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**Anti-tubercular therapy in patients with cirrhosis: Challenges and options**

Kumar N *et al*. ATT in cirrhosis

Naveen Kumar, Chandan Kumar Kedarishetty, Sachin Kumar, Vikas Khillan, Shiv Kumar Sarin

**Naveen Kumar, Chandan Kumar Kedarishetty, Shiv Kumar Sarin,** Departments of Hepatology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi 110070, India

**Sachin Kumar,** Departments of Pulmonology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi-110070, India

**Vikas Khillan,** Departments of Microbiology, Institute of Liver and Biliary Sciences, Vasant Kunj, New Delhi-110070, India

**Author contributions:** All authors contributed to the manuscript.

**Correspondence to:** **Dr. Shiv Kumar Sarin, MD, DM, DSc, FNA, Professor and Head,** Department of Hepatology, Institute of Liver and Biliary Sciences, Vasant Kunj, Plot No.D-1, New Delhi 110070, India. shivsarin@gmail.com

**Telephone:** +91-11-46300000 **Fax:** +91-11-26123504

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**Abstract**

Tuberculosis is a disease known to mankind for centuries. Its frequency is increased many fold in patients with liver cirrhosis. The gold standard of tuberculosis management is a 6-month course of isoniazid, rifampicin, pyrazinamide and ethambutol. Although good results are seen with this treatment in general, the management of group of patients with underlying cirrhosis is a challenge. The underlying depressed immune response results in alteration in many diagnostic tests. The tests used for latent tuberculosis has many flaws in this group of patients. Three of four first-line anti-tuberculosis drugs are hepatotoxic and baseline liver function is often deranged in patients with underlying cirrhosis. Frequency of hepatotoxicity is increased in those with liver cirrhosis frequently leading to severe liver failure. There are no established guidelines for the treatment of tuberculosis in relationship to the severity of liver disease. There is no consensus on the frequency of liver function tests required and on the cut-off used to define hepatotoxicity. No specific treatment exists for prevention or treatment of hepatotoxicity making monitoring even more important. High risk of MDR tuberculosis is another major worry due to prolonged and interrupted treatment

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**Key words:** Anti-tubercular therapy; Antitubercular drug hepatotoxicity; Anti-tubercular drug Hepatotoxicity; Multidrug-resistant tuberculosis; Tuberculosis immune dysfunction

**Core tip:** Treatment of tuberculosis in patients with underlying cirrhosis is a challenge because of the compromised liver functions and high risk of hepatotoxicity. There is no consensus regarding the treatment and monitoring of tuberculosis in this group of patients. This paper reviews the differences in diagnosis, treatment, monitoring, hepatotoxicity and other issues in treatment of tuberculosis in patients with cirrhosis. Suggestion for treatment of tuberculosis in different grade of cirrhosis as well as monitoring guidelines is being provided. Finally issue like liver transplantation, MDR tuberculosis and reactivation of tuberculosis by interferon are being briefly reviewed.

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**INTRODUCTION**

Tuberculosis (TB) has aﬄicted mankind from the time immemorial[1]. About one-third of the world’s population is infected with *Mycobacterium tuberculosis.* Tuberculosis is widely prevalent all over the world especially the developing countries in Africa and Asia with an estimated 40%-50% of the adult population being infected[2]. India has the highest TB burden in the world as per the World Health Organisation (WHO) statistics for 2011, giving an estimated incidence of 2.2 million cases in India out of a global incidence of 8.7 million cases[3]. Primary infection with *M. tuberculosis* leads to clinical disease in only about 10% of individuals and in rest latent tuberculosis infection (LTBI) develops. In approximately 5%-10% of latently infected persons, the infection will reactivate and cause active tuberculosis[4]. The progression from latent infection to active disease depends on a number of factors, of which the most important is the presence of underlying immunodeficient state[5]. Cirrhosis is a widely prevalent disease which leads to immune suppression and a higher prevalence of tuberculosis than the general population[6]. But the treatment in patients with underlying cirrhosis is complicated by poor tolerance, higher incidence of hepatotoxicity, no consensus regarding monitoring and treatment regimens and higher chances of MDR tuberculosis. This paper reviews the differences in diagnosis, treatment, monitoring, hepatotoxicity and other issues in treatment of tuberculosis in patients with cirrhosis.

**CIRRHOSIS AND TUBERCULOSIS**

***Prevalence and relationship***

Cirrhosis of liver is also a relatively common condition with autopsy studies showing a prevalence of 5%-10%[6]. Evidence suggests a higher prevalence of tuberculosis in patients with cirrhotic as compared to the general population. High incidence of tuberculosis in patients with liver cirrhosis has been ascribed mainly to immune dysfunction of cirrhotic with associated higher virulence as compared to the general population[7]. In a cohort study of patients with liver cirrhosis from Denmark (1977-1993), the incidence rate of tuberculosis was found to be 168.6 per 100000. It was highest in men over 65 years of age, with an incidence rate of 246 per 100000[8]. Furthermore, patients with liver cirrhosis who acquire tuberculosis had a poor prognosis in the study. A study conducted in western India showed the prevalence rate to be 15 times higher than in the general population[9]. Another study from India showed that there is nearly five times higher prevalence of TB in cirrhosis patients (8.1%) compared to the general population (1.6%), pulmonary TB being the commonest form[10].

