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CONSENSUS

Drug-induced liver injury: Asia Pacific Association of Study of Liver consensus guidelines

Harshad Devarbhavi[1] · Guruprasad Aithal[2] · Sombat Treeprasertsuk[3] · Hajime Takikawa[4] · Yimin Mao[5] · Saggere M. Shasthry[6] · Saeed Hamid[7] · Soek Siam Tan[8] · Cyriac Abby Philips[9] · Jacob George[10] · Wasim Jafri[7] · Shiv K. Sarin[6] on behalf of on behalf of the Asia Pacific Association of Study of Liver

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Abstract
Idiosyncratic drug-induced liver injury mimics acute and chronic liver disease. It is under recognized and underrecognised because of the lack of pathognomonic diagnostic serological markers. Its consequences may vary from being asymptomatic to self-limiting illness to severe liver injury leading to acute liver failure. Its incidence is likely to be more common in Asia than other parts of the world, mainly because of hepatotoxicity resulting from the treatment of tuberculosis disease and the ubiquitous use of traditional and complimentary medicines in Asian countries. This APASL consensus guidelines on DILI is a concise account of the various aspects including current evidence-based information on DILI with special emphasis on DILI due to antituberculosis agents and traditional and complementary medicine use in Asia.

Keywords APASL · DILI · Consensus · Guidelines · Hepatotoxicity · Drug-induced liver injury · Medications · Risk factors · Tuberculosis · Antituberculosis drugs · Monitoring · Treatment · Traditional and complimentary medicine

Introduction

Drug-induced liver injury (DILI) is an underdiagnosed and underappreciated causal or contributing factor to liver injury. DILI can mimic features of the entire spectrum of acute and chronic liver disease. The diagnosis of DILI is challenging not only by the lack of specific objective diagnostic tests but also by the low incidence and suspicion for the diagnosis in the first place. Furthermore, several diseases that need treatment are themselves capable of producing liver test abnormalities which complicate causality; hence, exclusion of a host of diseases by blood tests constitutes a critical part of the diagnosis of DILI.

✉ Harshad Devarbhavi
harshad.devarbhavi@gmail.com

✉ Shiv K. Sarin
shivsarin@gmail.com

1 Department of Gastroenterology and Hepatology, St John's Medical College Hospital, Bangalore, India

2 NIHR Nottingham Biomedical Research Centre, Nottingham University Hospitals NHS Trust and University of Nottingham, Nottingham, UK

3 Department of Medicine, Chulalongkorn University, Bangkok, Thailand

4 Faculty of Medical Technology, Emeritus Professor, School of Medicine, Tokyo, Japan

5 Division of Gastroenterology and Hepatology, Shanghai Institute of Digestive Disease, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, and Clinical Research Center, Shanghai Jiao Tong University School of Medicine, Shanghai, China

6 Department of Hepatology, Institute of Liver and Biliary Sciences, New Delhi, India

7 Department of Medicine, Aga Khan University Hospital, Karachi, Pakistan

8 Department of Medicine, Hospital Selayang, Bata Caves, Selangor, Malaysia

9 The Liver Institute, Center of Excellence in GI Sciences, Rajagiri Hospital, Aluva, Kerala, India

10 Department of Gastroenterology and Hepatology, Westmead Hospital and Sydney West Local Health District, Sydney, Australia

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The consequences from DILI are overarching; it affects patients and their caretakers, regulatory authorities, and drug-development processes. Unintended consequences from a known drug may lead to substantial morbidity and mortality. The occurrence of severe liver disease in a handful of subjects may mar the potential of a new drug gaining approval leading to attrition, and huge clinical financial and logistic losses.

Epidemiology

Asia–Pacific region is characterized by two unique features; the high prevalence of tuberculosis (TB) in the population and the ubiquitous use of traditional and complimentary medicines. Asia is home to 7 of the top 10 countries with TB burden [1]. The first-line drugs used in the treatment of tuberculosis are a major cause of DILI [2]. Similarly, traditional and complimentary medicines are indigenous to the culture of a number of countries and are often integrated into the health system of these countries [3]. Traditional and complementary medicine use is exemplified by the ubiquitous use of traditional and Chinese medicines in China and Korea and ayurvedic medicines in India, with increasing reports of hepatotoxicity from these agents [4, 5]. The incidence varies from 14 per 100,000 people in France [6] to 19 per 100,000 people in Iceland [7]. In South Korea it is 12 per 100,000 inhabitants [8], while it is higher in China with an estimated incidence of 24 per 100,000 [4].

