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TOPIC HIGHLIGHT

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Antitubercular therapy in patients with cirrhosis: Challenges and options

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Abstract

Tuberculosis (TB) has been a human disease for centuries. Its frequency is increased manyfold in patients with liver cirrhosis. The gold standard of TB management is a 6-mo course of isoniazid, rifampicin, pyrazinamide and ethambutol. Although good results are seen with this treatment in general, the management of patients with underlying cirrhosis is a challenge. The underlying depressed immune response results in alterations in many diagnostic tests. The tests used for latent TB have many flaws in this group of patients. Three of four first-line antitubercular drugs are hepatotoxic and baseline liver function is often disrupted in patients with underlying cirrhosis. Frequency of hepatotoxicity is increased in patients with liver cirrhosis, frequently leading to severe liver failure. There are no established guidelines for the treatment of TB in relation to the severity of liver disease. There is no consensus on the frequency of liver function tests required or the cut-off used to define hepatotoxicity. No specific treatment exists for prevention or treatment of hepatotoxicity, making monitoring even more important. A high risk of multidrug-resistant TB is another major worry due to prolonged and interrupted treatment.

Key words: Antitubercular therapy; Drug hepatotoxicity; Multidrug-resistant tuberculosis; Immune dysfunction

Core tip: Treatment of tuberculosis (TB) 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 TB in this group of patients. This paper reviews the differences in diagnosis, treatment, monitoring, hepatotoxicity and other issues in treatment of TB in patients with cirrhosis. Suggestions for treatment of TB in patients with different grades of cirrhosis, as well as monitoring guidelines, are provided. Finally, issues such as liver transplantation, multidrug-resistant TB and reactivation of TB by interferon are briefly reviewed.

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INTRODUCTION

Tuberculosis (TB) has afflicted humans for many centuries[1]. About one-third of the world's population is infected with *Mycobacterium tuberculosis* (*M. tuberculosis*). TB is widely prevalent worldwide, especially in 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 according to World

Health Organization (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 approximately 10% of individuals and in the rest, latent TB infection develops. In 5%-10% of latently infected persons, the infection reactivates and causes active TB[4]. The progression from latent infection to active disease depends on a number of factors, of which the most important is the presence of an underlying immunodeficient state[5]. Cirrhosis is a widely prevalent disease that leads to immunosuppression and a higher prevalence of TB than in the general population[6]. However, 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 multidrug-resistant (MDR) TB. This paper reviews the differences in diagnosis, treatment, monitoring, hepatotoxicity and other issues in treatment of TB in patients with cirrhosis.

CIRRHOSIS AND TB

Prevalence and relationship

Liver cirrhosis is also a relatively common condition with autopsy studies showing a prevalence of 5%-10%[6]. Evidence suggests a higher prevalence of TB in patients with cirrhosis as compared to the general population. The high incidence of TB in patients with cirrhosis has been ascribed mainly to immune dysfunction 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 of TB was 168.6 per 100000. It was highest in men aged > 65 years, with an incidence of 246 per 100000[8]. Furthermore, patients with cirrhosis who acquired TB had a poor prognosis in that study. A study conducted in Western India showed that the prevalence rate was 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%), with pulmonary TB being the commonest form[10].

Pulmonary TB is generally responsible for 80%-85% of all cases of TB reported[11]. Cirrhosis has been suggested as a risk factor for extrapulmonary TB in a previous study[12]. In a Korean study, 31% patients with cirrhosis had extrapulmonary TB, as compared to 12% in the non-cirrhosis control group with a predominance of peritoneal TB[7]. There are several reports of unusual manifestation of TB in patients with cirrhosis[13]. Little is known about the immunopathogenesis of TB in such clinical conditions. Although most of the host defense systems, especially the clearance capacity 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 extrapulmonary TB than pulmonary TB.