Pulmonary tuberculosis is generally responsible for 80-85% of all cases of tuberculosis reported[11]. Liver cirrhosis has been suggested as a risk factor for extra pulmonary TB in a previous study[12]. In a Korean study, 31% patients of cirrhosis had extra pulmonary tuberculosis as compared to 12% in the non-cirrhosis control group with predominance of peritoneal tuberculosis[7]. There are several reports of unusual manifestation of tuberculosis in patients with cirrhosis[14]. Little is known about the immunopathogenesis of tuberculosis in such clinical conditions. Although most of the host defence systems, especially the clearance capacities of the reticuloendothelial system, are thought to be diminished in patients with cirrhosis, there is no simple explanation as to how this immune dysfunction results in patients being more likely to develop extra pulmonary TB than pulmonary TB.

***Cirrhosis- immune system dysfunction***

Cirrhosis-associated immune dysfunction syndrome is a multifactorial process in which the ability to clear cytokines, bacteria, and endotoxins from circulation is decreased[14]. The liver is the major organ of reticuloendothelial system and contains 90% of the cells of the reticuloendothelial system that are central to clearing bacteria, such as Kupffer cells and sinusoidal endothelial cells[14]. There is reticuloendothelial system dysfunction in patients with cirrhosis which leads to significantly reduced monocyte spreading, chemo taxis, bacterial phagocytosis, and bacterial killing in cirrhosis compared with controls and hence a compromised innate immunity system[14]. These patients also have decreased neutrophil mobilization and phagocytic activity with reduced oxidative burst, a phenomenon that has been shown to correlate with the severity of liver disease. Hyperammonemia and hyponatremia have been shown to lead to reduced neutrophil function and impaired phagocytosis[15]. Furthermore specific aetiology of liver disease like alcohol and hepatitis B and C have been shown to be associated with additional impairment in immune function and/or increase in proinflammatory cytokines[16].

Toll-like receptors (TLRs) are encoded pattern recognition receptors (PRRs) that play a central role in host cell recognition and responses to microbial pathogens.  About 10 functional human TLRs (TLR1-10) have been described, each one being involved in the sensing of distinct microbial products[17]. Toll-like receptor 2 (TLR2) is capable of recognizing pathogen-associated molecular patterns expressed by M. tuberculosissuch as a 19-kDa lipoprotein, lipoarabinomannan, and soluble tuberculosis factor[18]. Immune evasion allows M. tuberculosis to establish persistent or latent infection in macrophages and results in Toll-like receptor 2 (TLR2)-dependent inhibition of MHC class II transactivator expression, MHC class II molecule expression and antigen presentation[19]. TLR2 genetic polymorphisms have been shown to influence susceptibility to pulmonary TB. TLR2 variants play a role in the development of TB phenotypes, probably by controlling the expansion of NK cells[20]. Patients with stable alcoholic chronic liver disease showed an attenuated TLR2-mediated innate immune response[21]. The extent to which cirrhosis interacts with TLR polymorphism in promoting mycobacterial immune evasion is not known.

***Diagnosis of tuberculosis in cirrhosis***

Diagnosis of latent as well as clinical tuberculosis can be extremely challenging in the setting of cirrhosis. There can be overlap between the symptoms of tuberculosis and decompensation of cirrhosis leading to delay in diagnosis. These patients demonstrate impaired delayed type of hypersensitivity; hence there is a higher likelihood of false negative tuberculin test[22]. The exact mechanism of anergy to skin testing is not well known. Schirren CA et al had shown that, although in patients with alcoholic liver cirrhosis, T cell-dependent functions are impaired *in vivo*, T cell activation pathways are not responsible for the observed immune defect[23]. A strong association was observed between increased soluble intercellular adhesion molecule (ICAM)-1 concentrations and impairment of delayed-type hypersensitivity skin tests suggesting that soluble ICAM-1 may be implicated in the immune depression seen in patients with chronic liver disease[24]. In the same study, serum alkaline phosphatase levels were also correlated with the impaired delayed-type hypersensitivity skin test[24]. The tuberculin skin test (TST) is further confounded by the aetiology of cirrhosis. A recent study by Çelikbilek M et al showed that TST findings were falsely positive more in end-stage liver disease caused by viral aetiologies compared to non-viral aetiologies[25]

Interferon-gamma release assay is an alternative to PPD testing. The test requires only a single contact with a patient. In addition, unlike the PPD, which is subject to interpretation bias, interferon-gamma release assays are machine read and have single cut offs. Thus, there is little subjectivity to the reading of results. Interferon-gamma release assays have been tested and found to perform reasonably well in healthy populations as well as in patients with end-stage liver disease[26]. Several controversies still exist regarding their operational value, such as their discordance with the TST, role in immunocompromised subgroups, role in HCWs, role of serial testing, and ability to identify people who are likely to progress to active TB[27]. In high-burden settings, IGRAs tend to have decreased sensitivity because of the confounding effects of malnutrition, NTM exposure (especially *Mycobacterium kansasii* and *Mycobacterium marinum*), leprosy, and parasitic and other tropical infections that may alter the host’s T helper 1/T helper 2 cell balance[28].