A simplistic but common classification is to stratify DILI into intrinsic or dose dependent or predictable DILI which affects patients who ingest a toxic dose of a drug as in paracetamol (or acetaminophen) toxicity and idiosyncratic (idios "one's own", synkrasis "mixture of personal characteristics") DILI in which the host characteristics rather than a dose of a drug causes DILI as in amoxicillin-clavulanate or phenytoin induced liver injury [9, 10].

This Asia Pacific Association of Study of Liver (APASL) consensus Guidance on DILI will focus primarily on idiosyncratic DILI. The aim is to provide hepatologists, gastroenterologists, internists and other clinical health care providers with information about DILI with emphasis on agents that will enhance awareness, aid diagnosis and help the management of patients with DILI. Furthermore, we will provide clinical practice-based recommendations for the diagnosis and treatment of DILI due to antituberculosis therapy (ATT).

We used GRADE criteria for evidence and recommendations based on the Grading of Recommendations Assessment Development and Evaluation (GRADE) system (Table 1) [11]. The strength of recommendations reflects the quality of the underlying evidence, which has been classified into one of three levels, according to the GRADE system: high (A), moderate (B) or low (C). The GRADE system offers two grades of recommendation: strong (1) and weak (2) (Table 1) [11].

Risk factors

Host dependent risk factors

Age and sex

Advanced age has been associated with a higher incidence of adverse reaction to drugs [12]. Age is considered as a general risk factor for the development of DILI. The causality assessment score Council for International Organizations of Medical Sciences (CIOMS)/Roussel-Uclaf causality assessment method (RUCAM) gives an extra point for age > 55 years [13]. This is possible because of impaired drug clearance with age, as dose-related adverse drug reactions (ADRs) are more common in elderly.

Table 1 Evidence grade used for the APASL guidelines adopted from Atkins et al.

Grading of evidence	Notes	Symbol
High quality	Further research is very unlikely to change our confidence in the estimate effect	A
Moderate quality	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect	B
Low or very low quality	Further research is very likely to have an important impact on our confidence in the estimate of effect and may change the estimate effect. Any estimate of effect is uncertain	C
Grade of recommendation	Notes	Symbol
Strong recommendation warranted	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient- important outcomes, and cost	1.
Weaker recommendation	Variability in preferences and values, or more uncertainty: more likely a weak recommendation is warranted. Recommendation is made with less certainty; higher cost or resource consumption	2

The findings from the population study from Iceland showed an increased incidence of DILI with advancing age in both men and women [7]. The age standardised incidence increased from 9/100,000 in the age group 15–29 years to the highest incidence of 41/10,000 in those aged above 80 [7]. Contrastingly, the Spanish DILI registry [14] evaluated 603 cases of idiosyncratic DILI between 1994–2007 and found 46% of the cases in those above 60 years; cholestatic pattern of hepatitis was more common in elderly compared to hepatocellular pattern in the younger patients. There was no gender preponderance in patients with DILI but more severe disease (liver failure/liver transplantation) was seen in younger females. Both men and women in the > 60 years age group exhibited higher body mass index ($p < 0.0001$) and a shorter time from onset and duration of treatment prior to the onset of DILI compared with younger patients. In the US DILIN registry of 899, older adults (65 years or older) constituted only 16.6% of the overall cohort with a preponderance of cholestatic pattern of liver injury [15]. Mortality and rate of liver transplantation were not different across different age groups and more women (65%) had hepatocellular injury [15].

Some specific drugs also have age-specific increase in adverse effects. Advanced age is a risk factor for Isoniazid hepatotoxicity [16] with a twofold more prevalence in the 35–49 years age group and almost a fivefold more prevalence in those over 50 years in comparison to patients in the 25–34 years cohort [17]. In contrast, valproic acid-related hepatotoxicity is more common in young patients with a higher risk in less than 10-year-old and the highest risk in those below 2 years of age [18].

Guidance statement

Age is possibly a risk factor for the development of DILI with a higher prevalence of cholestatic type in the elderly (grade B evidence, Retrospective cohort studies).

