CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://doi.org/10.5281/zenodo.7951289

Available online at: http://www.iajps.com *Review Article*

ANTI-TUBERCULOSIS DRUG INDUCED HEPATOTOXICITY

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Abstract:

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 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. One ofthe adverse effects affecting TB treatment outcome is anti-TB drug induced hepatotoxicity. 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.

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Please cite this article in press Liya S Saji et al, Anti-Tuberculosis Drug Induced Hepatotoxicity., Indo Am. J. P. Sci, 2023; 10 (05).

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.

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. 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/orjaundice, 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.

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

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 (meningitis), lymphatic system, circulatory system (Miliary TB), genitourinary system, bones and joints. [(1)]

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 burden countries. Eight countries accounted for two thirds of the new 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 milliondied. [(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 747 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 centred TB care and prevention, bold policies and supportive systems, and intensified research and innovation. Continued commitment to and strengthening of TB control programs is essential to the goal of TB elimination.

ETIOLOGY:
TB is caused by M. tuberculosis, an aerobic bacillus that resist 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 organisms in that it replicates slowly once every 24 hours instead of every 20 to 40 minutes as with other organisms. The bacillus thrives in environment where the oxygen tension is relatively high, such as the apices of lungs, the renal parenchyma, and the growing ends of bones. [6,7]

CLINICAL MANIFESTATION:
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,

- A bad cough that lasts 3 weeks or longer.
- Pain in the chest.
- Coughing up blood or sputum (phlegm from deep inside the lungs)Other symptoms of TB disease are
- Weakness or Fatigue
- Weight loss
- No appetite
- Chills
- Fever
- Sweating at night
  Symptoms of TB disease in other parts of the body depend on the area affected.People who have latent TB infection
- Do not feel sick
- Do not have any symptoms, and
- Cannot spread TB to others.

DIAGNOSIS:
The most widely used screening method for tuberculous 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 exhibita positive test after an initial negative test, and this is referred to as a booster effect. Confirmatory diagnosis of a clinical suspicion of TB must be made via chest x-ray and microbiologic examination of sputum or other infected material to rule out active disease. When active TB is suspected, attempts should be made to isolate M. tuberculosis from the infected site. Daily sputum collection over 3 consecutive days is recommended. [8]
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. [9]
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 susceptibilityto other first line anti-TB drugs. Drug-susceptibility testing still needs to be done on isolates grown on culture media. DNA fingerprinting, or strain typing, is useful in the public health management of TB. In 2010, a new method, mycobacterial interspersed repetitive unit/variable number of tandem repeats (MIRU/VNTR) 24-loci strain typing, became available in the UK. Strain typing will help in establishing links between cases not previously identified, disproving links between apparent clusters of cases, and also in detecting cross contamination in laboratories. [9]

Tuberculin testing:

Tuberculin testing is used to detect latent TB infection (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 Staten's 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. [9]

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. [9]

PATHOPHYSIOLOGY:

Primary infection is initiated by the alveolar implantation of organisms in droplet nuclei that are small enough (1 to 5 mm) to escape the ciliary epithelial cells of the upper respiratory tract and reach the alveolar surface. Once implanted, the organisms multiply and are ingested by pulmonary macrophages, where they are killed, or, they continue to multiply. With bacterial multiplication, the macrophages eventually rupture, releasing many bacilli. Large numbers of activated macrophages surround the solid caseous (cheese-like) TB foci (the necrotic area) as a part of cell-mediated immunity. Delayed-type hypersensitivity also develops through activation and multiplication of T lymphocytes. Macrophages form granulomas to contain the organisms. Successful containment of M. tuberculosis requires activation of a subset of CD4 lymphocytes, referred to as Th-1 cells, which activate macrophages through secretion of interferon γ. Approximately 90% of patients who experience primary disease have no further clinical manifestations other than a positive skin test either alone or in combination with radiographic evidence of stable granulomas. Tissue necrosis and calcification of the originally infected site and regional lymph nodes may occur, resulting in the formation of a radiodense area referred to as a Ghon complex. Approximately 5% of patients (usually children, the elderly, or the immunocompromised) experience progressive primary disease at the site of the primary infection (usually the lower lobes) and frequently by dissemination, leading to meningitis and often to involvement of the upper lobes of the lung as well. Approximately 10% of patients develop reactivation disease, which arises subsequent to the hematogenous spread of the organism. In the United States, most cases of TB are believed to result from reactivation. Occasionally, a massive inoculum of organisms may be introduced into the bloodstream, causing widely disseminated disease and granuloma formation known as miliary TB. [8]