Cirrhosis-associated immune dysfunction

Cirrhosis-associated immune dysfunction syndrome is a multifactorial process in which the ability to clear cytokines, bacteria and endotoxins from the circulation is decreased[14]. The liver is the major organ of the 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, chemotaxis, bacterial phagocytosis, and bacterial killing in cirrhosis compared with controls, and hence compromised innate immunity[14]. These patients also have decreased neutrophil mobilization and phagocytic activity with reduced oxidative bursts; 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 etiology of liver disease, such as 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 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]. TLR-2 is capable of recognizing pathogen-associated molecular patterns expressed by *M. tuberculosis*, such as a 19-kDa lipoprotein, lipoarabinomannan, and soluble TB factor[18]. Immune evasion allows *M. tuberculosis* to establish persistent or latent infection in macrophages and results in TLR-2-dependent inhibition of MHC class Ⅱ transactivator expression, MHC class Ⅱ molecule expression, and antigen presentation[19]. TLR-2 genetic polymorphisms have been shown to influence susceptibility to pulmonary TB. TLR-2 variants play a role in the development of TB phenotypes, probably by controlling the expansion of natural killer cells[20]. Patients with stable alcoholic chronic liver disease show an attenuated TLR-2-mediated innate immune response[21]. The extent to which cirrhosis interacts with TLR polymorphism in promoting mycobacterial immune evasion is not known.

Diagnosis of TB in cirrhosis

Diagnosis of latent as well as clinical TB can be challenging in the setting of cirrhosis. There can be overlap between the symptoms of TB and decompensation of cirrhosis leading to delay in diagnosis. These patients demonstrate impaired delayed-type hypersensitivity; hence, there is a higher likelihood of false-negative tuberculin test results[22]. The exact mechanism of anergy to skin testing is not well known. Schirren *et al*[23] have 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. 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 etiology of cirrhosis. A recent study by Çelikbilek *et al*[25] showed that TST findings were more often falsely positive in the end-stage liver disease caused by viral as compared to nonviral etiology.

Interferon (IFN)-γ release assay(IGRA) is an alternative to purified protein derivative (PPD) testing. The test requires only a single contact with a patient. In addition, unlike the PPD, which is subject to interpretation bias, IFN-γ release assays are machine read and have single cut-offs. Thus, there is little subjectivity to the reading of results. IFN-γ-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 healthcare workers, role of serial testing, and ability to identify people who are likely to progress to active[27]. In high-burden settings, IFN-γ release assays tend to have decreased sensitivity because of the confounding effects of malnutrition, nontuberculous mycobacterium (NTM) exposure (especially *Mycobacterium kansasii* and *Mycobacterium marinum*), leprosy, and parasitic and other tropical infections that may alter the host T helper 1/T helper 2 cell balance[28].

Great efforts have been made globally to accelerate the development and expansion of new diagnostic technologies. However, pulmonary TB case detection remains dependent upon sputum smear and culture, radiography and clinical symptomatology. The role of sputum smear and radiography in the presence of cirrhosis is similar to that in patients without underlying cirrhosis. The *M. tuberculosis*-specific nucleic acid amplification tests (NAAT) performed on bronchopulmonary specimens is the most frequently used molecular test for laboratory diagnosis of pulmonary TB. NAAT results can be available to the clinician within 1 d after obtaining sputum or bronchoalveolar lavage (BAL) fluid and can have important implications for the management of patients. Unfortunately, NAAT amplification targets are not standardized and the diagnostic accuracy of the tests is highly heterogeneous[28,29]. In individuals with positive acid-fast bacillus (AFB) sputum smears, the sensitivity of NAAT to detect *M. tuberculosis* nucleic acid on these specimens is > 95%[29]. When AFBs are found on sputum or BAL smears, the presumptive diagnosis of TB can thus be rapidly confirmed. Apart from rare exceptions, a negative NAAT result in this situation strongly indicates the presence of an NTM species. Currently available serological tests cannot be recommended for the diagnosis of TB 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 TB[30]. The authors concluded that none of the antigen sensitivity was high enough to replace sputum smear microscopy. A recent test has been approved by the FDA (MTB/RIF test), which provides sensitive detection of TB and rifampin resistance directly from untreated sputum in < 2 h with minimal hands-on time. The role of this test in cirrhosis needs to be evaluated as the proportion of patients with pulmonary TB is much lower than in the general population[31].

The diagnosis of extrapulmonary TB in cirrhosis is similar to the disease in the general population. TB peritonitis possibly mimics spontaneous bacterial peritonitis. TB peritonitis occurs in less-advanced cirrhosis and ascitic fluid analysis usually shows lower white blood cell counts, higher proportions of mononuclear cells, and 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 the United States, > 50% of TB peritonitis cases had underlying cirrhosis, predominantly alcohol-related[33]. Although 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 TB is a paucibacillary disease and AFB smears are generally negative in such patients. Sometimes the TB manifestation in cirrhosis could be just the worsening of the liver function.

