, exfoliative dermatitis is more common. Patients taking the drug 3 times a week, adverse effects including temporary oliguria, dyspnea and hemolytic anemia have been

reported. If the regimen is changed to daily dosage these reactions usually subsided. In the beginning of treatment, moderate rises in serum concentrations of bilirubin and transaminases are common adverse effects are often transient and not clinically significant. A potentially fatal condition is dose-related hepatitis, it is therefore important to not exceed the maximum recommended daily dose of 600 mg

Pyrazinamide:

This drug has been reported to cause various skin reactions, like maculopapular rash, erythema multiforme, exfoliative dermatitis and drug rash with eosinophilia and systemic symptoms (DRESS) syndrome. Among the first-line drugs, pyrazinamide has shown to be the most common drug to cause cutaneous ADRs. Pyrazinamide may cause gastrointestinal intolerance. Hypersensitivity reactions are rare, but have been reported in some patients with modest flushed skin. During the early phases of the treatment, moderate rises in serum transaminase concentrations are common. A rare complication is severe hepatotoxicity. A degree of hyperuricemia may also occur asymptotically as a result of inhibition of renal tubular secretion. The treatment may also result into gout, which can be treated with allopurinol. Arthralgia, especially of the shoulders, may occur which can be treated with simple analgesics (especially aspirin). By prescribing regimens with intermittent administration of pyrazinamide, hyperuricemia and arthralgia may be eliminated. Sideroblastic anemia and photosensitive dermatitis are some of the rare ADRs associated with this drug.

Streptomycin:

Streptomycin injections are painful, and rash, induration, or sterile abscesses can be formed at injection sites. Numbness and tingling around the mouth occur immediately after injection and cutaneous hypersensitivity reactions can occur. The incidence of ototoxicity associated with the use of

ATT may be as high as 25%. With currently recommended doses, the complications like impairment of vestibular function are uncommon. Vertigo is more common than hearing loss. Indications of injury at the 8th cranial (auditory) nerve include ringing in the ears, ataxia, vertigo and deafness. The damage is impermanent and can be reversed by reducing in dosage, or the stopping the treatment with this drug. This damage is commonly occurring within the first 2 months of treatment. More commonly, the other aminoglycoside antibiotics e.g., kanamycin, amikacin and capreomycin are more nephrotoxic than streptomycin. If urinary output falls, albuminuria occurs, or tubular casts are detected in the urine, streptomycin should be stopped, and renal function should be evaluated. Though WHO's recommendation is not to use injectable streptomycin, we should take into consideration that other recommended treatments with aminoglycosides may cause similar types of ADRs.

Ethambutol:

Dose-dependent optic neuritis caused by Ethambutol can result in impairment of visual acuity and color vision in one or both eyes. Early changes are usually reversible, but blindness can occur if treatment is not discontinued promptly. Ocular toxicity is rare when ethambutol is used for 2–3 months at recommended doses. Peripheral neuropathy has been reported in approximately 20% of patients treated with ethambutol. Other rare adverse events include generalized cutaneous reaction, arthralgia and, very rarely, hepatitis. Several studies have reported that the drugs used to treat TB may cause ADRs. Management and prevention of such ADRs are important measures to be adopted to increase tolerance. Generally, with non-serious ADRs, the drugs do not need to be stopped, while with serious ADRs, the drugs often have to be stopped and a modified regimen has to be implemented.

Adverse Drug Reaction	Symptoms and signs	Responsible Drug
Audio vestibular manifestations	Hearing loss, vertigo, new-onset tinnitus	Aminoglycosides, Capreomycin
Blood sugar abnormalities	Dizziness, sweating, fainting, poor response to infections	Fluroquinolones (FQ), Rifampicin (R), Pyrazinamide (Z)
Dermatitis	Itching, rash, hives, fever, petechial rash	Pyrazinamide, Rifampicin, Thiacetazone
Gastro-intestinal	Anorexia, nausea, vomiting, epigastric pain	Pyrazinamide, Rifampicin; p-Amino salicylic acid

