



Pharmacovigilance Study On Anti-Tuberculosis Drugs

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Abstract: Tuberculosis (TB) remains one of the deadliest infectious diseases worldwide, disproportionately affecting low- and middle-income countries. The disease, caused by *Mycobacterium tuberculosis*, primarily affects the lungs but can spread to other organs. TB transmission occurs through airborne droplets from individuals with active pulmonary TB. Despite global efforts, drug-resistant TB poses a significant challenge, necessitating continuous research and novel treatment strategies. This paper provides a comprehensive overview of TB, including its etiology, transmission, epidemiology, pathophysiology, diagnostic methods, and treatment regimens. It also highlights adverse drug reactions associated with first-line and second-line anti-tubercular drugs, emphasizing the need for effective pharmacovigilance to ensure patient safety. Furthermore, advancements in TB treatment, emerging drug-resistant strains, and future directions in TB management are discussed. The study underscores the importance of early diagnosis, adherence to treatment protocols, and ongoing research to achieve global TB elimination goals.

Keywords: TB, Treatment, Symptoms, Precautions etc.

I. INTRODUCTION

Tuberculosis (TB) remains one of the world's most deadly infectious diseases, with over 95% of deaths occurring in low- and middle-income countries. TB primarily affects young adults during their most productive years, though individuals of all ages are at risk. Since the last edition of this guide in 2010, TB care has garnered significant political attention. High-level political events have been held to address the disease, including its inclusion in the 2017 G20 Leaders' Declaration as part of the fight against antimicrobial resistance. Additionally, the BRICS nations agreed to promote research and development of innovative medical products, including TB drugs, during the 2017 Health Ministers Meeting. The first Global Ministerial Conference on "Ending TB in the Sustainable Development Era: A Multi-Sectoral Response" was held in Moscow in 2017. In 2018, the United Nations held its first High-Level Meeting (HLM) on Ending TB in New York, resulting in a historic Political Declaration with specific, measurable milestones to be achieved by 2022. These milestones include:

Diagnosing and treating 40 million people with TB by 2022.

Diagnosing and treating 3.5 million children with TB by 2022.

Diagnosing and treating 1.5 million people with drug-resistant TB, including 115,000 children, by 2022.

Providing preventive treatment to at least 30 million people, including 4 million children under five, 20 million household contacts of TB patients, and 6 million people living in high-risk environments.

Tuberculosis

Tuberculosis is an airborne infectious disease caused by the bacterium *Mycobacterium tuberculosis*. It is one of the most widespread communicable diseases globally. TB primarily affects the lungs but can also impact other parts of the body, such as the lymph nodes, brain, kidneys, and bones. The disease spreads when a person with active TB in the lungs or throat coughs, speaks, or sings, releasing TB germs into the air. These germs can remain airborne for several hours, depending on environmental conditions.

How TB Spreads

TB is transmitted when a person with active pulmonary TB releases germs into the air through coughing, sneezing, talking, singing, or even laughing. Only individuals with active pulmonary TB are contagious. Most people who inhale TB bacteria can fight off the infection, leading to latent TB, where the bacteria remain inactive in the body.

History of Tuberculosis

The history of TB dates back thousands of years. The earliest evidence of TB in humans was found in the remains of a child and mother from the sunken city of Atlit Yam, Israel, around 9,000 years ago. Written accounts of TB date back to India (3,300 years ago) and China (2,300 years ago). During the Middle Ages, TB was known as the "king's evil" in England and France, where it was believed that a royal touch could cure the disease.

Etiology

TB is caused by bacteria belonging to the *Mycobacterium tuberculosis* complex, which includes *M. tuberculosis*, *M. bovis*, and *M. africanum*. While these are the primary causative agents, other mycobacteria, known as atypical mycobacteria, can also cause pulmonary diseases resembling TB. These atypical mycobacteria are found in soil, milk, and water. Another notable mycobacterium is *Mycobacterium leprae*, which causes leprosy.