Female sex is generally considered a risk factor for the development of DILI. (Grade C evidence, case series).

Hepatocellular DILI progressing to acute liver failure and need for transplant is more frequent in female gender and younger patients (grade B evidence, Retrospective cohort studies).

Race/genetics: Various single nucleotide polymorphisms (SNP) have been associated with the responses of an individual drug. Slow type SNPs in *N*-acetyltransferase 2 (NAT2) were associated with an increased risk of ATT-related DILI in East Asian and Middle Eastern regions [19] but the risk was only minimal in an Indian study [20]. Human leukocyte antigen (HLA) class II haplotype, HLA-DRB1*15:01-DQB1*06:02 and Class I allele, HLA-A*02:01 have been independently associated with Amoxicillin-clavulanic acid-related liver injury [21]. A recent multi-ethnic genome-wide association study (GWAS) study involving a large cohort of patients, identified rs2476601 a nonsynonymous polymorphism that encodes a substitution of tryptophan with arginine in the protein tyrosine phosphatase, non-receptor type 22 gene (PTPN22) as a non-HLA variant associated with risk of liver injury caused by multiple drugs; these results were validated in a separate cohort [22].

Statement: Ethnicity (both HLA and non-HLA polymorphisms) is an important risk factor for the development of DILI (grade A evidence, large multi-ethnic cohort studies).

Alcohol: Alcohol consumption has been considered a risk factor for the development of DILI and any level of consumption merits an extra point in the CIOMS/RUCAM causality assessment scale [13]. Chronic alcohol use induces CYP2E1, and hence increasing acetaminophen-related toxicity via increased formation of *N*-acetyl-*p*-benzoquinone imine (NAPQI). Alcohol is also a risk factor for idiosyncratic DILI caused by many drugs like isoniazid, methotrexate, and halothane [23]. However, alcohol had no or minimal effect in the DILIN study [15].

Statement: Chronic alcohol consumption can be an important risk factor for DILI due to acetaminophen, isoniazid, halothane and methotrexate (level C evidence, case series).

Pregnancy: Pregnancy as a risk factor for the development of DILI is debatable and no strong evidence is available either to support or refute the association. Many drugs like methyldopa, hydralazine, propylthiouracil, and antimicrobials have been implicated in DILI during pregnancy. Tetracycline is known to cause microvesicular steatosis of the liver/acute fatty liver of pregnancy. Overall, the role of pregnancy as an independent risk factor for DILI is debatable.

Statement: Pregnancy as an increased risk factor for the development of DILI is debatable with the current level of evidence (level C evidence, case series).

Comorbidities: The data on the effect of comorbidities on susceptibility to DILI is lacking. No RCTs or good-quality studies are available to confirm or refute the same. The risk of development of fatty liver with tamoxifen was increased when restricted to obese and overweight women on 2 years follow-up. The other risk factors implicated in the development of fatty liver were the presence of hypercholesterolemia and hypertension [24]. In another study, the odds of development of non-alcoholic steatohepatitis (NASH) increased 8.2 fold when the breast cancer patients were treated with tamoxifen and the liver enzymes returned to baseline after it's discontinuation [25]. Additionally the odds of NASH increased by 13% for every kilogram increase in weight and decreased by 5% for every year increase in age. Hence the presence of metabolic syndrome or obesity increases the risk of tamoxifen-related DILI.

There is a paucity of regarding the risk of DILI in patients with chronic liver disease because such patients are excluded from clinical trials of new drugs. Patients with chronic liver

disease are not uniformly prone to develop DILI [26, 27]. Presence of liver cirrhosis is likely to increase the risk of development of DILI with a higher risk for the complicated course and adverse outcome from DILI [28]. In the USDILI network data, 10% of the 899 patients had pre-existing chronic liver disease and the severity of the liver injury tended to be higher in those with pre-existing liver disease; there was also a higher mortality in that group in comparison to those without liver disease (16% vs 5.2%; $p < 0.01$) [15]. Altered pharmacokinetics and pharmacodynamics, due to altered liver synthetic and metabolizing functions along with low albumin, presence of ascites, portal hypertension and collaterals, are deemed to have an effect on drug-related adverse effects in patients with pre-existing liver disease.

Statement: Presence of pre-existing metabolic syndrome and obesity poses an increased risk of DILI due to specific drugs like tamoxifen, and methotrexate (level A evidence).

