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Insight of Tuberculosis: Complications and Adverse Drug of Anti-Tubercular Medication

Mohemediya Afreen Sultana*
Pharm D. Student, Department of Pharmacotherapy, Malla Reddy College of Pharmacy, Secunderabad, India

***Abstract*: Tuberculosis (TB) remains a leading infectious killer globally. TB is c Tuberculosis (TB) is a persistent global health challenge with significant complications. Apart from its direct effects on the lungs and other organs, TB can also lead to complications such as meningitis, bone and joint infections, and even pericardial involvement. These complications can be severe and may require extensive treatment and management. Additionally, the long-term use of anti-TB drugs can introduce its own set of complications. Hepatotoxicity is a well-known concern with drugs like isoniazid, rifampicin, and pyrazinamide, potentially leading to liver inflammation and dysfunction. Arthralgia, flu-like symptoms, hyperuricemia, thrombocytopenia, and peripheral neuropathy are also possible complications associated with prolonged use of these medications. Managing these complications requires close monitoring by healthcare providers and pharmacists, along with patient education on recognizing and reporting adverse effects promptly to ensure effective TB treatment while minimizing drug-related complications.**

***Keywords*: tuberculosis, latent tuberculosis, drug toxicity, tuberculosis complications.**

1. Introduction

Tuberculosis (TB) poses a significant global public health challenge, prompting the World Health Organization (WHO) to declare it a global emergency in 1993 due to a rise in reported cases across continents. Particularly worrying is the increase in multidrug-resistant TB outbreaks worldwide, attributed partly to HIV infections and inadequate treatment.

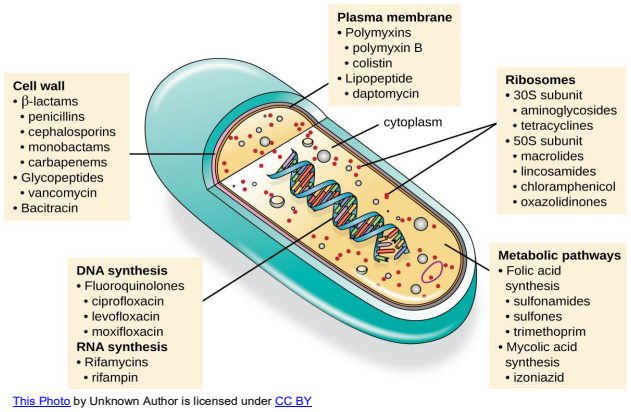


Fig. 1.

Since the late 1980s, the UK has seen a surge in TB cases, mainly affecting larger urban areas in England. The 2004 TB Action Plan for England outlines crucial strategies to curb TB transmission.

TB primarily targets the lungs but can affect other body parts like the kidneys, spine, and brain. Not everyone infected develops symptoms, leading to two conditions: latent TB infection (LTBI) and TB disease. Without proper treatment, TB disease can be fatal.

2. Etiology and Pathogenesis

Any infection caused by M. tuberculosis is referred to as tuberculosis. Three types of tubercle bacilli are pathogenic to humans-human, bovine, and avian. Avian tuberculosis is extremely rare in the United States and bovine has decreased with the advent of pasteurization of milk and testing of cows. Therefore, the human type is the most important. The most prevalent means of spreading tuberculosis between individuals is by coughing and sneezing. The sputum of actively infected patients is contaminated with many bacilli. These droplets become airborne and may be inhaled by unsuspecting persons. If the organisms in the inhaled droplets reach the bronchioles or alveoli, these people may develop a tuberculous infection; however, if the bacilli only reach the upper bronchi, they will be eliminated without subsequent infection [1].

Since the tuberculous bacillus is an aerobe, the high oxygen tension in the apices of the lungs offers an ideal environment for harboring the organism. Al- Although pulmonary infection is the most common, tuberculosis may affect any organ in the body. With few exceptions, the infecting organism gains entry into the body via the lungs. It is here that primary tuberculosis is established. From the lungs, infection spreads to other organs by way of the lymphatic system and the bloodstream.