Remarkable efforts have been made globally to accelerate the development and expansion of new diagnostic technologies. However, pulmonary tuberculosis case detection still remains dependent upon sputum smear and culture, radiography and clinical symptomatology. Their role in presence of cirrhosis is similar as in normal patients with the same drawbacks. The *M. tuberculosis*-specific nucleic acid amplification tests (NAAT) performed on bronchopulmonary specimen is the most frequently used molecular tests for laboratory diagnosis of pulmonary tuberculosis. NAAT results can be available to the clinician within 1 day after obtaining sputum or bronchoalveolar lavage (BAL) fluid and can have important implication for the management of a patient. Unfortunately, NAAT amplification targets are not standardized and the diagnostic accuracy of the tests is highly heterogenous[28,29]. In individuals with positive AFB sputum smears, the sensitivity of NAAT to detect *M. tuberculosis* nucleic acid on these specimens is greater than 95% [29].When AFB are found on sputum or BAL smears, the presumptive diagnosis of tuberculosis can thus be rapidly confirmed. Apart from rare exceptions, a negative NAAT result in this situation strongly indicates the presence of a non-tuberculous mycobacterium (NTM) species in this specimen. Currently available serological tests cannot be recommended for the diagnosis of tuberculosis because of poor sensitivity and specificity. Recently, Steingart and colleagues conducted a meta-analysis of the published studies of distinct single antigens and multiple-antigen combinations in terms of their performance in diagnosing pulmonary tuberculosis[30]. The authors concluded that none of the antigens' sensitivity was high enough to replace sputum smear microscopy. A recent test has been approved by FDA (MTB/RIF test) which provides sensitive detection of tuberculosis and rifampin resistance directly from untreated sputum in less than 2 hours with minimal hands-on time. The role of this test in cirrhotic needs to be evaluated as the proportion of patient with pulmonary tuberculosis is much lower than in general population[31].

The diagnosis of extra pulmonary tuberculosis in cirrhotic is similar as compared to the disease in general population. TB peritonitis possibly mimics spontaneous bacterial peritonitis (SBP). TB peritonitis occurs in less advanced cirrhosis and ascitic fluid analysis usually shows lower white blood cell count, higher proportion of mononuclear cells, higher levels of protein and adenosine deaminase (ADA)[32]. In developed countries where TB peritonitis is uncommon, the diagnosis of TB peritonitis should prompt a workup for cirrhosis. In a study from United States, more than 50% of TB peritonitis cases had underlying cirrhosis, predominantly alcohol-related[33]. Though ADA level is generally helpful in the detection of TB peritonitis, the presence of cirrhosis may reduce its sensitivity to 30%[33-35]. In addition, abdominal tuberculosis is a paucibacillary disease and AFB smears are generally negative in such patients. Sometimes the tuberculosis manifestation in cirrhosis could be just the worsening of the liver function.

***Drugs used in tuberculosis***

There is no consensus regarding the use of anti-tubercular drugs in patients with cirrhosis. The potential hepatotoxicity of anti-tubercular drugs is a major concern. Firstly, in the setting of pre-existing liver disease, the likelihood of developing drug-induced hepatitis may be higher. Secondly, the outcome of drug-induced hepatitis in patients with compromised liver function may be poor. Thirdly, monitoring of drug-induced hepatitis may be confounded in the presence of underlying liver disease due to fluctuating liver function tests related to the pre-existing liver disease[36-38].

***First-line drugs***

**Isoniazid (INH):** It is a synthetic analogue of pyridoxine and the most potent tuberculocidal drug[39]. It is an essential component of all regimens. INH is effective against both intra- and extra-cellular organisms since it inhibits the synthesis of mycolic acids in the bacterial cell wall[39]. INH is metabolized in the liver through two main pathways. Acetyl hydrazine, a non-toxic metabolite, is formed when metabolism proceeds along the N-acetyltransferase 2 (NAT 2) pathway while hydrazine, the toxic metabolite, is formed when it proceeds along the amidase pathway[40]. Most previous research had identified acetyl hydrazine as the toxic metabolite of isoniazid[41, 42]. Later studies, however, suggested that hydrazine, and not isoniazid or acetyl hydrazine, was most likely to be the cause of isoniazid induced hepatotoxicity[43].

Asymptomatic, self-limited increase in aminotransferase levels is observed in the majority of patients treated with INH, which does not progress to more serious forms of liver injury 44]. Frequency of liver damage increases with age and in general is less than 2 %. A meta-analysis of six studies estimated the rate of clinical hepatitis in patients given INH alone to be 0.6%[45]. Hepatotoxicity due to INH therapy seems to be idiosyncratic in most patients and does not recur with rechallenge, hence can be reintroduced after complete clinical recovery[46]

**Rifampicin:** It is a bactericidal agent which inhibits mycobacterium DNA-dependent RNA polymerase. It has profound early bactericidal activity against rapidly dividing cells and also against semi dormant bacterial populations[47]. Transient elevation of hepatitis enzymes are however routinely observed in these patients. However, they return to normal on continuation of therapy. Yee *et al*[48] reported a rate of 0.05 per 100 person-months for hepatitis caused by Rifampicin (RIF). Conjugated hyperbilirubinemia probably results from RIF inhibiting the major bile salt exporter pump, impeding secretion of conjugated bilirubin at the canalicular level[49]. RIF can cause hepatocellular changes such as centrilobular necrosis, associated with cholestasis[37].