Causative Agents

The primary causative agents of TB are:

- a. *Mycobacterium tuberculosis* (M. tuberculosis)
- b. *Mycobacterium bovis* (M. bovis) – rare in humans
- c. *Mycobacterium africanum* (M. africanum) – rare in humans

Transmission

TB is transmitted through:

- **Droplet transmission:** Coughing, sneezing, or talking.
- **Contact transmission:** Close contact with an infected person.
- **Airborne transmission:** Inhalation of contaminated air.
- **Contaminated surfaces and objects** (rare).

Epidemiology

- Global incidence: 10 million cases (2020).
- Global mortality: 1.5 million deaths (2020).
- Highest burden countries: India, China, Indonesia, Pakistan, Nigeria.

Increasing drug resistance is a growing concern.

Evaluation

- Medical evaluation for TB typically includes:
- Medical history.
- Physical examination.
- TB blood test or TB skin test.
- Chest radiograph.
- Bacteriologic examination.

A positive TB test indicates the presence of TB germs, while a negative result suggests that TB is unlikely. However, additional tests may be required if symptoms of active TB, such as coughing, chest pain, fever, weight loss, or fatigue, are present. Other tests include sputum tests, breath tests, and urine tests.

II. PATHOPHYSIOLOGY

- Infection:** *M. tuberculosis* enters the lungs through inhalation.
- Phagocytosis:** Macrophages engulf the bacteria.
- Latency:** Bacteria remain dormant in macrophages.
- Activation:** Bacteria reactivate, causing active TB.
- Spread:** Bacteria disseminate through the bloodstream or lymphatic system.

III. TYPES OF TB

1. **Pulmonary TB** (lung TB).
2. **Extrapulmonary TB** (outside the lungs).
3. **Miliary TB** (widespread dissemination).
4. **Latent TB** (asymptomatic infection).

Stages of TB

Primary

- ii. **Latent**
- iii. **Active TB disease.**

Symptoms of Active TB

- Persistent cough (lasting more than two weeks).
- Chest pain.
- Coughing up blood or sputum.
- Fatigue or weakness.
- Loss of appetite.
- Weight loss.
- Chills.
- Fever.
- Night sweats.

Causes

TB is caused by *Mycobacterium tuberculosis*. The bacteria spread through the air and typically infect the lungs, though other parts of the body can also be affected. TB is infectious but does not spread easily; prolonged contact with an infected person is usually required for transmission.

Risk Factors

- Close contact with a TB patient.
- Weakened immune system (e.g., HIV/AIDS, immunosuppression).
- Age (elderly, young children).
- Malnutrition.
- Chronic diseases (e.g., diabetes, kidney disease).

infection.
infection.

- Smoking.
- Alcohol consumption.
- Poverty and overcrowding.
- Travel to TB-endemic areas.
- Occupation (e.g., healthcare workers, laboratory personnel).

Diagnostic Tests

- Sputum smear microscopy.
- Culture and sensitivity testing.
- Interferon-gamma release assays (IGRAs).
- Tuberculin skin test (TST).
- Chest X-ray.
- Computed tomography (CT) scan.

Mode of Transmission

TB is transmitted through:

Human being acquire infection with tuberculosis bacilli by one of the following routes

Inhalational of organism present in fresh cough droplets or in dried sputum from an open case of pulmonary tuberculosis

Ingestion sputum of an open case of pulmonary tuberculosis or ingestion of bovine tubercle bacilli from milk of diseased cows

Inoculation of the organisms into the skin may rarely occur from infected postmortem tissue.