Drugs used in tuberculosis

There is no consensus regarding the use of antitubercular drugs in patients with cirrhosis. The potential hepatotoxicity of antitubercular drugs is a major concern. First, in the setting of pre-existing liver disease, the likelihood of developing drug-induced hepatitis may be higher. Second, the outcome of drug-induced hepatitis in patients with compromised liver function may be poor. Third, 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: Isoniazid is a synthetic analog of pyridoxine and the most potent tuberculocidal drug[39]. It is an essential component of all regimens. Isoniazid is effective against both intra- and extracellular organisms because it inhibits the synthesis of mycolic acids in the bacterial cell wall[39]. Isoniazid is metabolized in the liver through two main pathways. Acetyl hydrazine, a nontoxic metabolite, is formed when metabolism proceeds along the N-acetyltransferase (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].

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

Rifampicin: Rifampicin is a bactericidal agent that inhibits mycobacterium DNA-dependent RNA polymerase. It has profound early bactericidal activity against rapidly dividing cells and also against semidormant 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. Conjugated hyperbilirubinemia probably results from rifampicin inhibiting the major bile salt exporter pump, impeding secretion of conjugated bilirubin at the canalicular level[49]. Rifampicin can cause hepatocellular changes such as centrilobular necrosis, associated with cholestasis[37].

Pyrazinamide: Pyrazinamide 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 semidormant organisms contained within macrophages or the acidic environment of caseous foci[50]. Historically, it was considered the most hepatotoxic antitubercular 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 is rare when pyrazinamide is used at a daily dose of < 35 mg/kg[52]. In murine models, pyrazinamide inhibits CYP45058 activity and NAD59 levels are altered in association with free-radical-species-mediated hepatotoxicity[53]. Bridging necrosis, lymphocytic infiltration, focal cholestasis, increased fibrosis, and micronodular 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 dose is unknown. However, more data on the safety of pyrazinamide are needed to clarify its use in patients with cirrhosis.

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

Third-line antitubercular drugs

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

ANTITUBERCULAR THERAPY IN CIRRHOSIS: THE CHALLENGES

Challenges in the treatment of TB in patients with cirrhosis arise because three of the first-line antitubercular 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 for different grades of liver injury, although the WHO guidelines mention that the more unstable or severe the liver disease is, the fewer hepatotoxic drugs should be used[58].

Incidence of antitubercular drug hepatotoxicity

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

An asymptomatic, self-limited increase in aminotransferase levels was observed in most patients treated with isoniazid. Approximately 0.5% of all patients treated with isoniazid monotherapy for latent TB developed clinically important increases in aminotransferase levels in a large study. The percentage was higher in combination therapy[59]. Isoniazid-induced hepatotoxicity is seen mainly as

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

Drugs used	Total no. of patients	Patients with hepatotoxicity	Incidence of hepatotoxicity
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.

hepatocellular steatosis and necrosis, and it has been suggested that toxic drug metabolites may bind covalently to cell macromolecules[60].

Hepatotoxicity associated with rifampicin is usually idiosyncratic. Rifampicin 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, rifampicin can cause hepatocellular injury and can potentiate hepatotoxicity of other antitubercular drugs[49].

Hepatotoxicity is a major toxic effect of pyrazinamide. Previously reported studies have shown high rates of hepatotoxicity with high doses of pyrazinamide. Doses used currently (< 35 mg/kg per day) are considered much safer[60].

A study by Park *et al*[38] in patients with chronic liver disease and TB found that the incidence of hepatotoxicity was 17%, with no difference in patients with or without cirrhosis. The incidence of antitubercular-drug-induced hepatotoxicity when used as part of combination regimens in various studies is shown in Table 2[38,61-75].

