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# Interpretation of expert recommendation on diagnosis and treatment of anti-tuberculosis drug-induced liver injury

*Feng Li, Shuihua Lu*

Department of Tuberculosis, Shanghai Public Health Clinical Center, Public Health Clinical Center Affiliated to Fudan University, Shanghai 201508, China

Chinese Society for Tuberculosis, Chinese Medical Association and Editorial Committee of Chinese Journal of Tuberculosis and Respiratory Disease together have formulated an expert recommendation on diagnosis and treatment of anti-tuberculosis (TB) drug-induced liver injury (DILI) (hereafter expert recommendation).[1] The expert recommendation provides specific suggestions regarding the diagnosis and treatment of DILI due to anti-TB drugs, which is of practical values to clinical practice. We aim to interpret expert recommendation so as to better guide the management of anti-TB DILI in clinical practice.

## FORMULATING DEFINITION OF ANTI-TUBERCULOSIS DRUG-INDUCED LIVER INJURY

Expert recommendation definitely states that "Anti-tuberculosis drug-induced liver injury refers to hepatocellular toxicity that drugs or their metabolites induce or to hypersensitivity-induced pathological process in which the liver reacts to drugs or their metabolites." Diagnosis is made when serum biochemical indicators meet one of the following criteria:

1. Alanine aminotransferase > twice of the upper limit of normal (ULN) or conjugated bilirubin > twice of the ULN;
2. Simultaneously elevated aspartate aminotransferase, alkaline phosphatase, and total bilirubin, and at least one item > twice of the ULN.

**Address for correspondence**:
Dr. Shuihua Lu, Department of Tuberculosis,
Shanghai Public Health Clinical Center, Public Health Clinical Center Affiliated to Fudan University, Shanghai 201508, China.
E-mail: tubercle@shaphc.org

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This definition clearly elucidates that diagnosis of anti-TB DILI is based on abnormalities of serological, biochemical indicators as well as a corresponding relationship between DILI and administration of anti-TB drugs. Moreover, DILI due to other factors rather than anti-TB drugs needs to be excluded. Guidelines released by different countries and regions all emphasize abnormalities in hepatic indicators, yet differences exist in specific criteria. The expert recommendation has a higher sensitivity and safety. Those patients whose hepatic indicators do not meet the diagnostic criteria should undergo monitoring.

## INCIDENCE AND RISK FACTORS OF ANTI-TUBERCULOSIS DRUG-INDUCED LIVER INJURY

The reported incidence of anti-TB DILI differs among different countries and regions, even greatly in some cases. Its rate is approximately 2.55% in China.[2] This difference is associated with multiple factors, such as race, social and economic status, geographical position, the diagnostic criteria that researchers adopted, the prevalence, and preventive treatment of viral hepatitis. Reports regarding DILI primarily come from European and Asian countries as well as the United States. India has a higher incidence of DILI than any other Asian countries. Morbidity of DILI due to anti-TB drugs differs in a drug-specific manner. Isoniazid is a more common drug to induce DILI in Europe and the United States, whereas aldinamide and rifampicin are among the most common drugs in China. So far, aminoglycoside, capreomycin, cycloserine, or linezolid have been rarely reported to induce DILI.

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Clarifying risk factors will contribute to the prevention and early detection of and subsequent timely intervention for DILI; however, different risk factors have been reported in different regions. Expert recommendation recognizes aging, heavy alcohol consumption, infection with a hepatitis virus, or comorbided with other acute, or chronic liver diseases, malnutrition, HIV infection, genetic susceptibility factors, etc., are well-established risk factors for DILI. Bringing up these risk factors is of significance to clinicians to identify the high-risk population of DILI.[3]

China is gradually stepping into an aging society, and HIV infection manifests an increasing trend year by year. For people with these risk factors, special attention should be given during anti-TB treatment. Particularly, China bears a high burden of viral hepatitis B. According to a retrospective cohort study in 2007, the incidence of liver injury was markedly higher in TB patients with positive hepatitis B virus markers or a history of liver diseases than in TB patients without. Moreover, social issues due to rapid economic development, such as food safety, quality of Chinese herbal medicine, environmental pollution and life stress, might affect the liver function of healthy individuals. As a result, it is necessary to screen patients undergoing anti-TB treatment.