At this stage, the infection usually becomes dormant, and immunity on the part of the host prevents further spread. The lesions may be walled off by the production of fibrous tissue and calcification. The time during which tuberculosis remains dormant varies greatly. Organisms may remain inactive for the life of the host or, following a breakdown in the host's defenses, they may become reactivated at any time. Three to 10% of the patients infected develop the disease within the first year, and the incidence increases with subsequent years [2].

*Corresponding author: afreensultana1703@gmail.com

Following the period of dormancy, reactivation of a latent infection may take one of two courses, chronic tuberculosis or miliary tuberculosis. The factors affecting the recurrence of infection are not completely understood; however, a breakdown in the host's immune mechanism is an important factor. Thus, reactivation is more common in patients suffering from or recovering from another illness. Reactivation may also occur in a patient receiving immunosuppressive drugs or corticosteroid therapy.

Epidemiology Tuberculosis (TB) presents a significant global health challenge, leading the World Health Organization (WHO) to declare it a global emergency in 1993 due to rising cases worldwide.

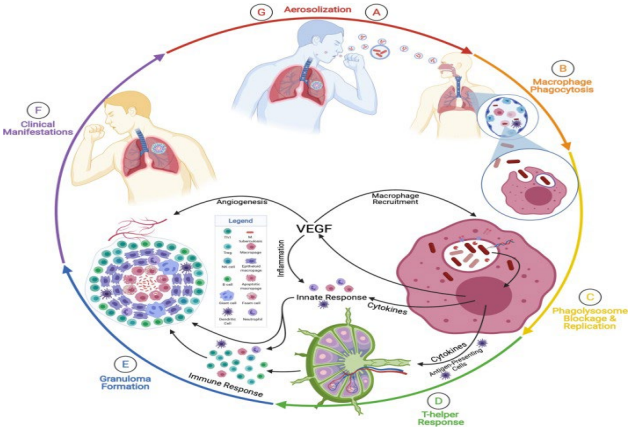


Fig. 2.

TB claims approximately 2 million lives annually, with a third of the global population carrying the tuberculosis bacterium. Particularly concerning is its status as a leading cause of death among individuals living with HIV.

While over 4 million cases of TB disease are officially reported each year worldwide, experts estimate the actual number of new cases to be around 9 million. While most cases occur in impoverished nations in the southern hemisphere, TB is resurging in Eastern Europe, with more than a quarter-million cases reported annually in the region.

WHO region	Case notifications 2004	Case notification rates per 100 000 population 2004	Estimated number of new cases 2004	Estimated incidence rate per 100 000 population 2004
Africa	1 105 952	153	2 572 988	356
Americas	221 358	25	363 246	41
Eastern Mediterranean	235 797	45	644 531	122
Europe	290 772	33	444 777	50
South-East Asia	1 609 891	99	2 967 328	182
Western Pacific	1 061 520	61	1 925 332	111
Global	4 525 290	71	8 918 203	140

Fig. 3.

3. Risk Groups

Certain groups face an elevated risk of latent TB infection, and potentially developing tuberculosis disease upon exposure. These groups include:

- Close contacts of individuals with tuberculosis, especially those with sputum smear-positive pulmonary disease.
- Casual contacts, such as work colleagues, particularly if they are immunocompromised.

People hailing from countries with a high tuberculosis incidence (40/100,000 population or greater).

Individuals with specific medical conditions are also at a higher risk of progressing from latent TB infection to active tuberculosis.

Certain groups are at increased risk of latent TB infection, and possibly tuberculosis disease if exposed. These include:

- HIV POSITIVE patients
- Infective drug users
- Have had solid organ transplantation, jejunoileal bypass or gastrectomy
- Have a hematological maligancy, e.g. leukaemia and lymphomas
- Have chronic renal failure or are receiving haemodialysis
- Are receiving anti-TNF- alfa -treatment
- Have silicosis
- Risk factor depending on age group