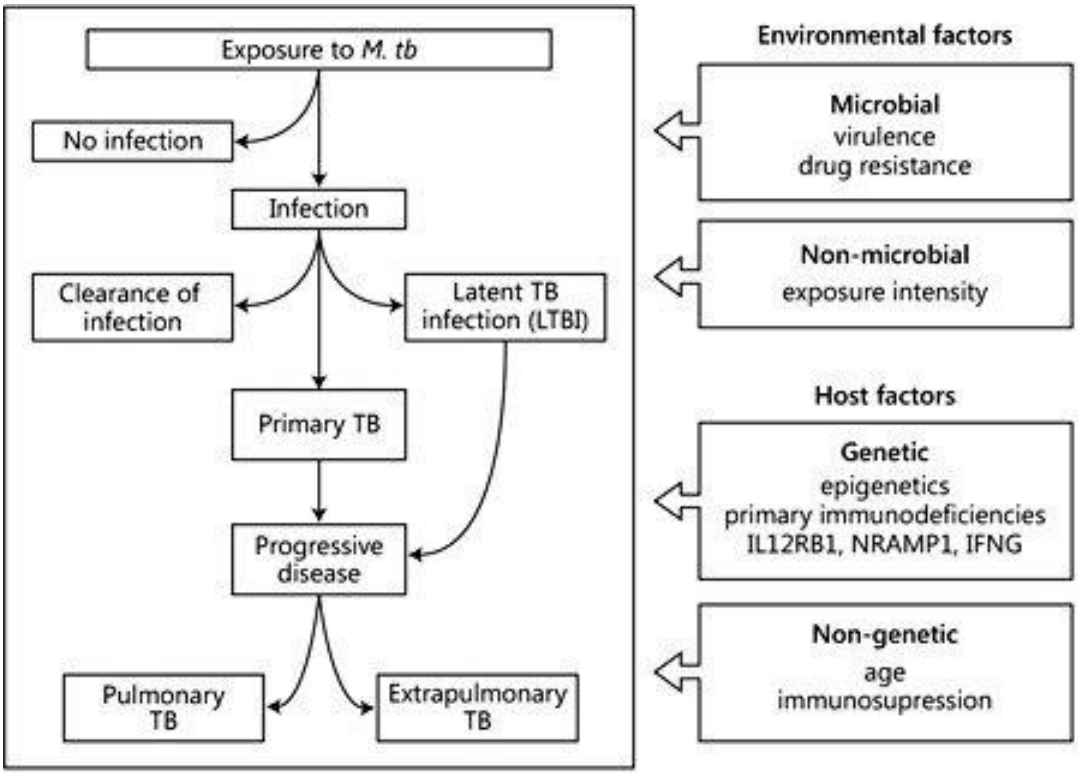

FIGURE 1: PATHOPHYSIOLOGY 0F TUBERCULOSIS

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 mycobacteriaare less prevalent. [1]

First Line Anti-TB Drugs:

(Isoniazid, Rifampicin, Pyrazinamide, Ethambutol, Streptomycin)

The most commonly used standard chemotherapeutic regime 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.

(10,11)

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). [11,12]

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.

[13] 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. [14] DOTS is the most effective strategy available for controlling TB. 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. [15]

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. [16] 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 MDR-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. [17]

BASIC REGIMENS FOR THE TREATMENT OF TB:

Preferred Regimen	Alternative Regimen	Alternative Regimen
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-weeklyINH, RIF, PZA, and EMB for 24 doses (8 weeks)
Continuation Phase Daily INH and RIF for 126 doses (18 weeks) or Twice-weeklyINH 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)

TABLE 1: BASIC REGIMEN FOR TB TREATMENT

COMPLICATIONS:

Tuberculosis complications include:

- **Spinal pain.** Back pain and stiffness are common complications of tuberculosis.
- **Joint damage.** Arthritis that results from tuberculosis (tuberculous arthritis) usually affects the hips and knees.
- **Swelling of the membranes that cover your brain (meningitis).** This can causea lasting or intermittent headache that occurs for weeks and possible mental changes.
- **Liver or kidney problems.** Your liver and kidneys help filter waste and impurities from your bloodstream. Tuberculosis in these organs can impair theirfunctions.
- **Heart disorders.** Rarely, tuberculosis can infect the tissues that surround your heart, causing inflammation and fluid collections that might interfere with your heart's ability to pump effectively. This condition, called cardiac tamponade, can be fatal.