Haematology	Leukopenia, thrombocytopenia, anaemia, eosinophilia	Rifampicin (intermittent); Linezolid, Isoniazid, capreomycin
Hepatitis	Anorexia, nausea, vomiting, jaundice, abdominal pain	Isoniazid, Rifampicin, Ethambutol, Pyrazinamide
Hypothyroidism	Fatigue, weight gain, depression	P-amino salicylic acid, pro/Ethionamide
Joint, tendon	Gout-like manifestations; SLE; tendinopathies	Pyrazinamide; Isoniazid (Rarely rifampicin); Fluroquinolones;
Neuro/psychiatric	Headaches, depression, agitation; suicidal ideation	Isoniazid, Fluroquinolones, Cycloserine
Peripheral neuropathy	Numb feet or hands	Ionized linezolid; Cycloserine, Aminoglycosides
Renal impairment	Uraemia; haematuria	Aminoglycosides, Capreomycin; Rifampicin (intermittent)
Visual disorders	Vision loss and colour blindness; uveitis	Ethambutol, Linezolid; Rifabutin, Rifapentine;

ADRs associated with second-line anti-TB drugs:

Resistant -TB is usually treated with a combination of drugs that are more toxic than isoniazid and rifampicin. These drugs include fluoroquinolones, aminoglycosides, ethionamide, cycloserine, amino salicylic acid, linezolid and clofazimine, among others. The main ADRs associated with the use of cycloserine are reported as neurological disorders, including headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression, rashes, allergic dermatitis, megaloblastic anemia, and changes in liver function tests. Minor adverse effects are relatively common, and they can be easily managed with symptomatic treatment. However, some adverse effects can be life-threatening, for example, nephrotoxicity due to aminoglycosides, cardiotoxicity due to fluoroquinolones, gastrointestinal toxicity due to ethionamide or para-amino-salicylic acid, central nervous system toxicity due to cycloserine, etc.

Multi Drug-resistant TB (MDR-TB):

MDR-TB is caused by organisms that are resistant to isoniazid and rifampicin. As per the WHO reports, an estimated 480 000 worldwide patients developed MDR-TB in 2015, in addition to the 100 000 patients with rifampicin-resistant TB that were newly eligible for MDT-TB treatment. Again, according to WHO, the second highest MDR-TB incident country in the world, China, accounted for 45% of the 580 000 cases, together with Indian and the Russian Federations, with 6.6% of new TB cases and 30% of previously treated cases having MDR/Rifampicin resistant TB. The

novel anti tubercular drugs, namely BDQ and DLM, now included in WHO second-line treatment. as well as in some countries, have received conditional approval for use in adults with MDR-TB. BDQ, a new anti TB- drug, has been given approval by the United States Food and Drug Administration in 2012, and by the European Medicines Agency in 2014. In India, BDQ was introduced under the conditional access program in 2015. The safety profile and tolerability of a BDQ-containing treatment regimen used in India has been established. QT prolongation in electrocardiogram reading has been reported as one of the most common ADRs with the use of BDQ; the others include peripheral neuropathy, vomiting, breathlessness and thrombocytopenia.

Drug resistance in tuberculosis

Tuberculosis (TB) is a disease caused by bacteria that are spread from person to person through the air. TB usually affects the lungs, but it can also affect other parts of the body, such as the brain, the kidneys, or the spine. In most cases, TB is treatable and curable; however, people with TB can die if they do not get proper treatment. Sometimes drug-resistant TB occurs when bacteria become resistant to the drugs used to treat TB. This means that the drug can no longer kill the TB bacteria. Drug-resistant TB (DR TB) is spread the same way that drug-susceptible TB is spread. TB is spread through the air from one person to another. The TB bacteria are put into the air when a person with TB disease of the lungs or throat coughs, sneezes,

speaks, or sings. People nearby may breathe in these bacteria and become infected. [21]

Types of drug resistance in tuberculosis:

Multidrug-Resistant TB (MDR TB):

Multidrug-resistant TB (MDR TB) is caused by TB bacteria that are resistant to at least isoniazid and rifampin, the two most potent TB drugs. These drugs are used to treat all persons with TB disease. TB experts should be consulted in the treatment of MDR TB.