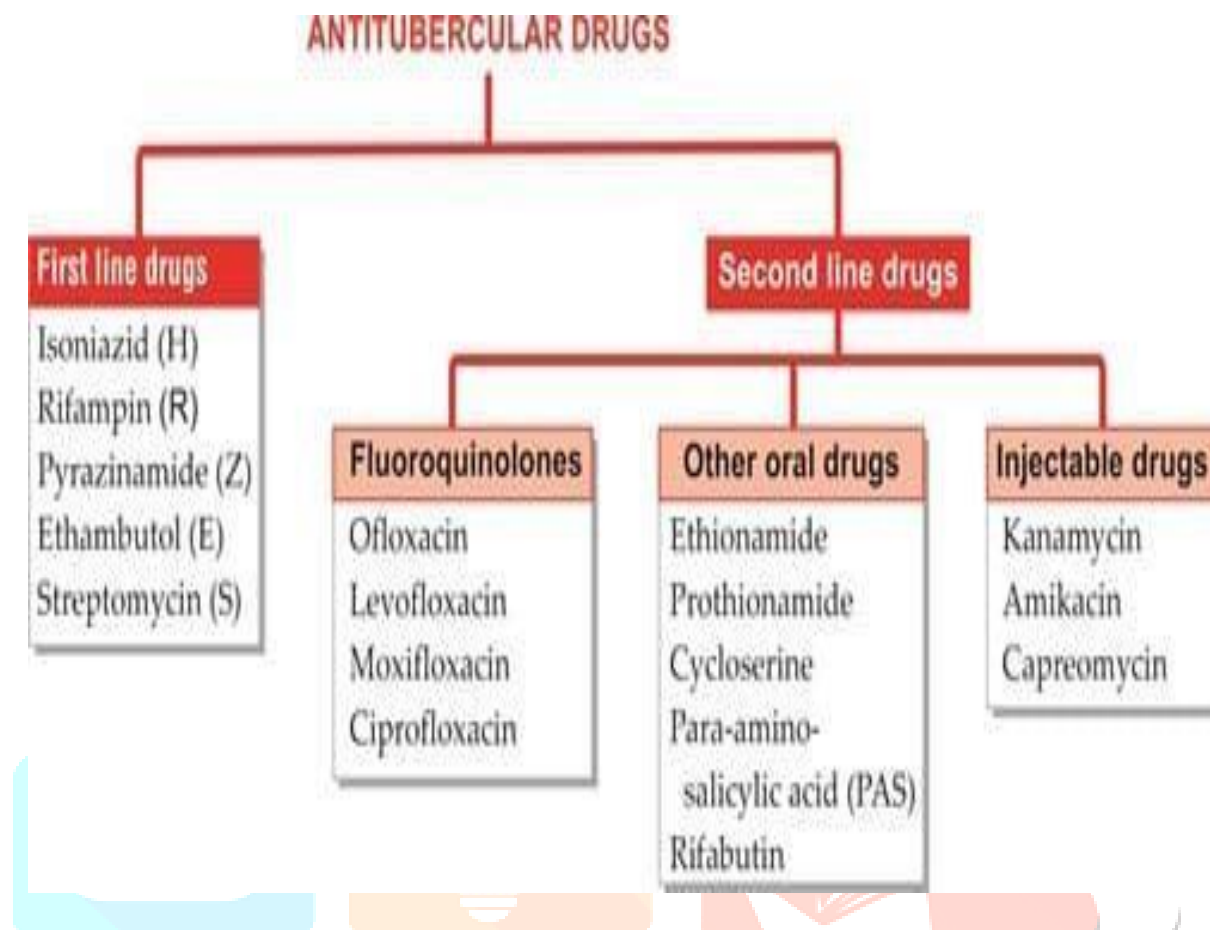
Transplacental route in development of congenital tuberculosis in foetus from infected mother and is a rare mode of transmission.

IV. ANTI-TUBERCULOSIS DRUGS

Anti-tuberculosis drugs are used to treat or prevent TB. They are classified into first-line and second-line drugs.

First-line drugs: These include isoniazid, rifampin, pyrazinamide, and ethambutol. They are highly effective and have low toxicity.

Second-line drugs: These are used when first-line drugs are ineffective or intolerable. Examples include kanamycin, capreomycin, and amikacin.



V. LITERATURE SURVEY

1. Forget Eric J., (2018) -A total of 105 ADR'S were reported in 67(13.2%) of 50 patients.
2. Gastrointestinal disorders were the most frequently observed ADR'S
3. (65.5%) ADR'S are less frequent in children than adult. The most severe ADR is hepatotoxicity, caused by isoniazid.
4. Forget, Eric J et al (2018) - of the total,127 patients (73%) had minor adverse reaction and 45 patients (26.2%) experienced major adverse reactions. predominant adverse reaction included gastrointestinal disorder (34%) and drug included hepatitis (60%).
5. Albanna, Amr S (2019)– Among the 750 patient with TB ,402 were females, and 348 were males the mean age of PWTB was 36 to 45 years. Gastrointestinal ADR'S were seen, followed by joint pain for detection of all pulmonary TB patients chest radio graph was done.
6. Rahana Pervin et. al. (Dec.2023) – Both EPTB and PTB patient were seen more in groups (94%) and PTB was slightly higher (49%) Vs (45%) EPTB around 61% of EPTB caused Around 11-18 age group, with higher prevalence amongst female (61%) compared to males.
7. Richard Delali D et al (2023) – The study involved 378 participants who were diagnosed with drug susceptible tuberculosis with a mean (SD) age of 45.3 (15.1) years. The majority of participants were males (62.3%), employed (75.6%) had basic education (60.9%) and were males (62.2%) diagnosed with pulmonary

TB.