**Pyrazinamide:** It is a weak bactericidal drug. Its active form, pyrazinoic acid, disrupts the bacterial membrane and inhibits membrane transport functions. It exerts greatest activity against the population of dormant or semi-dormant organisms contained within macrophages or the acidic environment of caseous foci[50]. Historically it is considered the most hepatotoxic anti-tubercular drug. When the drug was first introduced in the 1950s, a high incidence of hepatotoxicity was reported and the drug was nearly abandoned[51]. This appeared to be related to the high dosage of 40-70 mg/kg used at that time. Toxicity has rare when pyrazinamide has been used at a daily dosage of less than 35 mg/kg[52]. In murine models, pyrazinamide inhibited CYP45058 activity and NAD59 levels were altered in association with free radical species mediated hepatotoxicity[53]. Bridging necrosis, lymphocytic infiltration, focal cholestasis, increased fibrosis, and micro nodular cirrhosis have been observed in the liver of a patient who died of rifampicin- and pyrazinamide-induced hepatotoxicity[54]. The rate of hepatotoxicity of pyrazinamide monotherapy in its currently used dosage is unknown. But more data on safety of pyrazinamide is needed to clarify its use in patients with cirrhosis.

**Ethambutol:** It is a bacteriostatic antibiotic approved for the treatment of tuberculosis. It works by preventing the formation of the bacterial cell wall. Hepatotoxic effects of this agent are not clinically significant[55].

***Second line antitubercular drugs***

The second line drugs are considered as the reserved therapy for tuberculosis treatment. These drugs are often used in special conditions. When situations like resistance to first line therapy, extensively drug-resistant tuberculosis (XDR-TB) or multidrug-resistant tuberculosis (MDR-TB) arise, the second-line drugs are implemented for the treatment of tuberculosis[56]. These include: (1) aminoglycosides: *e.g.,* amikacin, kanamycin; (2) polypeptides: *e.g.,*capreomycin, viomycin, enviomycin; (3) fluroquinolone: *e.g.,* ciprofloxacin, levofloxacin, moxifloxacin; (4) thioamides: *e.g.,* ethionamide, prothionamide; (5) cycloserine; and (6) terizidone.

***Third line anti tubercular drugs***

These include rifabutin, macrolides (clarithromycin), linezolid, thioacetazone, thioridazine, arginine, vitamin D etc. These drugs may be considered "third-line drugs" because they are not very effective (*e.g.,* clarithromycin) or because their efficacy has not been proven (*e.g.,* linezolid)[57].

**ANTI-TUBERCULAR THERAPY IN CIRRHOSIS: THE CHALLENGES**

Challenges in treatment of tuberculosis in patients with cirrhosis arise because three of the first line anti-tubercular drugs are potentially hepatotoxic. The administration of these drugs can lead to worsening liver function with decompensation of stable cirrhosis and sometimes cause fulminant hepatic failure with a high mortality. There is no consensus on the drugs to be given in different grades of liver injury although the WHO guidelines mentions that the more unstable or severe the liver disease be, the fewer hepatotoxic drugs should be used[58].

***Incidence of antitubercular drug hepatotoxicity***

There is high incidence of hepatotoxicity ranging from 2% to 28%. Tuberculosis is usually treated is with multiple drugs to prevent emergence of MDR strains. This makes the determination of exact drug responsible for hepatotoxicity difficult. Temporal data are sometimes helpful in providing evidence for hepatotoxicity of particular drug. Therefore, there is limited data on toxicity rates of individual antituberculosis drugs, except for isoniazid, which has been widely used as prophylactic monotherapy for latent TB infections. A meta-analysis of development of toxic hepatitis with isoniazid and rifampicin alone and in combination was done by Steele *et al*[59] the summary of which is provided in Table 1.

Asymptomatic, self-limited increase in aminotransferase levels was observed in majority of patients treated with INH. Approximately 0.5% of all patients treated with INH monotherapy for latent tuberculosis developed clinically important increases in aminotransferase levels in a large study. The percentage was higher in combination therapy[59]. INH induced hepatotoxicity is seen mainly as hepatocellular steatosis and necrosis, and it has been suggested that toxic INH metabolites may bind covalently to cell macromolecules[60].

Hepatotoxicity associated with RIF is usually idiosyncratic. RIF may occasionally cause dose dependent interference with bilirubin uptake due to competition with bilirubin for clearance at the sinusoidal membrane, resulting in mild, asymptomatic unconjugated hyperbilirubinemia or jaundice without hepatocellular damage. Occasionally RIF can cause hepatocellular injury and can potentiate hepatotoxicity of other ATD[49].

Hepatotoxicity is a major toxic effect of pyrazinamide. Previously reported studies had showed high rates of hepatotoxicity with higher dosage of pyrazinamide. Doses employed currently (< 35 mg/kg per day) are considered much safer[60].

A study done by Park WB *et al*[38] in patients of chronic liver disease and tuberculosis found incidence of hepatotoxicity to be 17 percent with no difference in patients with or without cirrhosis. The incidence of anti-tubercular drug induced hepatotoxicity when used as part of combination regimens in various studies is shown in Table 2[38,61-75].