ANTITUBERCULOSIS DRUG INDUCED HEPATOTOXICITY:

A common definition of Antituberculosis drug induced hepatotoxicity (ATDH) is a treatment-emergent increase in serum alanine aminotransaminase greater than three or five times the upper limit of normal, with or without symptoms of hepatitis, respectively. The severity of hepatotoxicity is classified according to the WHO Toxicity Classification Standards. [18]

WHO definition of hepatotoxicity	
Grade 1 (mild)	10 times ULN (ALT > 500 U/L) Grade 2 (mild) 2.5–5 times ULN (ALT 126–250 U/L)
Grade 3 (moderate)	5–10 times ULN (ALT 251–500 U/L)
Grade 4 (severe)	>10 times ULN (ALT > 500 U/L)

TABLE 2: WHO TOXICITY CLASSIFICATION STANDARDS

ALT, alanine aminotransferase; ULN, upper limit of normal, i.e., 50 U/L

EPIDEMIOLOGY:

The incidence of ATDH during standard multidrug TB treatment has been variably reported as between 2% and 28%. Most studies on ATDH have been performed in Europe, Asia and the USA and the incidence varies between different world regions. Orientals are reported to have the highest rates, especially Indian patients. In general, rifampicin is a well- tolerated drug and hepatotoxicity occurs in about 1–2% of patients treated with prophylactic rifampicin monotherapy. Hepatotoxicity is a major toxic effect of pyrazinamide. When the drug was introduced in the 1950s, a high incidence of hepatotoxicity was reported and the drug was nearly abandoned. This appeared to be related to the high dosage of 40–70 mg/kg. Toxicity was not a major problem when pyrazinamide was used at a daily dosage of 20–30 mg/kg. Nowadays, pyrazinamide is used in the intensive phase of TB treatment. The rate of hepatotoxicity of pyrazinamide monotherapy in its currently used dosage is unknown. It was recently reported that pyrazinamide causes more hepatotoxicity than isoniazid or rifampicin. In a recent study, seven out of 12 patients (58%) treated for latent TB with ethambutol and pyrazinamide developed transaminase elevation of more than four times the upper limit of normal. Because ethambutol alone is not hepatotoxic, pyrazinamide was likely to be the offending agent. [19] The incidence rate of drug induced hepatotoxicity in India is 2-28%.

ETIOLOGY:

- NUTRITIONAL STATUS: Malnutrition is common in TB and associated with higher incidence of anti-TB drug induced hepatotoxicity. A recent retrospective observational study revealed that a weight loss of 2 kg or more developing within 4 weeks during TB treatment is highly significant independent risk factor for hepatotoxicity. [20]
- ALCOHOL INTAKE: Alcohol can induce enzymes and has potential to cause liver injury.
- HEPATITIS B VIRUS: The risk of anti-TB drug induced hepatotoxicity is higher in patients with chronic hepatitis B virus (HBV) patients compared to uninfected subjects (16% vs 4.7% $p < 0.001$) and the severity was much higher in the HBV patients in thisstudy (4.7% vs 2.5% $p < 0.001$).

CLINICAL MANIFESTATION:

SIGN AND SYMPTOMS:

Signs and symptoms of hepatotoxicity include,

- Nausea
- Vomiting
- Malaise
- Low-grade fever
- Anorexia

DIAGNOSIS:

- **Physical exam.** Your doctor will likely perform a physical exam and take a medical history. Be sure to bring to your appointment all medications you're taking, including over-the-counter drugs and herbs, in their original containers. Tell your doctor if you work with industrial chemicals or may have been exposed to pesticides, herbicides or other environmental toxins.
- **Blood tests.** Your doctor may order blood tests that look for high levels of certain liver enzymes. These enzyme levels can show how well your liver is functioning.
- **Imaging tests.** Your doctor may recommend an imaging test to create a picture of your liver using ultrasound, computerized tomography (CT) or magnetic resonance imaging (MRI). Additional imaging tests may include magnetic elastography and transient elastography.
- **Liver biopsy.** A liver biopsy can help confirm the diagnosis of toxic hepatitis and help exclude other causes. During a liver biopsy, a needle is used to extract a small sample of tissue from your liver. The sample is examined under a microscope.