Treatment of TB in compensated cirrhosis

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

Treatment in decompensated cirrhosis

Treatment of TB in decompensated cirrhosis is challenging because treatment is a double-edged sword. Treatment may lead to hepatotoxicity and progressive TB may lead to liver decompensation. Treatment regimens should ideally contain one of either isoniazid or rifampicin because they are the most potent antitubercular drugs. Currently, rifampicin is generally the preferred single hepatotoxic agent due to its potentially lower hepatotoxicity, although this has not been proven in an RCT. The high efficacy of isoniazid against mycobacteria 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 agents include ethambutol, fluoroquinolone, injectable aminoglycoside, and cycloserine. No data on duration of therapy are available but treatment duration usually exceeds 12 mo, depending upon the site and extent of the disease.

In patients with 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 aminoglycosides. Altered mental status may also hamper administration of oral drugs. The outcome in such group patients is 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 American Thoracic Society (ATS) guidelines advise the use of ethambutol with fluoroquinolone, cycloserine and capreomycin or aminoglycoside for 18-24 mo if the patient has liver cirrhosis with encephalopathy[45]. Proposed regimens are: (1) rifampicin, ethambutol, fluoroquinolone with/without aminoglycoside for 9-12 mo; (2) isoniazid, ethambutol, fluoroquinolone with/without aminoglycoside for 9-12 mo; and (3) ethambutol, fluoroquinolone 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 TB but there could be a need for prolongation of antitubercular therapy in cases of central nervous system or skeletal TB. Bone infections 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 antitubercular therapy 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

Table 2 Studies on hepatotoxicity of antitubercular drugs in combination therapy

Ref.	Definition of hepatotoxicity	Incidence	Risk factors
Døssing *et al*[61] 1996	AST > 6 × ULN and confirmation by re-challenge	2.0	Female sex, advanced age
Ormerod *et al*[62] 1996	ALT > 5 × pre-treatment level	2.3	Advanced age
Tost *et al*[63] 2005	ALT/AST > 10 × ULN	2.6	Alcoholism, hepatitis B carrier state, other hepatotoxic drugs
Yee *et al*[48] 2003	ALT > 3 × ULN	3.0	Advanced age, female sex, Asian, HIV positive
Van Hest *et al*[64] 2004	ALT > 5 × ULN	3.4	Female gender
Teleman *et al*[65] 2002	ALT/AST > 3 × ULN	5.3	Abnormal baseline values, female sex, 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 *et al*[67] 2007	ALT > 5 × ULN	10.7	Baseline CD4 < 100 cells/mL, bilirubin > 13 mmol/L or ALT > 51 U/L
Schaberg *et al*[68] 1996	ALT/AST > 3 × ULN	11.0	Advanced age, past history of hepatitis, female sex
Saigal *et al*[69] 2001	AST/ALT > 5ULN or > 400 IU/mL Bilirubin rise > 2.5 mg/dL	12.9	Advanced child status
Breen *et al*[70] 2006	ALT/AST > 5 × ULN	13.0	HIV infection, Asian
Huang *et al*[71] 2003	ALT > 3 × ULN	15.0	Advanced age, low BMI, slow acetylator status, CYP2E1 c1/c1 genotype
Sharma *et al*[72] 2002	ALT/AST > 5 × ULN, or any increase + symptoms	16.1	Advanced age
Park *et al*[38] 2010	ALT > 3 × ULN	17.0	Female sex, total no. of hepatotoxic drugs administered and baseline ALP levels
Ungo *et al*[73] 1998	ALT/AST > 3 × ULN	19.0	HIV or hepatitis C infection
Sharifzadeh *et al*[74] 2005	ALT > 3 × ULN with or > 5 × ULN without symptoms	27.7	No significant risk factors
Pande *et al*[75] 1996	AST > 3 × ULN	ND	Advanced age, high alcohol intake, slow acetylators

ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; ALP: Alkaline phosphatase; ULN: Upper limit of normal; BMI: Body mass index; HIV: Human immunodeficiency virus.