Pre-Extensively Drug-resistant TB (pre-XDR TB):

Pre-Extensively Drug-resistant TB (pre-XDR TB) is a type of MDR TB caused by TB bacteria that are resistant to isoniazid, rifampin, and a fluoroquinolone OR by TB bacteria that are resistant to isoniazid, rifampin, and a second-line injectable (amikacin, capreomycin, and kanamycin).

Extensively Drug-resistant TB (XDR TB):

TB bacteria that are resistant to isoniazid and rifampin, a fluoroquinolone, and a second-line injectable (amikacin, capreomycin, and kanamycin) OR by TB bacteria that are resistant to isoniazid, rifampin, a fluoroquinolone, and bedaquiline Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB caused by or linezolid.

Because XDR TB is resistant to the most potent TB drugs, patients are left with treatment options that are much less effective.

XDR TB is of special concern for people with HIV infection or other conditions that can weaken the immune system. These people are more likely to develop TB disease once they are infected, and also have a higher risk of death once they develop TB.

TB experts should be consulted in the treatment of XDR

Causes of drug resistance in Tuberculosis:

Drug-resistant TB can occur when the drugs used to treat TB are misused or mismanaged. Examples of misuse or mismanagement include

- People do not complete a full course of TB treatment
- Health care providers prescribe the wrong treatment (the wrong dose or length of time)
- Drugs for proper treatment are not available
- Drugs are of poor quality

Drug-resistant TB is more common in people who

- Do not take their TB drugs regularly
- Do not take all of their TB drugs

- Develop TB disease again, after being treated for TB disease in the past
- Come from areas of the world where drug-resistant TB is common
- Have spent time with someone known to have drug-resistant TB disease

Treatment of drug resistance in Tuberculosis:

Drug-resistant TB is caused by TB bacteria that are resistant to at least one first-line anti-TB drug. Multidrug-resistant TB (MDR TB) is resistant to more than one anti-TB drug and at least isoniazid (INH) and rifampin (RIF). Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Treating and curing drug-resistant TB is complicated. Inappropriate management can have life-threatening results. Drug-resistant TB should be managed by or in close consultation with an expert in the disease. Safety Announcement Regarding Fluoroquinolone Antibacterial Drugs. The US Food and Drug Administration (FDA) has advised restricting fluoroquinolone antibiotic use for certain uncomplicated infections because of adverse effects from these medications specifically, FDA indicated that the risks of adverse effects of fluoroquinolone antibacterial drugs generally outweigh the benefits for patients with sinusitis, bronchitis, and uncomplicated urinary tract infections who have other treatment options. While patients receiving fluoroquinolone antibacterial drugs for tuberculosis (TB) also have a chance of experiencing the adverse effects noted by FDA, fluoroquinolone antibacterial drugs are absolutely necessary for some patients who have drug-resistant TB disease or drug-resistant latent TB infection or who cannot tolerate first-line TB drugs. For these TB patients, there are no better alternatives, and the benefits of fluoroquinolone antibacterial drugs outweigh the risks because TB is not a minor infection, but potentially fatal or debilitating. If you are a TB patient receiving fluoroquinolone antibacterial drugs and have questions, please contact your medical provider or local or state TB control program. If you are a medical provider and have questions about the use of fluoroquinolone antibacterial drugs in TB treatment.

Prevention of drug resistance in Tuberculosis:

The most important way to prevent the spread of drug-resistant TB is to take all TB drugs exactly as prescribed by the health care provider. No doses should be missed and treatment should not be stopped early. People receiving treatment for TB disease

should tell their health care provider if they are having trouble taking the drugs. Health care providers can help prevent drug-resistant TB by quickly diagnosing cases, following recommended treatment guidelines, monitoring patients' response to treatment, and making sure therapy is completed. Another way to prevent getting drug-resistant TB is to avoid exposure to known drug-resistant TB patients in closed or crowded places such as hospitals, prisons, or homeless shelters. People who work in hospitals or health-care settings where TB patients are likely to be seen should consult infection control or occupational health experts.