***Treatment of tuberculosis in compensated cirrhosis***

Due to better functional reserve, patient with compensated cirrhosis have more treatment options and better tolerability. There has been no study till date comparing the full anti-tubercular therapy (ATT) course with regimens containing only two potentially hepatotoxic drugs in these patients. Some authors do not favour at all use of pyrazinamide but at currently used doses pyrazinamide has not been shown to be more hepatotoxic[60]. Pyrazinamide is generally substituted with a fluroquinolone or an aminoglycoside as per the clinician preference. It will be prudent to use only 2 hepatotoxic drugs in treating compensated cirrhotic till a randomised controlled trial proves the safety of low dose pyrazinamide containing combination of three potentially hepatotoxic drugs. Proposed regimens are: (1) rifampicin, isoniazid, pyrazinamide and ethambutol for 2 mo followed by 4 mo of rifampicin and isoniazid; (2) rifampicin, isoniazid, fluroquinolone/aminoglycoside and ethambutol for 2 mo followed by 4 mo of rifampicin and isoniazid; and (3) rifampicin, isoniazid, and ethambutol for 2 mo followed by 7 mo of rifampicin and isoniazid.

***Treatment in decompensated cirrhosis***

Treatment of tuberculosis in decompensated cirrhosis is challenging as treatment is a two edged sword. Treatment may lead to hepatotoxicity as well as progressive tuberculosis may lead to liver decompensation also. Treatment regimen should ideally contain one of either isoniazid or rifampicin as they are the most potent anti-tubercular drugs. Currently rifampicin is generally the preferred single hepatotoxic agent used due to its potentially lower hepatotoxicity although this has not been proven in a RCT. Higher efficacy of isoniazid against mycobacterium warrants a head to head comparison between isoniazid and rifampicin when only one agent can be used. Other agents that are combined in regimens with single hepatotoxic agent include ethambutol, fluroquinolone, injectable aminoglycoside and cycloserine. No data on duration of therapy is available but treatment duration usually exceeds 12 mo depending upon the site and extent of the disease.

In patients with very advanced liver disease with complications of cirrhosis and signs of liver failure, it may not be possible to use even a single hepatotoxic drug. The presence of hepatorenal syndrome or other renal dysfunction further complicates the situation, limiting the use of aminoglycoside. Altered mental status may also hamper administration of oral drugs. The outcome in such group of patient is very poor with high mortality due to the underlying poor hepatic function. There are no data to guide the choice of agents or the duration of treatment or that indicate the effectiveness of such a regimen. Expert opinion suggests that a regimen of this sort should be given for at least 18-24 mo[58]. The ATS guidelines advise the use of ethambutol with fluroquinolone, cycloserine and capreomycin or aminoglycoside for 18-24 mo if the patient has liver cirrhosis with encephalopathy[45]. Proposed regimens are: (1) rifampicin, ethambutol, fluroquinolone with/without aminoglycoside for 9-12 mo; (2) isoniazid, ethambutol, fluroquinolone with/without aminoglycoside for 9-12 mo; and (3) ethambutol, fluroquinolone with/without aminoglycoside for 12-24 mo.

We propose treatment options according to Child’s class as shown in Table 3. Studies are needed in this grey zone. It would be interesting to evaluate the safety and efficacy of low dose isoniazid and rifampicin in advanced decompensated cirrhosis.

There is generally no difference in treatment of pulmonary or extrapulmonary tuberculosis but there could be a need for prolongation of ATT in cases of CNS or skeletal tuberculosis. Infections in bones have always been difficult to eradicate, which is why prolonged antitubercular therapy (9-18 mo) is routinely prescribed in endemic countries such as India[76]. No consensus or data on the duration of ATT in these conditions with concomitant cirrhosis is available.

***Monitoring for development of hepatotoxicity***

Drug induced liver injury usually occurs in the first 2 mo of treatment. Clinical, biochemical and histological features of drug hepatotoxicity are hard to distinguish from viral hepatitis[44,77]. The signs and symptoms of liver injury include but are not limited to jaundice, abdominal pain, nausea, vomiting and asthenia[78]. Antitubercular treatment drug toxicity (ATDH) is usually reversible on withdrawal of the offending drug. Monitoring liver function tests more frequently at the start of therapy is a reasonable way to identify these patients. No recommendation for monitoring interval duration exists but once weekly liver function test for initial 2 mo followed by once every month should be reasonable. It should be supplementated by liver function test done in between if clinically warranted (Figure 1).

***Diagnosis of hepatotoxicity***

The definition of hepatotoxicity in patients with previous liver diseases is controversial, because of difficulty in defining the influence of the natural evolution of the underlying liver disease. There is need to better define the level of AST/ALT and serum bilirubin at which to consider hepatotoxicity to avoid unnecessary treatment withdrawal and also to avoid dangerous continuation of ATT when hepatotoxicity has set in. The baseline AST/ALT and serum bilirubin are already elevated prior to the institution of anti-tubercular therapy. Although it is generally recommended that therapy be interrupted when transaminase levels increase to 3–5 times the ULN, this limit has not been defined in patients with transaminase values already elevated before starting ATT[79]. Schenker *et al*[80] reported that elevations in the ALT and/or AST levels to 50-100 IU/ L more than the baseline levels might define toxicity. In a study by Saigal *et al*[59] hepatotoxicity was diagnosed if ALT/AST levels increased to more than fivefold the baseline level, or to more than 400 IU/L, or if the bilirubin increased by 2.5 mg/dL after exclusion of superimposed acute hepatitis. The role of fibroscan and other newer blood test needs to be evaluated in early detection of hepatotoxicity and differentiation hepatic adaptation from toxicity.