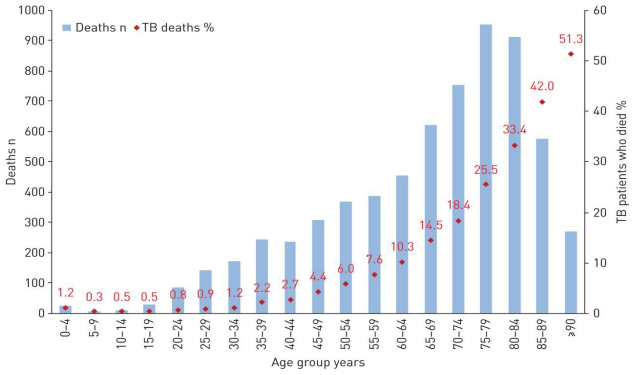


Fig. 4.

4. Clinical Presentation

The typical presentation of TB is outlined below. TB's onset can be gradual, and diagnosis may not be considered until a chest X-ray is conducted. Unfortunately, many patients delay seeking medical help until more severe symptoms, like significant coughing up of blood, emerge. By this stage, patients often have large cavities in their lungs teeming with M. tuberculosis bacteria. The expectoration or swallowing of infected sputum can spread the disease to other body parts. Physical examinations, while nonspecific, can suggest advancing pulmonary disease.

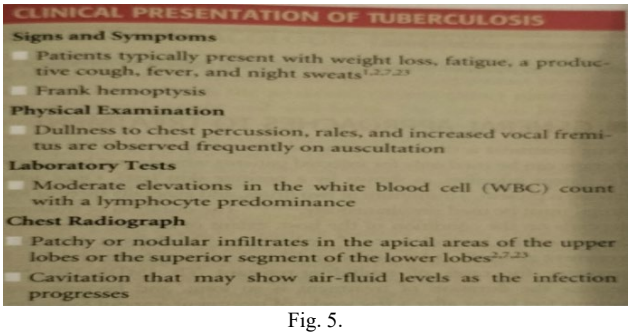


Fig. 5.

A. Chronic Tuberculosis

Although chronic tuberculosis may develop in any organ of the body, the most frequently encountered sites are those with the greatest oxygen tension. Therefore, the kidneys and brain provide a suitable environment for M. tuberculosis to grow. When the primary infection occurs during childhood, the epiphyses of the long bones (wrist, elbow, knee) and spine undergo rapid growth. The oxygen tension at these sites is high. Tuberculosis may remain dormant in these areas for many decades only to manifest itself in elderly patients.

Other organs involved in tuberculosis include the lymph nodes, meninges, skin, peritoneum, eyes, larynx, pericardium, adrenal glands, and gastrointestinal tract. The infection of these sites by the invading organism results from the spread of small quantities of tubercle bacilli by hematogenous dissemination.

B. Miliary Tuberculosis

It is also possible for large numbers of bacilli to be released from a primary focus, spreading throughout the body. This is referred to as miliary tuberculosis. Like chronic tuberculosis, miliary tuberculosis may develop any time after primary infection. However, the occurrence of this form of tuberculosis is seen most frequently in children under 4 years of age. It is the greatest concern to clinicians since death may rapidly ensue.

C. Respiratory TB

It refers to active TB affecting the lungs, pleural cavity, mediastinal lymph nodes, or larynx. The standard 6-month treatment regimen is recommended for adults with active respiratory TB, regardless of HIV status, as well as for children.

D. TB of peripheral lymph nodes

It can be effectively treated with a 6-month regimen, as trials have shown it to be as effective as a 9-month regimen for fully susceptible bacilli.

E. Meningeal TB

A serious form affecting the brain's protective membranes, requires a 12-month treatment regimen with rifampicin, isoniazid, pyrazinamide, and possibly ethambutol for the initial phase. Glucocorticoids are also recommended and should be tapered gradually.

F. Bone and joint TB

Typically affects the spine and can be treated with standard agents like isoniazid and rifampicin for 6 months, along with pyrazinamide and a fourth drug during the initial phase.

G. Pericardial TB

Though rare in the UK, requires the standard 6-month treatment regimen along with high-dose glucocorticoids.