## MECHANISMS AND CLINICAL MANIFESTATIONS OF DRUG-INDUCED LIVER INJURY

Expert recommendation points out there are mainly two mechanisms of anti-TB DILI. (1) The first one refers to direct hepatotoxicity, also termed predictable DILl, caused by drug metabolites, characterized by a dose-dependent relationship. (2) Idiosyncratic liver injury, also termed unpredictable DILI, falls into the scope of hypersensitivity, without the presence of a dose-dependent relationship. The former acts by anti-TB drugs are directly passing into the hepatocytes, inducing direct organelle (such as mitochondria and microsome) injury. The latter can be nonimmunological or immunological specific. In terms of nonimmunological pathways, the drug intermediates impair the cytomembrane and protease through lipid peroxidation and covalent bonding proteins, eventually resulting in cell necrosis or apoptosis. In the immunological approach, drug intermediates react with autologous proteins, forming antigens and triggering antibody-dependent cell mediated cytotoxicity and T-cell mediated delayed hypersensitivity, giving rise to serious hepatitis, malformation, or even cancer. In idiosyncratic liver injury, congenital factors (gene polymorphism) play a part in some cases whereas acquired factors may be involved in others. Far more complicated than the direct hepatotoxicity, the latter may also give rise to varied prognosis. A rapid recovery is expected in some cases while progressive exacerbation is seen in others. Clinically, DILI with severe outcomes more often works through this manner.

Anti-TB DILI is often seen within 3 months after exposure to the causative drug. Its clinical manifestations show no apparent difference, as compared with those of DILI due to other drugs. It is asymptomatic in mild cases, with abnormal liver function detected only in liver function tests, whereas liver failure even death may ensue in severe cases. Expert recommendation classifies DILI into five categories according to clinical manifestations, covering all types from asymptomatic to liver failure. In general, major manifestations of anti-TB DILI mainly include those due to liver system dysfunction and systemic manifestations as a result of hypersensitivity reaction.[4]

## DIAGNOSIS OF ANTI-TUBERCULOSIS DRUG-INDUCED LIVER INJURY

Serological testing and clinical manifestations may facilitate the diagnosis of liver injury, yet thorough analysis is needed to confirm the relevance between liver injury and the use of anti-TB drugs. Anti-TB DILI does not have any specific clinical manifestations, biochemical or molecular indicators. The reliability of evaluation is therefore mainly determined by the integrity of data and strength of supportive data of the patient. It should be noted that to exclude liver injury due to causative agents (even nonmedical factors), a thorough and detailed history including past history, complications, medical history, and personal history is quite crucial.

First, liver injury caused by preexisting liver diseases and comorbidities should be ruled out. Any history of liver or biliary tract disease or history of alcoholism consumption should be further queried. As for comorbidities, attention should be paid to the exclusion of liver injury due to autoimmune diseases, hereditary or metabolic hepatopathy, occupation or environmental toxins.

For liver injuries of undetermined origin, it's important to rule out the possibility of autoimmune diseases. Read the package insert closely no matter what drugs are taken, including those for comorbidities. Now that prolonged administration of Chinese herbal medicine or health products is prevalent among geriatric patients; it is significant to refer multiple resources of the certain medicine or health product. Should never rush to the conclusion of anti-TB drug inducing DILI.

Four diagnostic criteria put forward by expert recommendation are (1) time of onset: Usually, liver injury in most cases occur 5 days to 2 months after taking the anti-TB drug, but it can occur within 5 days when idiosyncratic reactions arise. (2) Clinical course: Abnormal biochemical indicators of the liver restore to normal after drug withdrawal. (3) Liver injury due to other causative factors or diseases should be ruled out. (4) Positive drug reaction is present when the drug is reused. All DILI is characterized by medication exposure before the liver injury, whereas the latency of liver injury varies from one drug to another.

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DILI caused by anti-TB drug occurs approximately 2 or 3 months after medication exposure generally and at the middle or late stage of therapy rarely. In general, the elevated biochemical indicators of the liver may gain a rapid recovery, but may linger for some time when the drug is discontinued. As for "Positive drug reaction is present when the drug is reused," one would not fail to notice that this serves as a significant diagnostic evidence for confirming its correlation with DILI. However, it still suffers risks, especially for those patients with a history of severe liver injury. Such risk sometimes can be fatal. Moreover, reusing the drug does not always result in a relapse of liver injury. As a result, the absence of positive drug reaction itself cannot exclude the possibility that previous liver injury was induced by the drug. In this situation, more clinical information is needed to make an integral analysis.