**REINSTITUTION OF ANTI-TUBERCULOSIS DRUGS**

Guidelines for management of ATDH have been published by the American Thoracic Society (ATS), the British Thoracic Society (BTS) and the Task Force of the European Respiratory Society, the WHO and the International Union against Tuberculosis and Lung Disease[81-83]. No universally accepted consensus on management is available. All confounding factors like superimposed acute viral hepatitis and recidivism towards alcohol should be looked into. Usually asymptomatic transaminase elevations resolve spontaneously. When the initial ATT regimen has been interrupted due to hepatotoxicity, it is reasonable to maintain at least 3 non hepatotoxic drugs if possible. These generally include ethambutol, a fluroquinolone and an amino glycoside.

After TB treatment has been stopped because of hepatotoxicity, both the BTS and ATS advice restarting the antituberculosis drugs one at a time. The Task Force advises restarting all the drugs simultaneously; after a second episode of hepatotoxicity the drugs need to be reintroduced consecutively. These recommendations are in general and not specific to group of patient with underlying cirrhosis. It is more prudent to start one drug at a time after the serum bilirubin and AST/ALT level has returned to near the baseline. After bilirubin and AST/ALT returns to the baseline rifampicin may be restarted first at a reduced dose of 150 mg/days and increased every 3 d with simultaneous LFT monitoring to the full dose. After successful reintroduction of one hepatotoxic drug the second agent isoniazid may be restarted at reduced dose of 50 mg/d and increased slowly every 3-4 d like rifampicin. Rifampicin is generally restarted first because it is thought to be less likely to cause hepatotoxicity than isoniazid. There is no data on reintroduction of pyrazinamide after development of hepatotoxicity episode. The rationale for reintroduction is that majority of hepatotoxicity episodes are hepatic adaptation and it is likely that rechallenge in a gradual manner may be easily tolerated without any evidence of hepatotoxicity. If any single drug is implicated as the cause it is permanently eliminated from the regimen. If a second episode of hepatotoxicity occurs after full institution of ATT, all hepatotoxic drugs should be stopped and an extended duration ATT with no potentially hepatotoxic drugs should be provided (Figure 2).

***Liver transplantation***

ATDH can worsen the liver functions in a cirrhotic and lead to drug withdrawal. This makes the situation difficult as ongoing infection is generally considered as a contraindication for liver transplant. In these cases, the strategy for the treatment of TB is poorly defined. In patients with acute decompensation and/or not tolerating antitubercular drugs, liver transplantation has been done as an urgent basis[84]. In such cases in post transplantation setting rifampicin should be used carefully as drug interactions may change the drug levels significantly and switching to rifabutin may be beneficial[85]. There is also a risk of graft rejection by rifampicin induced reduction in the level of immunosuppressant as rifampicin is a strong enzyme inducer.

***Special situations***

Hepatitis B and/or C infections are common causes of the chronic liver disease that is frequently seen in populations at risk for TB infection and these patients have increased risk of ATDH. In a study from Korea, amongst 110 inactive HBsAg carriers and 97 controls without HBV infection, 38 inactive HBsAg carriers (35%) and 19 control subjects (20%) developed elevated liver enzyme levels during ATT (*P* = 0.016). A higher proportion of inactive HBsAg carriers who received ATT experienced moderate-to-severe drug-induced hepatotoxicity when compared with the control subjects (8% *vs* 2%, *P* < 0.05)[86]. Ungo *et al*[73] showed that the relative risk of developing hepatotoxicity if the patient was hepatitis C or HIV positive was fivefold and fourfold, respectively (*P* < 0.05). Interestingly, if a patient was co-infected with both hepatitis C and HIV the relative risk of developing DIH was increased 14.4-fold (*P* < 0.002). Alcoholism is associated with a higher risk of ATDH because of enzyme induction. Patients with ongoing alcohol abuse and concomitant use of other hepatotoxic drugs also have increased risk of hepatotoxicity. In the USPHS surveillance study[87], alcohol consumption appeared to more than double the rate of probable isoniazid hepatitis, with daily consumption increasing the rate more than four times. It is highly likely that this subgroup of patients may have additional risk for hepatotoxicity as compared to other patient group with cirrhosis and warrants a close monitoring.

Genetic polymorphisms in drug-metabolizing enzymes affect enzyme activity. This may lead differences in treatment response or drug toxicity, for example, due to an increased formation of reactive metabolites. Data on genetic risk factors for ATDH are still limited. Human genetic studies have shown that cytochrome P450 2E1 (CYP2E1) is involved in ATDH. Huang *et al*[70] demonstrated that slow acetylators for isoniazid have a more than two-fold risk of developing ATDH compared with fast acetylators. Deficiency of GST activity, because of homozygous null mutations at GSTM1 and GSTT1 loci, may modulate susceptibility to drug and xenobiotic-induced hepatotoxicity. Polymorphisms at GSTM1, GSTT1 and CYP2E1 loci had been linked to various forms of liver injury[88].