VI. ADVERSE DRUG REACTIONS

Common adverse reactions to TB drugs include gastrointestinal disorders, hepatotoxicity, and joint pain. Females are at higher risk for adverse events than males.

Isoniazid (INH)

Isoniazid is one of the most effective first-line drugs for TB treatment. However, it is associated with several ADRs, particularly affecting the liver and nervous system.

Common ADRs:

Hepatotoxicity: Elevated liver enzymes, jaundice, and in severe cases, hepatitis. This is the most serious ADR associated with INH.

Peripheral Neuropathy: Numbness, tingling, or burning sensations in the hands and feet due to vitamin B6 (pyridoxine) deficiency.

Gastrointestinal Disturbances: Nausea, vomiting, and loss of appetite.

Central Nervous System Effects: Dizziness, headache, and rarely, seizures.

Hypersensitivity Reactions: Skin rashes, fever, and in rare cases, anaphylaxis.

Management:

Hepatotoxicity: Regular monitoring of liver function tests (LFTs) is essential. If hepatotoxicity is detected, INH should be discontinued immediately.

Peripheral Neuropathy: Pyridoxine (vitamin B6) supplementation is recommended to prevent or treat neuropathy.

Gastrointestinal Issues: Taking INH with food can help reduce nausea and vomiting.

Rifampicin (RIF)

Rifampicin is another key first-line drug, but it is known for causing a range of ADRs, particularly affecting the liver and immune system.

Common ADRs:

Hepatotoxicity: Similar to INH, rifampicin can cause elevated liver enzymes and hepatitis.

Gastrointestinal Disturbances: Nausea, vomiting, abdominal pain, and diarrhea.

Flu-like Syndrome: Fever, chills, and muscle pain, especially with intermittent dosing.

Hypersensitivity Reactions: Skin rashes, itching, and in rare cases, severe allergic reactions.

Hematological Effects: Thrombocytopenia (low platelet count) and hemolytic anemia.

Orange-Body Fluids: Rifampicin can turn urine, sweat, and tears orange, which is harmless but can be alarming to patients.

Management:

Hepatotoxicity: Regular LFT monitoring is crucial. Rifampicin should be stopped if severe hepatotoxicity occurs.

Flu-like Syndrome: Switching to daily dosing may help reduce these symptoms.

Hypersensitivity Reactions: Antihistamines or corticosteroids may be used to manage mild reactions. Severe reactions require discontinuation of the drug.

Pyrazinamide (PZA)

Pyrazinamide is highly effective in the initial phase of TB treatment but is associated with significant ADRs, particularly affecting the liver and joints.

Common ADRs:

Hepatotoxicity: Elevated liver enzymes and hepatitis.

Hyperuricemia: Increased uric acid levels, leading to gout-like symptoms such as joint pain and swelling.

Gastrointestinal Disturbances: Nausea, vomiting, and loss of appetite.

Arthralgia: Joint pain, especially in the knees, ankles, and wrists.

Management:

Hepatotoxicity: Regular LFT monitoring is essential. PZA should be discontinued if hepatotoxicity is severe.

Hyperuricemia: Allopurinol may be prescribed to manage high uric acid levels.

Arthralgia: Non-steroidal anti-inflammatory drugs (NSAIDs) can help relieve joint pain.

Ethambutol (EMB)

Ethambutol is generally well-tolerated, but it can cause serious ADRs, particularly affecting the eyes.

Common ADRs:

Optic Neuritis: Blurred vision, loss of visual acuity, and color blindness. This is the most serious ADR associated with EMB.

Gastrointestinal Disturbances: Nausea, vomiting, and abdominal pain.