H. Special Considerations

TB in children necessitates adjusted drug doses and ethambutol use with caution due to potential toxicity.

In pregnancy, standard therapy is safe except for streptomycin, which should be avoided due to fetal toxicity.

Patients with renal disease can generally receive standard TB drugs except for ethambutol, which requires dose adjustment.

Liver disease patients need liver enzyme monitoring during treatment, especially with rifampicin, isoniazid, and pyrazinamide.

Immunocompromised patients, including those with HIV, may need extended treatment and careful management due to increased risk of relapse.

Drug-resistant TB requires individualized treatment by experienced physicians, often involving costly and complex regimens.

Overall, TB treatment must be tailored to specific patient groups and conditions to ensure optimal outcomes and minimize complications.

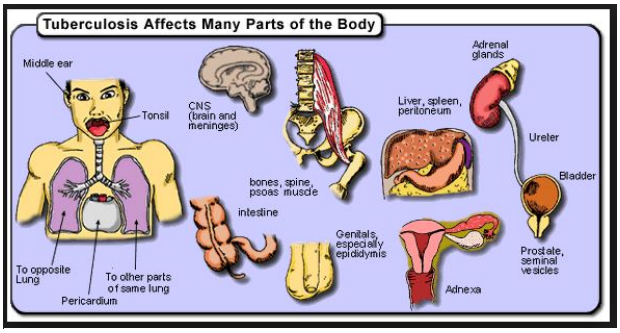


Fig. 6.

I. Drugs used and toxicities

Drug (once daily)	Children	Adults	Main side effects
Streptomycin	15 mg/kg	15 mg/kg (max dose 1 g daily)	Tinnitus, ataxia, vertigo, renal impairment
Amikacin	15 mg/kg	15 mg/kg	As for streptomycin
Capreomycin		15 mg/kg	As for streptomycin
Kanamycin		15 mg/kg	As for streptomycin
Ethionamide or prothionamide	15–20 mg/kg	<50 kg, 375 mg twice a day ≥50 kg, 500 mg twice a day	Gastrointestinal, hepatitis, avoid in pregnancy
Cycloserine		250–500 mg twice a day	Depression, fits
Ofloxacin		400 mg twice a day	Abdominal distress, headache, tremulousness
Ciprofloxacin		750 mg twice a day	As ofloxacin plus drug interactions
Azithromycin		500 mg	Gastrointestinal upset
Clarithromycin		500 mg twice a day	As for azithromycin
Rifabutin		300–450 mg	As for rifampicin, uveitis can occur with drug interactions e.g. macrolides. Often cross-resistance with rifampicin
Thiacetazone	4 mg/kg	150 mg	Gastrointestinal, vertigo, conjunctivitis, rash. Avoid if HIV positive (Stevens–Johnson syndrome)
Clofazimine		300 mg	Headache, diarrhoea, red skin discolouration
PAS[a] sodium	300 mg/kg	10 g every morning or 5 g twice a day	Gastrointestinal, hepatitis, rash, fever

[a] PAS, p-aminosalicylate.

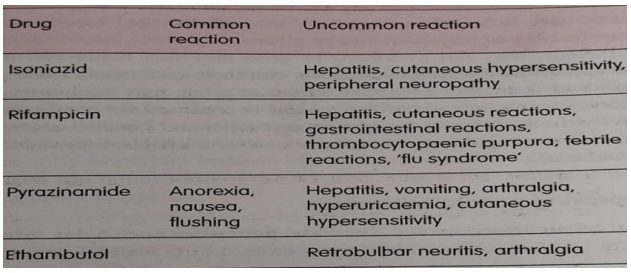
Fig. 7. Reserve drugs: Dosages and Side Effects

In the UK, the main drugs used to treat tuberculosis include rifampicin, isoniazid, pyrazinamide, ethambutol, and streptomycin. Rifampicin is available in liquid form for patients unable to swallow tablets or capsules, while liquid forms of isoniazid, ethambutol, and pyrazinamide are not commercially available but can be obtained through special orders. In cases where oral administration is not possible, rifampicin can be given intravenously, and isoniazid can be administered via intravenous or intramuscular routes, especially for severely ill patients. Monitoring liver function is generally not necessary unless abnormalities are present before treatment or if hepatitis symptoms arise during treatment. Peripheral neuropathy due to isoniazid is rare at standard doses but is a concern in certain patient groups, necessitating pyridoxine supplementation. Hypersensitivity reactions, though uncommon, are more

pronounced with rifampicin and may require discontinuation of the drug. Ethambutol carries a risk of ocular toxicity, which necessitates regular visual checks or close monitoring for symptoms during treatment.