***Prevention of antitubercular drug hepatotoxicity***

There is very little effective treatment available for antitubercular drug hepatotoxicity (ATDH). This further exerts importance on early detection of hepatotoxicity and prompt withdrawal of the offending drug. Polypharmacy should be avoided to prevent inadvertent use of potentially other hepatotoxic drug. Close clinical and biochemical monitoring are strictly needed for early detection of this potentially reversible liver injury.

Genetic profiling of patients for polymorphisms associated with increased risk of hepatotoxicity will be very helpful but is currently not available in the clinical setting. NAT2 genotype could be used to divide patients into low isoniazid dose and high isoniazid dose groups. N-Acetyl cysteine has been shown in one study to prevent ATT induced hepatotoxicity[89]. In that randomized clinical trial 60 new TB patients aged 60 years or more were randomized into two groups. In group I (*n* = 32), drug regimen included daily doses of isoniazid, rifampicin, pyrazinamide, and ethambutol. Patients in group II (*n* = 28) were treated with the same regimen and NAC. The mean values of aspartate aminotransferase and alanine aminotransferase were significantly higher in group I than in group II (with NAC) after 1 and 2 wk of treatment[89]. This study thus proved that NAC protects against anti-TB drug-induced hepatotoxicity. More studies are needed on the potentially protective effect of such compounds in humans and possible interactions with antituberculosis drugs. A hepatoprotective effect of silymarin also on ATDH has been shown in rats[90]. Study in patients with cirrhosis is highly warranted as demonstration of NAC efficacy may strengthen the already depleted armour in fight against tuberculosis.

The herbal formulation of Curcuma longa and Tinospora cordifolia prevented hepatotoxicity significantly and improved the disease outcome as well as patient compliance without any toxicity or side effects in a randomized study[91]. Caution must be exercised before using any indigenous drug formulation due to unknown drug interactions and side effects. Ultimately, a strategy that incorporates new analytical approaches-addressing both the immune response and pharmacogenetic vulnerability-can be envisioned.

***MDR tuberculosis***

Many studies for risk factors for drug resistant tuberculosis have found that presence of hepatic cirrhosis is a risk factor for the development of drug resistant tuberculosis[92]. A study for risk factors for drug resistant tuberculosis found the prevalence of drug resistant tuberculosis to be 46% among cirrhotic patients although the number of patients with liver cirrhosis was only eleven[93]. The drug resistance may occur from reduced immune response and the inability to use most potent drugs in many patients due to risk of hepatotoxicity.

***Interferon induced reactivation of tuberculosis-a special scenario***

The standard of care for patients with chronic hepatitis C infection is pegylated interferon-α (Peg-IFN) and ribavirin. Interferon treatment induces immunomodulation[94]. Theoretically interferon induced immunomodulation should increase tuberculosis occurrence as other bacterial infections but there is paucity of reported cases. There had been few case reports of patient developing reactivation of tuberculosis as a consequence of interferon therapy but overall there had been paucity of data about development of tuberculosis in patients after interferon treatment[95-98]. A recent unpublished data from India has recently reported 10 cases of interferon induced reactivation of tuberculosis. There were many cases of tuberculosis which were occurring after completion of treatment[99]. There could well be underreporting of cases leading to lower incidence of tuberculosis seen with interferon administration as underreporting is normally very high in developing countries. Hence there is need for close surveillance of tuberculosis in patients receiving interferon for hepatitis C.

***Newer drugs***

There is an urgent need for development of newer drugs with high efficacy and low hepatotoxicity to reduce the incidence of ATDH. A new drug, bedaquiline has recently been approved for the treatment of MDR tuberculosis[100]. Bedaquiline is a member of the diarylquinoline class of drugs and has a unique mechanism of action, targeting the adenosine triphosphate (ATP) synthase enzyme of the TB mycobacteria. ATP-synthase is used in the process by which the bacillus generates its energy supply. It is active against both *M.tb* and the drug-resistant TB bacteria that cause MDR-TB. Laboratory tests and clinical trials have shown it to have strong bactericidal and sterilizing properties[100]. More data on safety of this drug is required. Moxifloxacin has been shown to be the most efficacious fluroquinolone in vitro. Many ongoing studies with this drug in various combinations are ongoing[101]. Many drugs in various stages of development are in progress namely DprE inhibitors, indazoles, mycobacterial gyrase inhibitors, pyrazinamide analogs, nitroimidazoles and RNA polymerase inhibitors[102,103].

**CONCLUSION**

Patients of cirrhosis are predisposed for tuberculosis, especially extra-pulmonary; Diagnosis of tuberculosis in patients of cirrhosis is challenging, due to hampered immune response and reduced sensitivity of the available diagnostic tests. Successful completion of antitubercular drug therapy remains a challenge in patients with cirrhosis due to reduced hepatic reserve and higher incidence of hepatotoxicity. Close monitoring and early detection is the mainstay to prevent drug induced liver injury. Successful reintroduction of anti-tubercular drugs is possible and should be done in stable patients. Liver transplantation is possible in patients not recovering but post transplantation anti-tubercular therapy is difficult with ongoing immunosuppression. Ongoing research for potent non hepatotoxic anti-tubercular drugs should be expedited.