Peripheral Neuropathy: Numbness and tingling in the extremities (less common than with INH).

Management:

Optic Neuritis: Regular eye examinations are recommended during treatment. If vision problems occur, EMB should be discontinued immediately.

Gastrointestinal Issues: Taking EMB with food can help reduce nausea and vomiting.

Streptomycin (SM)

Streptomycin is an injectable second-line drug used in drug-resistant TB. It is associated with significant ADRs, particularly affecting the kidneys and ears.

- **Common ADRs:**
- **Ototoxicity:** Hearing loss, tinnitus (ringing in the ears), and balance problems.
- **Nephrotoxicity:** Kidney damage, leading to elevated creatinine levels.
- **Hypersensitivity Reactions:** Skin rashes, fever, and in rare cases, anaphylaxis.
- **Neuromuscular Blockade:** Muscle weakness and respiratory paralysis (rare).
- **Management:**
- **Ototoxicity:** Regular audiometric testing is recommended. Streptomycin should be discontinued if hearing loss or balance problems occur.
- **Nephrotoxicity:** Regular monitoring of kidney function is essential. Dose adjustments may be necessary in patients with renal impairment.
- **Second-Line Drugs**
- Second-line drugs, such as **kanamycin**, **capreomycin**, **levofloxacin**, and **moxifloxacin**, are used in drug-resistant TB. These drugs are associated with more severe ADRs compared to first-line drugs.
- **Common ADRs:**
- **Ototoxicity and Nephrotoxicity:** Similar to streptomycin, injectable second-line drugs can cause hearing loss and kidney damage.
- **Gastrointestinal Disturbances:** Nausea, vomiting, and diarrhea.

- **QT Prolongation:** Fluoroquinolones (e.g., levofloxacin, moxifloxacin) can cause QT interval prolongation, leading to arrhythmias.
- **Tendon Rupture:** Fluoroquinolones are associated with tendon damage, particularly in elderly patients.
- **Management:**
- **Ototoxicity and Nephrotoxicity:** Regular monitoring of hearing and kidney function is essential.
- **QT Prolongation:** Electrocardiogram (ECG) monitoring is recommended during treatment with fluoroquinolones.
- **Tendon Rupture:** Patients should be advised to avoid strenuous physical activity during treatment.
- **General Management of ADRs in TB Treatment**
- **Patient Education:** Patients should be informed about potential ADRs and advised to report any unusual symptoms immediately.
- **Regular Monitoring:** Routine monitoring of liver function, kidney function, and hearing is essential, especially for patients on second-line drugs.
- **Symptomatic Treatment:** Many ADRs can be managed with supportive care, such as antiemetics for nausea or NSAIDs for joint pain.
- **Drug Discontinuation:** Severe ADRs, such as hepatotoxicity or optic neuritis, require immediate discontinuation of the offending drug.
- **Alternative Regimens:** In cases of severe ADRs, alternative TB treatment regimens may be considered

Treatment

TB treatment involves a combination of antibacterial medications taken for six to 12 months. Completing the treatment is crucial to prevent drug-resistant TB or disease recurrence. The TB Aarogya Sathi app helps improve patient adherence and provides healthcare providers with real-time data on treatment progress.

VII. MECHANISM OF ACTION OF ANTI-TB DRUGS

Isoniazid: Inhibits mycolic acid synthesis, essential for the bacterial cell wall.

Isoniazid (INH) is an antibiotic that treats tuberculosis (TB) by inhibiting the synthesis of mycolic acids, which are essential components of the mycobacterium's cell wall. Isoniazid (INH) is an antibiotic that treats tuberculosis (TB) by inhibiting the synthesis of mycolic acids, which are essential components of the mycobacterium's cell wall:

Activation: The bacterial enzyme catalase-peroxidase (KatG) activates INH. Target:

Activated INH targets mycolic acid (MA) synthesis.

Inactivation: Arylamine N-acetyltransferases (NATs) inactivate INH.

Rifampicin: Inhibits RNA polymerase, preventing bacterial RNA synthesis.