The major adverse reactions of first-line drug of anti-tuberculous drugs are due to the long-term use of anti-tuberculosis, it shows serious side effects on the body like

- hepatitis
- Arthralgia
- Flu syndrome
- Hyperuricemia
- Thrombocytopenia
- peripheral neuropathy



Drug	Common reaction	Uncommon reaction
Isoniazid		Hepatitis, cutaneous hypersensitivity, peripheral neuropathy
Rifampicin		Hepatitis, cutaneous reactions, gastrointestinal reactions, thrombocytopaenic purpura, febrile reactions, 'flu syndrome'
Pyrazinamide	Anorexia, nausea, flushing	Hepatitis, vomiting, arthralgia, hyperuricaemia, cutaneous hypersensitivity
Ethambutol		Retrobulbar neuritis, arthralgia

Fig. 8. Major adverse reactions of first line anti-tuberculous drugs

Hepatitis is liver inflammation, and among first-line TB drugs, isoniazid, rifampicin, and pyrazinamide can cause hepatotoxicity, with pyrazinamide posing a higher risk.

Arthralgia is joint pain, commonly associated with pyrazinamide and occasionally with ethambutol and isoniazid, requiring symptomatic management alongside addressing hyperuricemia.

Flu-like syndrome mimics flu symptoms and is often linked to rifampicin use, possibly due to rifampicin-dependent antibodies, while ethambutol can also induce similar symptoms.

Hyperuricemia, high uric acid levels, can result from pyrazinamide and ethambutol use, especially pyrazinamide, which strongly retains uric acid in the body.

Thrombocytopenia, low platelet count, has been associated with ethambutol and resolves upon drug discontinuation.

Peripheral neuropathy, nerve damage symptoms, is linked to various TB drugs, notably Linezolid, Cycloserine, Terizidone, and can cause weakness, numbness, and pain in the extremities.

5. Conclusion

Tuberculosis (TB) remains a significant global health concern, with its epidemiology reflecting a widespread and persistent challenge. Factors such as overcrowding, poor sanitation, poverty, and immunosuppression contribute to the continued prevalence of TB, especially in resource-limited settings. Key risk factors for TB include close contact with infected individuals, living in densely populated areas, compromised immune systems (such as HIV infection), and inadequate access to healthcare.

The complications of TB can be severe and varied, affecting multiple organ systems. Beyond its primary respiratory effects, TB can lead to complications such as meningitis, bone and joint infections, pericardial disease, and even disseminated TB affecting multiple organs. These complications significantly impact patient outcomes and treatment strategies.

Moreover, the long-term use of anti-TB drugs introduces its own set of challenges and complications. Hepatotoxicity is a well-recognized risk associated with drugs like isoniazid, rifampicin, and pyrazinamide, necessitating careful monitoring of liver function during treatment. Other complications due to anti-TB drugs include arthralgia, flu-like symptoms, hyperuricemia, thrombocytopenia, and peripheral neuropathy, which require vigilant management and may necessitate adjustments to treatment regimens.

TB is a global health concern causing millions of deaths annually, especially among HIV-positive individuals. Effective TB treatment requires patient adherence, and pharmacists play a crucial role in monitoring drug interactions, educating patients about treatment adherence, managing side effects like hepatotoxicity, joint pain, flu-like symptoms, hyperuricemia, thrombocytopenia, and peripheral neuropathy. Multidisciplinary teams are essential for successful TB therapy and patient support. Pharmacist interventions can improve treatment outcomes and patient quality of life.

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