Table 3 Proposed treatment according to stage of liver disease

Child's status	Treatment
A	Two hepatotoxic drugs can be used namely isoniazid and rifampicin with/without pyrazinamide (low dose). Duration 6-9 mo
B	Ideally one hepatotoxic drug is used in combination. Pyrazinamide generally avoided Duration generally 9-12 mo
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

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 hepatotoxicity (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 the initial 2 mo followed by once monthly should be reasonable. It should be supplemented by liver function tests 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 a need to define better the level of aspartate aminotransferase (AST)/alanine aminotransferase (ALT) and serum bilirubin at which to consider hepatotoxicity to avoid unnecessary treatment withdrawal and to avoid dangerous continuation of antitubercular therapy when hepatotoxicity has set in. The baseline AST/ALT and serum bilirubin are already elevated prior to the institution of antitubercular therapy. Although it is generally recommended that therapy be interrupted when transaminase levels increase to 3-5 times the upper limit of normal, this limit has not been defined in patients with transaminase values already elevated before starting therapy[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*[69], hepatotoxicity was diagnosed if ALT/AST levels increased to more than fivefold of 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

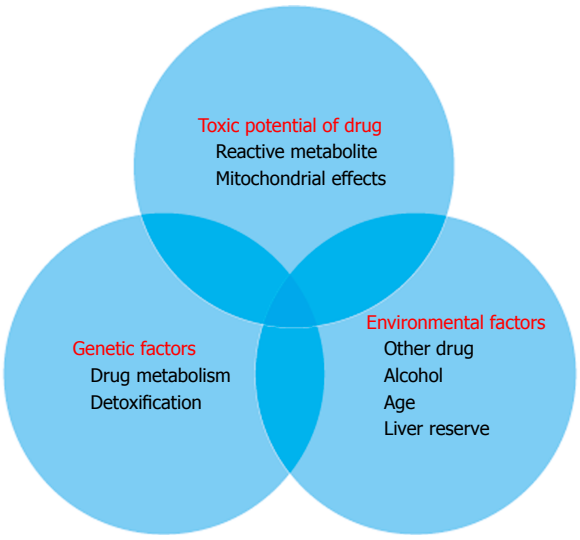

Figure 1 Interaction of factors to produce hepatotoxicity in cirrhosis.

of hepatotoxicity and for differentiation of hepatic adaptation from toxicity.

REINSTITUTION OF ANTITUBERCULAR DRUGS

Guidelines for management of ATDH have been published by the ATS, British Thoracic Society (BTS), Task Force of the European Respiratory Society, WHO and 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 investigated. Usually, asymptomatic transaminase elevation resolves spontaneously. When the initial antitubercular regimen has been interrupted due to hepatotoxicity, it is reasonable to maintain at least 3 nonhepatotoxic drugs if possible. These generally include ethambutol, a fluoroquinolone and an aminoglycoside.

After TB treatment has been stopped because of hepatotoxicity, both the BTS and ATS advise restarting the antitubercular 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 groups of patients with underlying cirrhosis. It is more prudent to start one drug at a time after the serum bilirubin and AST/ALT levels have returned to near the baseline. After bilirubin and AST/ALT levels return to baseline, rifampicin may be restarted first at a reduced dose of 150 mg/d and increased every 3 d with simultaneous liver function test monitoring to the full dose. After successful reintroduction of one hepatotoxic drug, the second agent isoniazid may be restarted at a 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 antitubercular therapy, all hepatotoxic drugs should be stopped and extended duration antitubercular therapy with no potentially hepatotoxic drugs should be provided (Figure 2).

Liver transplantation

ATDH can worsen the liver function in patients with cirrhosis and lead to drug withdrawal. This makes the situation difficult because ongoing infection is generally considered as a contraindication for liver transplantation. In these cases, the strategy for the treatment of TB is poorly defined. In patients with acute decompensation and/or intolerance of antitubercular drugs, liver transplantation has been performed on an urgent basis[84]. In such cases in a post-transplantation setting, rifampicin should be used carefully because 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 because 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 hepatitis B surface antigen (HBsAg) carriers and 97 controls without hepatitis B infection, 38 inactive HBsAg carriers (35%) and 19 controls (20%) developed elevated liver enzyme levels during antitubercular therapy ($P = 0.016$). A higher proportion of inactive HBsAg carriers who received antitubercular therapy experienced moderate-to-severe drug-induced hepatotoxicity when compared with the controls (8% *vs* 2%, $P < 0.05$)[86]. Ungo *et al*[73] showed that the relative risk of developing hepatotoxicity if the patient had hepatitis C or was HIV positive was fivefold and fourfold, respectively ($P < 0.05$). If a patient was co-infected with hepatitis C and HIV, the relative risk of developing drug-induced hepatitis was increased by 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 an 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 groups with cirrhosis, and warrants close monitoring.