Review of literature:

1. Akosua Agyeman, Richard Ofori- Asenso conducted a study on Tuberculosis- an overview. The study concludes that Tuberculosis remains one of the deadliest infectious diseases and has claimed millions of lives for many years. While significant progress has been made towards controlling the global burden of TB over the past decade, more efforts are still needed.
2. Habtamu Belew Mera et.al conducted a study on prevalence and predictors of pulmonary tuberculosis among prison inmate in sub – Saharan Africa: A systematic review and meta-analysis. The study concludes that In this systematic review and meta-analysis, the pooled prevalence of pulmonary TB among prisoners in SSA was considerably high which needs special attention to attain the end TB strategy.
3. Gebeyehu Assefa et.al conducted a study on Drug resistance in tuberculosis lymphadenitis molecular characterization this study found 3 MDR/RR-TB cases and heterogeneous strains of MTB among TBLN patients. The great extent of INH mono-resistance in HIV patients is a critical risk for potential development of MDR-TB, as INH monoresistance is a typical pathway to the occurrence of MDR-TB.
4. Asif Massud et.al conducted a study on frequency and management of adverse drug reactions among drug-resistant tuberculosis patients: analysis from a prospective study. The study is aimed to drug-resistant tuberculosis management is often linked with a higher rate of adverse drug reactions needing effective and timely management of these ADRs along with risk factor of ADRs occurrence among DR-TB patients at Nishtar Medical university, hospital, Multan, Pakistan. The study concludes the frequency of ADRs was high among the study cohort; however; these were managed effectively. Patients with recognized risk factor for ADRs occurrence need continuous clinical management efforts.
5. Daniel Brodie, MD, Neil W. Schluger, MD a conducted study on the diagnosis of tuberculosis. The study concludes the diagnosis testing for tuberculosis remained un-changed for nearly a century, but newer technologies hold the promise of a true revolution in tuberculosis diagnostics. In these tests are likely to play an ever-increasing role in the coming years. Ultimately, the appropriate and affordable use of any of these tests depends on the setting in which they are employed.
6. David p. Maison a conducted study on tuberculosis pathophysiology and anti-VEGF intervention. The study concludes, there are many steps in the pathophysiology of tuberculosis. Pharmaceutically, these steps are difficult to target as the bacteria is evasive in hijacking the immune system. Anti-VEGF treatments offer an avenue that has only yet seen brief exploration in humans with a drug exclusive to the A isoform of VEGF. As success exists with disseminated tuberculosis and anti-VEGF therapy using both small molecules and antibodies, clinical trials are warranted to evaluate all current anti-VEGF and anti-VEGFR drugs in tuberculosis treatment.
7. Solovic, M. Sester, et. al a conducted study on the risk of tuberculosis related to tumour necrosis factor antagonist therapies: a TBNET consensus statement. The study concludes, the introduction of TNF antagonist therapies into clinical practice has been a breakthrough in the history of the treatment of inflammatory diseases such as rheumatoid arthritis, ankylosing spondylarthritis, juvenile idiopathic arthritis and inflammatory bowel disease. TB screening and preventive chemotherapy for all individuals with latent infection with M. tuberculosis should become the standard of care for all individuals undergoing TNF antagonist therapies. Following the guidelines of this article will lead to a significant reduction in the number of cases of active TB in relation to TNF antagonist therapies.
8. Aboi Igwaran and chideu epiphany eoamodu a conducted study on the Bibliometric analysis on tuberculosis and tuberculosis-related trends in Africa: A decade-long study. The study concludes, this study provides quantitative and qualitative analyses of the top leading journals, most cited published papers, most relevant authors in publications on tuberculosis from 2010-2019. This bibliometric study also provides insights into authors research outputs, countries collaborations, and relevant countries by

corresponding authors. In addition, collaboration or partnerships among underdeveloped and developed African countries with high quality research infrastructure could help some of these African countries with low publication collaboration.