In many cases, an accurate and definite diagnosis of anti-TB DILI is not easy to make. For this reason, expert recommendation offers criteria for diagnosing suspected cases and recommends the Roussel Uclaf Causality Assessment Method Scale, the international consensus revised in 1993, for quantitative assessment. Currently, to assist clinicians in diagnosing DILI with better accuracy, plenty of research institutions have put forward multiple scoring systems, such as the CIOMS standard, the simplified CIOMS standard (M&V standard), and the DDW-J standard updated in 2004. Each of the criteria has its own benefits and drawbacks. These criteria, in general, are rather complicated and incapable of ruling out other drugs taken simultaneously. For this reason, they are by no means to replace the clinical diagnosis, but only used for quantitative assessment.[5,6] The Food and Drug Administration also set up the evaluation of drug-induced serious hepatotoxicity for the clinical trials.

## MANAGEMENT OF ANTI-TUBERCULOSIS DRUG-INDUCED LIVER INJURY

Timely detection and adequate management of anti-TB DILI are crucial to disease control and safety. However, due to complex mechanisms, comorbidities, and varied medications, the diagnosis of anti-TB DILI, more often, is just a general evaluation, with many controversies over specific medical measures. Therefore, expert recommendation introduces major principles employed in disease management.

As to discontinuation of the drug, expert recommendation offers suggestions for three subcategories according to biochemical indicators and clinical symptoms. It is so classified for the benefits of patients, i.e., safety. Among patients with anti-TB DILI, some suffer from adaptive liver injury. If they keep taking drugs at the same dosage, their abnormal hepatic function indicators may be gradually restored to normal. This is because the liver has adapted to the injury factors until complete compensation. Clinical reports on increased serum enzymes or even aminotransferase >1000 U/L can be seen in these patients. Rarely, bilirubin 4 times or greater than ULN can also be seen in very few patients with jaundice.[7] The mechanism of adaptive liver injury is not clear so far,[8] which makes the diagnosis of adaptive liver injury rather difficult. More importantly, a wrong diagnosis always leads to severe consequences. Thus, the similar assessments of patients who have shown apparently abnormal hepatic function are not recommended. However, for those with mild liver injury but with severe TB where drug discontinuation is not recommended, the original treatment regimen of anti-TB medications can be followed with hepatic function monitored.

Preventive treatment for hepatoprotection during anti-TB therapy refers to the use of liver-protective drugs before the abnormal hepatic function, which remains controversial.[9] On one hand, there were indeed some studies supportive of preventive treatment for hepatoprotection,[10] while on the other hand, credible and large-scale clinical data are scant. In China, there are clinical studies on liver-protective drugs. However, the quality of the literature was poor, and the evaluation of efficacy and safety were a lack of evidence. In addition, publication bias may be present in these studies.[11] For this reason, expert recommendation recommends the preventive treatment for hepatoprotection only for those patients with high-risk factors.

## APPLICATION OF ANTI-TUBERCULOSIS DRUGS AFTER LIVER FUNCTION RECOVERY

Similarly, there has been much controversy regarding the choice of the anti-TB drug after liver function recovery. Both American Thoracic Society (ATS) and British Thoracic Society (BTS) offered their own recommendations. However, reports showed that there were no statistically significant differences in the incidence of relapsed DILI between the ATS regimen, BTS regimen and the treatment regimen with high-dose isoniazid, rifampicin, and pyrazinamide since day 1 of medication.[12] Apparently, the latter regimen can be rather hard to be promoted in China. This is partly because the data analysis in this study necessitates further discussion. More importantly, the pathological mechanisms of DILI in different countries and races may differ. Therefore, an expert recommendation put forward a medication guide in adherence with the particular conditions in China. Generally speaking, anti-TB drugs should be used in accordance with specific conditions. If the severe liver injury is present, drugs in the original plan should be best avoided; If the liver injury is not severe, drugs in the original plan can be selected after weighing the benefits and risks; If the liver injury is actually an adaptive injury, then the original drugs can be used absolutely; for patients who ultimately fail to gain a full recovery from liver injury, the principle of no additional elevated hepatic function indicators should be observed as to the choice of anti-TB drugs for later treatment.

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## SUMMARY

DILI is the most common toxic adverse reaction during anti-TB therapy. If no timely and appropriate treatment is given, it may influence the efficacy of anti-TB therapy, or even jeopardize life. Currently, research in this field is inadequate, and differences have been shown among different countries and races. It is, hence, not appropriate to copy of foreign experience. Therefore, it is of significance to establish our country's own database and undertake research regarding high-risk factors, pathological mechanism, adaptive liver injury, and management of DILI, etc. As for the preventive therapy to protect the liver, large-scale well-designed, well-implemented, and evidence-based clinical experiments are urgently needed to provide support for clinicians.

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### Conflicts of interest
There are no conflicts of interest.

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