Rifampicin is a broad-spectrum antibiotic that works by inhibiting the bacterial enzyme RNA polymerase (RNAP), which is responsible for DNA transcription:

Inhibition of RNA polymerase: Rifampicin binds to the beta-subunit of RNA polymerase, which is essential for transcription of DNA into RNA.

Prevention of RNA chain initiation: By binding to RNA polymerase, rifampicin prevents the initiation of new RNA chain

Pyrazinamide: Disrupts fatty acid synthesis and membrane transport in TB bacteria.

Pyrazinamide (PZA) is an antibiotic used in combination with other medications to treat tuberculosis (TB). Its mechanism of action is complex and involves multiple targets. Here's a simplified explanation:

Inhibition of fatty acid synthase I (FASI): PZA is activated within Mycobacterium tuberculosis (M. tuberculosis) cells by the enzyme pyrazinamidase, which converts PZA into its active form, pyrazinoic acid (POA). POA then inhibits FASI, an enzyme essential for fatty acid synthesis, which is crucial for mycobacterial cell wall construction and energy metabolism.

Disruption of membrane transport: POA also disrupts membrane transport processes, including the efflux

pumps that remove toxic compounds from the bacterial cell. This disruption leads to an accumulation of toxic compounds within the cell, ultimately contributing to the bactericidal effect of PZA.

Interference with ATP synthesis: PZA may also interfere with ATP synthesis in *M. tuberculosis* cells. By inhibiting the enzyme ATP synthase, PZA reduces the energy available for bacterial growth and survival.

Streptomycin: Binds to bacterial ribosomes, causing misreading of genetic code and bacterial death.

Streptomycin is an antibiotic that works by binding to the ribosome of bacteria cells, preventing from creating proteins

Binding: Streptomycin binds to the 30s ribosomal subunit, near the aminoacyl transfer site of the 16s portion of the ribosomal RNA

Misreading : This binding causes the ribosome to misread the genetic code, resulting in the production of random proteins.

Killing The production of random proteins kills the bacteria

Streptomycin was the first antibiotic used to treat tuberculosis. However,

bacteria can develop resistance to streptomycin through mutations in the genes that code for rRNA 16S and protein S12.

Ethambutol: Inhibits arabinosyl transferases, preventing cell wall synthesis.

Ethambutol diffuses into *Mycobacterium* cells.¹² Once inside the cell, ethambutol inhibits the arabinosyl transferases (embA, embB, and embC), preventing formation of the cell wall components arabinogalactan and lipoarabinomannan, and preventing cell division.^{6,7,10,5} Decreased concentrations of arabinogalactan in the cell wall reduces the number of binding sites for mycolic acid, leading to the accumulation of mycolic acid, trehalose monomycolate, and trehalose dimycolate.^{9,7} Lipoarabinomannan is a component of a cell surface molecule involved in the interaction with host cells. Reduced levels of lipoarabinomannan may interfere with mycobacterial interaction with host cells.

III. PRECAUTIONS

To prevent the spread of tuberculosis (TB), people with TB should take precautions while they are infectious:

Cover your mouth and nose: Use a tissue to cover your mouth and nose when you cough, sneeze, or laugh.

Stay home: Avoid going to work, school, public places, or using public transportation.

Wear a mask: Wear a special face mask when you go to the clinic or hospital. You should also wear a surgical or procedure mask when leaving the home for essential medical appointments.

Isolate yourself: Sleep in a separate area from other people in your household.

Avoid visitors: Don't let visitors come to your home, especially children and those with compromised immune systems.

Air out your home: Open windows or use a fan to help move air around. Take your medication: Follow your TB treatment plan.

Tell your healthcare providers: Let your healthcare providers know that you have TB. Follow respiratory etiquette: Educate your family and guests on respiratory etiquette

IX. FUTURE SCOPE

The future of TB treatment and research includes:

Development of new vaccines and drugs.

Improved point-of-care testing for TB and drug resistance.

Active monitoring of high-risk populations.

The End TB Strategy aims to reduce TB cases and deaths globally.

X. CONCLUSION

The study highlights the frequency of adverse events in patients receiving anti-tuberculosis treatment (ATT). Females are more susceptible to adverse events than males, with the gastrointestinal system being the most affected. Effective pharmacovigilance measures can help mitigate these adverse events, which are a significant factor in treatment interruption.

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