PATHOPHYSIOLOGY:

Both animal and human case studies show that isoniazid-induced hepatotoxicity manifests mainly as hepatocellular steatosis and necrosis, and it has been suggested that toxic isoniazid metabolites bind covalently to cell macromolecules. [21] Hydrazine is the proposed toxic metabolite of isoniazid and animal studies have shown that hydrazine causes steatosis, hepatocyte vacuolation and glutathione depletion. Lipid vacuoles and mitochondrial swelling is found in periportal and midzonal hepatocytes. Rifampicin may cause transient hyperbilirubinemia, which is not a toxic effect but is due to interference with bilirubin excretion. Rifampicin can cause hepatic lesions characterized by hepatocellular changes, with centrilobular necrosis, possibly associated with cholestasis. Histopathological findings range from spotty to diffuse necrosis with more or less complete cholestasis. Bridging necrosis, lymphocytic infiltration, focal cholestasis, increased fibrosis, and micronodular cirrhosis were observed in the liver of a patient who died of rifampicin-

and pyrazinamide-induced hepatotoxicity. [22]

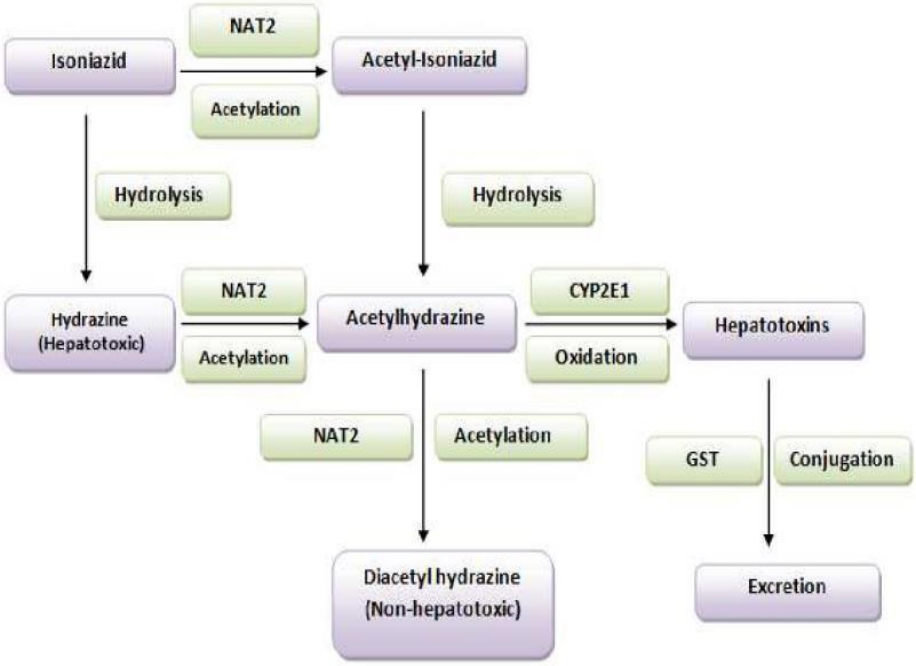

FIGURE 2: MOA OF ISONIAZID CAUSING HEPATOTOXICITY

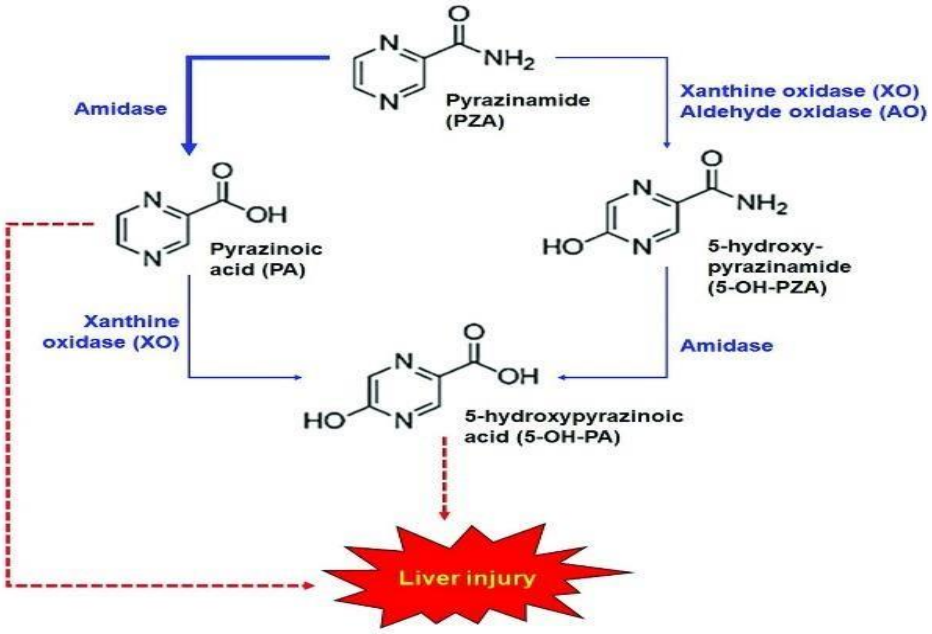

FIGURE 3: MOA OF PYRAZINAMIDE CAUSING HEPATOTOXICITY

TREATMENT:

There is no evidence to suggest that three times per week regimes are associated with lower risk of hepatotoxicity than daily dosing regimens. Guidelines from professional bodies provide advice on the choice of drugs, combinations and duration of therapy that are considered suitable to different clinical scenarios. Considerations should include the cost, affordability, access as well as efficacy and associated adverse effects.

As isoniazid and rifampicin are highly efficacious, their use in the treatment of latent or active TB infection is desirable whenever possible. However, considering that combination therapy increases the risk of DILI, [23] monotherapy with either isoniazid or rifampicin is preferable for the treatment of latent TB when particular individual is at higher risk of hepatotoxicity. In patients with unstable or advanced liver disease, if the serum alanine aminotransferase level is more than 3 times normal at baseline, the following regimens should be considered. The moreunstable or severe the liver disease is, the fewer hepatotoxic drugs should be used.

Possible regimens include [24]:

Two hepatotoxic drugs regimen (rather than the three in the standard regimen):

- 9 months of isoniazid and rifampicin, plus ethambutol
- 2 months of isoniazid, rifampicin, streptomycin and ethambutol,followed by 6 months of isoniazid and rifampicin;
- 6–9 months of rifampicin, pyrazinamide and ethambutol.

One hepatotoxic drug regimen:

- 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.