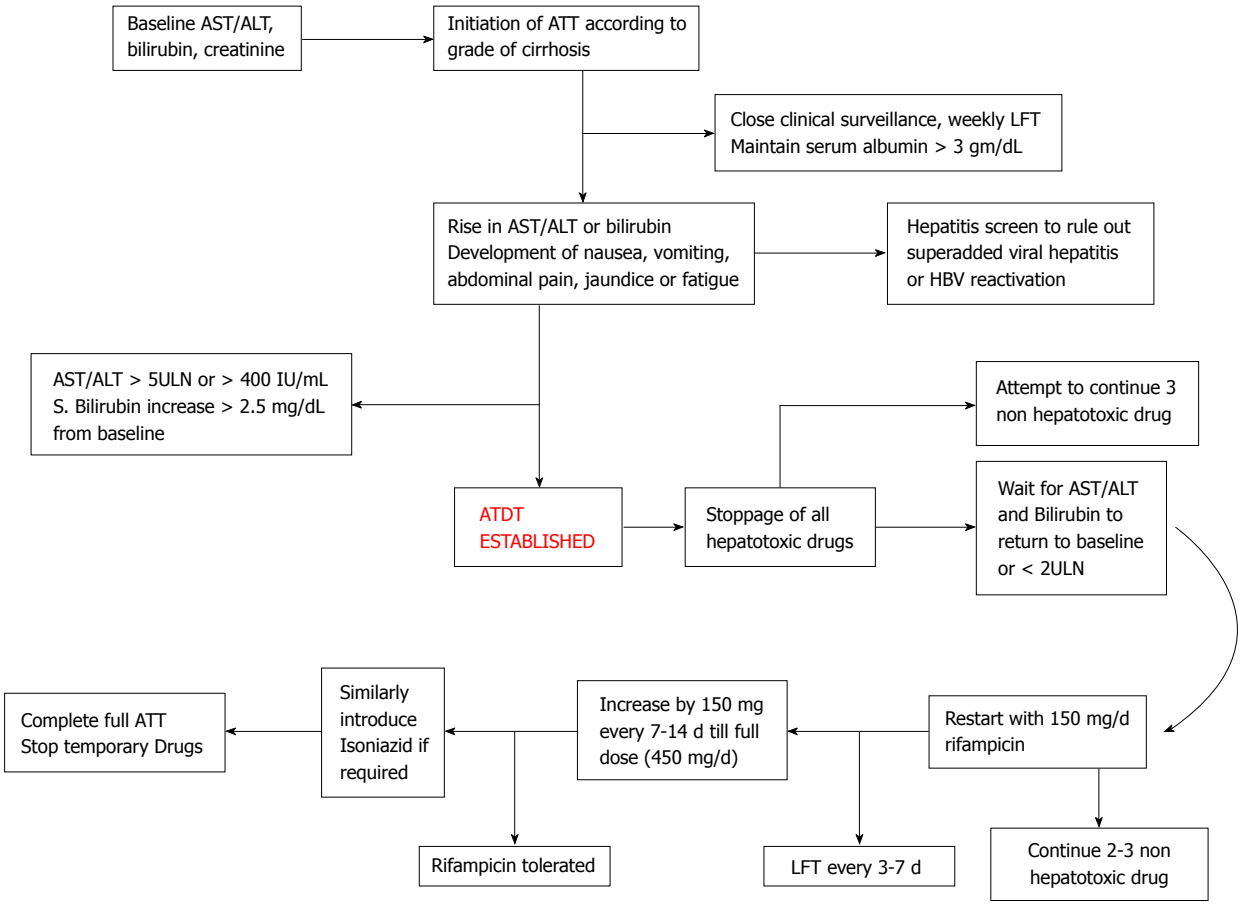

Figure 2 Proposed algorithm for monitoring and management of Antitubercular treatment drug hepatotoxicity. ALT: Alanine aminotransferase; ATDH: Antitubercular treatment drug hepatotoxicity; AST: Aspartate aminotransferase; ULN: Upper limit of normal; ATT: Antitubercular therapy; LFT: Liver function test.