9. Timothy R. Sterling et al. conducted a study on the HIV infection-related tuberculosis: clinical manifestations and treatment. The study concludes, the frequency of TB patients with HIV infection proves that TB diagnosis, treatment, and prevention are essential for all clinicians caring for persons infected with HIV. Although the treatment of HIV-related TB with standard anti-TB regimens usually highly effective, managing the important drug interactions, toxicities, and immune reconstitution inflammatory syndrome makes care of coinfecting patients particularly challenging.
10. Ben J. Marais, Robert P. et al. conducted a study on Childhood Pulmonary Tuberculosis: Old Wisdom and New Challenges. The study concludes, accurately quantifying the burden of childhood tuberculosis in endemic areas. Improving our understanding of the immune correlates of disease and protection, and evaluating the protective role of BCG and novel vaccine candidates. Defining the diagnostic contribution of novel T-cell-based assays in endemic and nonendemic areas. Identifying novel ways of diagnosing childhood tuberculosis in HIV-uninfected and in HIV-infected children, particularly in resource-limited settings. Operations research to improve the access of children in endemic areas to preventive therapy and treatment, using the existing DOTS framework. Evaluating the efficacy of short-course intermittent preventive chemotherapy regimens. Exploring shorter durations of treatment in immune competent children with smear-negative disease. Defining the optimal treatment regimen and treatment duration in HIV-infected children. Monitoring the impact of MDR tuberculosis on children and evaluating regimens for effective MDR disease prevention and treatment. Developing and evaluating new drugs that may shorten the treatment duration and/or assist with the treatment of MDR disease.
11. Soumya Swaminathan and Banu Rekha conducted a study on Paediatric Tuberculosis: Global Overview and Challenges. The study concludes, Refinement of existing tools and development and testing of new tools are urgently required to improve diagnosis and treatment of TB in children. Higher global priority and funding will be required to reduce the unnecessary and

avoidable morbidity and mortality occurring currently. In addition to reducing the burden of adult TB, attention to childhood nutrition and improvement in the socioeconomic and environmental condition of communities is likely to have a significant impact on TB transmission to children.

METHODOLOGY:

The study is a systematic review of various literatures which are available on the various sources. The review, discussion was carried out and are concluded.

DISCUSSION:

A review is conducted on the adverse drug reactions and drug resistance in tuberculosis and its management. The main aim of the review is to analyse the common drug resistance that may occur during the management of tuberculosis.

Tuberculosis is a chronic infectious disease that is caused by *Mycobacterium tuberculosis*, which commonly affects the lungs but can also affect the central nervous system, circulatory system, lymphatic system, genitourinary system, bones and joints. The symptoms associated with tuberculosis include coughing for three or more weeks, coughing up blood or mucus, chest pain, pain with breathing or coughing, unintentional weight loss, fever, night sweats, chills, loss of appetite.

From the review it was analysed that the most widely used screening method for tuberculosis infection is the tuberculin skin test which uses purified protein derivative. The other clinical diagnostic methods may include chest radiography, microscopy of sputum followed by culture and tuberculin skin testing. Immunization programs are associated with the management of tuberculosis. Many countries use BCG vaccine as a part of TB control programs, especially for infants. The effectiveness of BCG is much lower in areas where mycobacteria are less prevalent.

The common choice of drugs for the treatment of tuberculosis are first line choice of drugs. This may include Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin. This is followed by the usage of second line drugs which may include Amikacin, Kanamycin, Para Amino Salicylic Acid, Cycloserine, Ethionamide, Capreomycin, Ciprofloxacin. The second line drugs are often used for treatment of TB in special conditions such as extensively drug resistant tuberculosis or multi drug resistant tuberculosis. The second line drugs differ from first line ones as they may be less effective than

the first line drugs or may have toxic side effects. Drug resistance is more relevant in TB and is contributed by the poor management of chemotherapy, which makes the treatment more complex, increases its length and side effects. Direct Observational Therapy is the most effective strategy available for controlling TB. It plays a major role in global plans of WHO to stop TB. DOTS is managed chemotherapy and has a success rate exceeding 95% and prevents emergence of further multi drug resistant strains of tuberculosis.

CONCLUSION:

The review of this study was performed to TB treatment will cause a variety of ADR and sometimes it can be fatal if is not properly managed. Some of the ADRs are minor and can be managed without the discontinuation of treatment. But some may be severe and, in that case, either modification or discontinuation of treatment is required. The major culprit of severe irreversible ADR that occurred in DR-TB is pyrazinamide and kanamycin. The ADR will reduce both the compliance and the success rate of treatment. Regular monitoring of patients allows the identification and proper management of adverse reactions. The management is based on individual ADR, can treat symptomatically, withhold the drug or withdraw the drugs.

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