No hepatotoxic drug regimen: in patients with advanced cirrhosis or portosystemic encephalopathy

- 18–24 months treatment with a combination of ethambutol, fluoroquinolone, cycloserine and capreomycin or aminoglycoside has been suggested as an option.

PATIENT COUNSELLING:

Patients should be educated about the importance of adherence to medications, follow up visits for monitoring and symptoms of hepatotoxicity with appropriate reminders wherever possible. In the event of symptoms that are attributable to hepatotoxicity, patients should be forewarned to stop all anti-TB medications and seek medical advice in the event of any symptoms of hepatotoxicity and seek immediate medical advice. One report from a programme of INH based chemoprophylaxis suggested that regular inquiry and reporting of symptoms at monthly visits proved effective in averting serious Drug induced liver injury (DILI) without the need for routine measurements of liver biochemistry. Patients should be advised to refrain from alcohol and to seek medical advice about any prescription or non-prescription medication use as these could potentially increase toxicity leading to DILI. [25]

COMPLICATIONS:

- Unexplained loss of appetite, nausea or vomiting, brown urine, or jaundice (yellowing of skin or eyes)
- Persistent tingling, numbness, or burning of hands or feet.
- Persistent weakness, fatigue, fever, or abdominal tenderness.
- Easy bruising or bleeding
- Blurred vision or changed vision.

PATIENT COUNSELLING OF TUBERCULOSIS:

It is now a requirement for patients to be provided with a PIL (Patient information leaflet) for medication they are taking. Patients should be advised to read the PIL. The TB doctor, nurse and pharmacist should provide them with other relevant information orally. Patients taking rifampicin should be told that the drug will cause a harmless discolouration of their urine and other body fluids, for example sweat and tears. The staining of tears is important if the patient uses soft contact lenses as these may be permanently stained. Gas-permeable and hard lenses are unaffected. Women using the oral contraceptive pill should be advised to use other non-hormonal methods of contraception for the duration of rifampicin treatment and for8 weeks afterwards as the effectiveness of hormonal contraceptives is reduced by rifampicin. Although ocular side effects are rare when ethambutol is taken in normal dosages, patients should be warned of this potentially serious side effect. They should be advised to stop the drug and report to their doctor if they notice any changes in vision, such as a reduction in visual acuity or changes in colour vision. This is especially important because visual changes are usually reversible on

discontinuation of the drug but may be permanent if the drug is not stopped. [9]

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