Underlying liver disease increases the risk of development of DILI with an increased risk of adverse outcomes and mortality (level A evidence).

Drug-interactions Given the ever-increasing array of drugs that are being administered in the treatment of various human diseases, the potential for drug–drug interactions (DDI) also increases. The consequences of such interactions are highly variable and depend in part on the mechanism of action of the drug (whether the toxicity is a consequence of the administered drug or of a metabolite), its metabolism and whether the drug is a dose-dependent or idiosyncratic cause of hepatotoxicity. From first principles, DDI can lead to an increase or a decrease in the effects of a drug on a target leading to altered drug efficacy, increased toxicity of one or other drug and in some instances, adverse reactions which include hepatotoxicity. For many drugs, the metabolic and pharmacologic drug disposition pathways are not fully defined, though regulatory approval for newer drugs usually requires some knowledge of the metabolism and especially of drug–drug interactions. Metabolism and biotransformation of most drugs occur in the liver and the cytochrome P450 system, an inducible enzyme system, is responsible for many of these reactions. Among the P450s, CYP3A4/5 is responsible for the biotransformation of at least half of known medications. In the context of liver disease, the risk of DILI is usually similar in patients irrespective of the severity of the underlying liver disease or the presence of cirrhosis. However, as would be expected, should a DILI occur, then the consequences of the injury are more severe in those with cirrhosis and can lead to acute on chronic liver failure.

With the above considerations, there are a list of medications that increase the risk of drug interactions and, therefore, of hepatotoxicity. Among them are the anti-tuberculous and anti-retroviral medications. Perhaps the best-known example is that of isoniazid (INH) hepatotoxicity which is likely related to a byproduct of its metabolism, hydrazine. The latter in experimental studies results in oxidative liver damage. INH is a well-established cause of an acute (sometimes fatal) hepatitis. While concomitant liver disease including chronic viral hepatitis appears to increase the risk of INH hepatotoxicity, an increased predisposition to toxicity occurs likely in the context of rifampicin use [29]. Almost all classes of antiretroviral drugs have been known to cause hepatoxicity, some through mitochondrial dysfunction (e.g., with the nucleoside reverse transcriptase inhibitors) which results in steatosis. Ribavirin use in these patients has been associated with an increased risk of mitochondrial toxicity [30]. Among the non-nucleoside reverse transcriptase inhibitors, efavirenz-associated hepatotoxicity appears to be increased in those on concomitant protease inhibitor treatment [31].

Diagnosis and causality assessment

Clinical-pathological manifestations

No specific finding or test definitively proves that a suspected drug is the cause of liver injury. Exclusion of other possible causes of liver damage based on clinical history, blood tests, liver imaging and/or biopsy is essential for the diagnosis of DILI.

Clinical presentation

Clinical presentations of DILI are usually non-specific and can mimic other liver diseases with varying elevations in liver biochemical tests. Patients with severe DILI may have liver-specific symptoms, including jaundice, ascites and acute liver failure (ALF). Accurate clinical history of exposure to medication(s) and onset as well as the course of symptoms, and liver test abnormalities are important clues for diagnosis. There is increasing evidence for the use of herbal and dietary supplements (HDS) and their propensity to cause hepatotoxicity [32, 33]. A high degree of awareness and knowledge of potential drug-related adverse effects on the liver will enhance the precision of history taking. DILI events usually happen from several days to 3 months after taking a new medication, but there are exemptions. Some drugs can cause liver injury after years of use (minocycline, nitrofurantoin, statin, amiodarone) [15]. Most DILI cases resolve spontaneously after stopping the suspected drugs within 3 months (dechallenge) [34]. However, a minority of injuries can be progressed to ALF or chronic DILI [35]. Older age, dyslipidemia, acute severe DILI and statins are associated with chronicity [35]. Liver injury from drug-induced hypersensitivity reactions may have clinical features

of skin rash, fever, periorbital edema, lymphadenopathy, and eosinophilia. Skin rashes can vary from maculopapular rashes to severe lesions such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, and Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN) [36]. Prominent causes of liver injury with skin hypersensitivity reactions include carbamazepine, phenytoin, and allopurinol [37–39].