**FUTURE DIRECTIONS**

Need randomized controlled trials to decide the optimal regimen of ATT in cirrhosis, depending on the Child’s score. Better diagnostic armentarium for detection of latent tuberculosis, especially in patients of hepatitis C prior to starting of interferon regimens and as part of pre-transplant evaluation. To study the efficacy of hepatoprotective agents in combination with ATT to reduce drug induced liver injury

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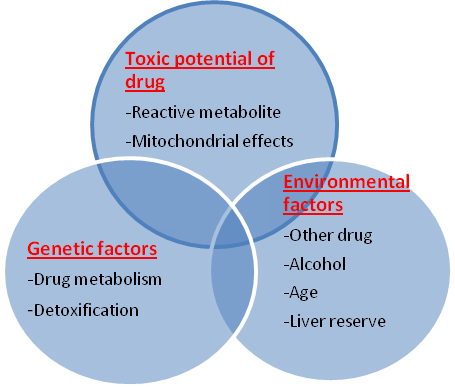
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**Figure 1 Interaction of factors to produce hepatotoxicity in cirrhosis.**



**Figure 2 Proposed algorithm for monitoring and management of ATDH.** AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; ATT: Antitubercular therapy; ATDT: Antitubercular therapy drug toxicity.

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**Table 1 Incidence of hepatotoxicity of isoniazid and rifampicin individually, and in combination[49**]

|  |  |  |  |
| --- | --- | --- | --- |
| **Drug(s) used** | **Total no. of patients** | **Patients with hepato-toxicity** | **Incidence of hepato-toxicity** |
| INH | 38257 | 210 | 0.6% |
| RIF | NA | NA | NA |
| INH + RIF | 6155 | 168 | 2.73% |
| INH + other drugs | 2053 | 33 | 1.6% |
| RIF + other drugs | 1264 | 14 | 1.1% |

INH: Isoniazid; RIF: Rifampicin.

**Table 2 Studies on hepatotoxicity of antitubercular drug in combination therapy**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Definition of hepatotoxicity** | **Incidence** | **Risk factors** |
| Døssing M *et al*[61] 1996 | AST > 6 × ULN and  confirmation by re-challenge | 2.0 | Female gender, advanced age |
| Ormerod LP *et al*[62] 1996 | ALT > 5 × pre-treatment level | 2.3 | Advanced age |
| Tost JR *et al*[63 2005 | ALT/AST > 10 × ULN | 2.6 | Alcoholism, hepatitis B carrier state, other  hepatotoxic drugs |
| Yee D *et al*[48] 2003 | ALT > 3× ULN | 3.0 | Advanced age, female gender, Asian, HIV positive |
| Van Hest R *et al*[64] 2004 | ALT > 5× ULN | 3.4 | Female gender |
| Teleman MD *et al*[65] 2002 | ALT/AST > 3 × ULN | 5.3 | Abnormal baseline values, female gender, advanced age |
| Fernández-Villar *et al*[66] 2004 | ALT/AST > 5 × ULN | 8.1 | Abnormal baseline liver function, low BMI,  hepatitis B/C, other drugs |
| Pukenyte E *et al*[67] 2007 | ALT > 5× ULN | 10.7 | Baseline CD4 < 100 cells/mL, bilirubin > 13 mmol/L or ALT > 51 U/L |
| Schaberg T *et al*[68] 1996 | ALT/AST > 3× ULN | 11 | Advanced age, Past history of hepatitis, female gender |
| Saigal S *et al*[69] 2001 | AST/ALT > 5ULN or > 400 IU/mL  S.Bilirubin rise > 2.5mg/dL | 12.9 | Advanced child status |
| Breen RA *et al*[70] 2006 | ALT/AST > 5× ULN | 13 | HIV infection, Asian |
| Huang YS *et al*[71] 2003 | ALT > 3 × ULN | 15 | Advanced age, low BMI, slow acetylator  status, CYP2E1 c1/c1 genotype |
| Sharma SK *et al*[72] 2002 | ALT/AST > 5 × ULN, or  any increase + symptoms | 16.1 | Advanced age |
| Park *et al*[38] 2010 | ALT > 3 × ULN | 17 | Female gender, Total no. of hepatotoxic drugs administered and baseline ALP levels |
| Ungo JR *et al*[73]1998 | ALT/AST > 3 × ULN | 19 | HIV or hepatitis C infection |
| Sharifzadeh M *et al*[74] 2005 | ALT > 3 × ULN with or > 5 × ULN without symptoms | 27.7 | No significant risk factors |
| Pande JN *et al*[75]1996 | AST > 3 × ULN | ND | Advanced age, high alcohol intake, slow  acetylators |

**Table 3 Proposed treatment according to stage of liver disease**

|  |  |
| --- | --- |
| **Child’s status** | **Treatment** |
| Child’s A | Two hepatotoxic drugs can be used namely isoniazid and rifampicin with/without pyrazinamide (low dose). Duration 6-9 mo. |
| Child’s B | Ideally one hepatotoxic drug is used in combination. Pyrazinamide generally avoided. Duration generally 9-12 mo. |
| Child’s C | No hepatotoxic drugs to be used. Can use second line drugs like streptomycin, ethambutol, fluoroquinolones, amikacin, kanamycin for extended duration of 12 mo or more. Role of aminoglycosides may be limited due to reduced renal reserve in these patients. |