Genetic polymorphisms in drug-metabolizing enzymes affect enzyme activity. This may lead to 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*[71] demonstrated that slow acetylators for isoniazid have a more than twofold risk of developing ATDH compared with fast acetylators. Deficiency of glutathione S-transferase (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 have been linked to various forms of liver injury[88].

Prevention of ATDH

There are few effective treatments available for ATDH. This emphasizes the importance of early detection of hepatotoxicity and prompt withdrawal of the offending drug. Polypharmacy should be avoided to prevent inadvertent use of other potentially hepatotoxic drugs. 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 helpful but is currently not available in the clinical setting. NAT2 genotype could be used to divide patients into low and high isoniazid dose groups. N-Acetyl cysteine (NAC) has been shown in one study to prevent antitubercular-therapy-induced hepatotoxicity[89]. In that RCT, 60 new TB patients aged ⩾ 60 years were randomized into two groups. In Group I (n = 32), the 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 proved that NAC protects against antitubercular-drug-induced hepatotoxicity. More studies are needed on the potentially protective effect of such compounds in humans and possible interactions with antitubercular drugs. A hepatoprotective effect of silymarin on ATDH has been shown in rats[90]. A study in patients with cirrhosis is warranted to demonstrate that NAC efficacy may strengthen the already depleted armor in the fight against TB.

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 TB

Many studies for risk factors for drug-resistant TB have found that the presence of hepatic cirrhosis is a risk factor for the development of drug-resistant TB[92]. A study for risk factors for drug-resistant TB found that the prevalence of drug-resistant TB was 46% among patients with cirrhosis, although the number of patients with cirrhosis was only 11[93]. Drug resistance may occur from reduced immune response and the inability to use the most potent drugs in many patients due to the risk of hepatotoxicity.

IFN-induced reactivation of TB - a special scenario

The standard of care for patients with chronic hepatitis C is pegylated IFN-α (Peg-IFN) and ribavirin. IFN treatment induces immunomodulation[94]. Theoretically, IFN-induced immunomodulation should increase TB occurrence as well as other bacterial infections but there is a paucity of reported cases. There have been few case reports of patients developing reactivation of TB as a consequence of IFN therapy, but overall, there is a paucity of data about development of TB in patients after IFN treatment[95-98]. Recent unpublished data from India have shown 10 cases of IFN-induced reactivation of TB. There are many cases of TB occurring after completion of treatment[99]. There could well be under-reporting of cases, leading to lower incidence of TB seen with IFN administration, and such under-reporting is normally high in developing countries. Hence, there is a need for close surveillance of TB in patients receiving IFN for hepatitis C.

New drugs

There is an urgent need for development of new 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 TB[100]. Bedaquiline is a member of the diarylquinoline class of drugs and has a unique mechanism of action, targeting ATP synthase of *M. tuberculosis*. ATP synthase is used by the bacterium for generation of its energy supply. Bedaquiline is active against both *M. tuberculosis* and drug-resistant bacteria that cause MDR TB. Laboratory tests and clinical trials have shown it to have strong bactericidal and sterilizing properties[100]. More data on the safety of this drug are required. Moxifloxacin has been shown to be the most efficacious fluoroquinolone *in vitro*. Many studies with this drug in various combinations are ongoing[101]. Many drugs are in various stages of development, namely DprE inhibitors, indazoles, mycobacterial gyrase inhibitors, pyrazinamide analogs, nitroimidazoles and RNA polymerase inhibitors[102,103].

CONCLUSION

Patients with cirrhosis are predisposed to TB, especially extrapulmonary TB. Diagnosis of TB in patients with 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 are the mainstay to prevent drug-induced liver injury. Successful reintroduction of antitubercular drugs is possible and should be done in stable patients. Liver transplantation is possible in patient's not recovering but post-transplantation antitubercular therapy is difficult with ongoing immunosuppression. Ongoing research for potent non-hepatotoxic antitubercular drugs should be expedited.

FUTURE DIRECTIONS

RCTs are needed to decide the optimal regimen of antitubercular therapy in cirrhosis, depending on Child's score. Better diagnostic methods are needed for detection of latent TB, especially in patients with hepatitis C, prior to starting IFN regimens and as part of pre-transplant evaluation. The efficacy of hepatoprotective agents to reduce drug-induced liver injury when given in combination with antitubercular therapy needs to be studied.

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