Recommendation 1 Suspected drug-induced liver injury patients should be evaluated completely which includes obtaining a thorough history of intake of drugs and assessment of the pattern of liver injury based on serum biochemical tests and exclusion of other causes of liver disease. Knowledge of potential drug-related adverse effects on the liver and a high degree of awareness of DILI would enhance the precision of history taking.

Grading of evidence: A. Grading of recommendation: strong (1).

Patterns of DILI

Case definition of DILI is proposed if one of these following thresholds are met 1) alanine aminotransferase (ALT) $\geq 5 \times$ upper limit of normal (ULN), 2) alkaline phosphatase (ALP) $\geq 2 \times$ ULN (especially with an elevation of gamma-glutamyl transferase (GGT) or after ruling out primary bone pathology in cases of isolated elevation of ALP), (3) ALT $\geq 3 \times$ ULN plus total bilirubin (TB) $> 2 \times$ ULN [10].

Acute DILI can be classified into three patterns based on serum biochemical profiles: hepatocellular, cholestatic, and mixed injury. Type of liver injury is categorized by *R* value, which is defined as serum ALT/ULN divided by serum ALP/ULN. The *R* ratio of ≥ 5 indicates hepatocellular, ≤ 2 cholestatic, and $2 < R < 5$ mixed injury [10, 40]. Certain drugs have signature injury patterns, for instance, acetaminophen, isoniazid, diclofenac for hepatocellular injury, and androgenic steroids, captopril, erythromycin, cloxacillin for cholestatic injury while others, such as phenytoin, sulfonamides, and enalapril cause mixed injury [41]. However, many drugs can cause more than one pattern of liver injury and the proposed signature for each drug should be made with caution [41].

Recommendation 2 Three patterns of DILI based on the baseline serum ALT and ALP ratio from the first available biochemical test help categorize DILI as hepatocellular, cholestatic, or mixed injury. The *R* value is a standard and reliable tool to correlate between the biochemical injury and the pathological injury pattern in DILI.

Grading of evidence: B. Grading of recommendation: strong (1).

Specific phenotype

Phenotype characterization of DILI (see Table 2) is helpful in defining the pathogenesis, diagnosis and causality assessment.

Table 2 Drugs producing DILI and their phenotypic presentations

Phenotype	Manifestations	Typical agents
Acute hepatic necrosis	Initially, abrupt AST and ALT elevation with mild ALP or TB elevation ± jaundice. Later marked AST and ALT and bilirubin elevation	Acetaminophen, isoniazid
Bland cholestasis	Marked and prolonged jaundice, pruritus. Moderate ALT and ALP elevation	Anabolic steroids, estrogens
Cholestatic hepatitis	Marked pruritus and jaundice with high ALP elevation, mild ALT elevation	Amoxicillin- clavulanate, Cephalosporins
Drug-induced autoimmune hepatitis	Acute DILI with serologic tests ± histology compatible with idiopathic autoimmune hepatitis	Nitrofurantoin, minocycline, diclofenac, statins
Acute fatty liver	Non-specific symptoms to ALF. Moderate ALT elevation and lactic acidosis.	Didanosine, stavudine, aspirin and valproate
Drug-associated fatty liver disease	Non-alcoholic fatty liver disease due to specific drugs. Mild ALT ± ALP elevation	Tamoxifen, glucocorticoids,
Granulomatous hepatitis	Moderate to high ALP elevation ± jaundice	Isoniazid, allopurinol, carbamazepine, sulfa drugs
Nodular regenerative hyperplasia	Non-cirrhotic portal hypertension, minimal ALT and ALP elevations	Azathioprine, oxaliplatin, didanosine
Sinusoidal obstruction syndrome	Abdominal pain, hepatomegaly ± jaundice. Variable enzyme variations	Busulfan, cyclophosphamide, gemtuzumab ozagamicin
Vanishing bile duct syndrome	Persistent pruritus and jaundice with prolonged ALP and bilirubin elevation	Amoxicillin/clavulanate, penicillins, sulfa drugs, NSAIDs
Liver tumors	Liver mass(es)	Androgenic steroids, estrogens

DILI secondary to drug-induced autoimmune hepatitis (DIAIH) is a syndrome characterized by liver injury with laboratory and/or histology evidence of autoimmunity due to drug ingestion. DIAIH has been reported in 9% of patients with DILI [42]. Female predominance, acute onset, and absence of cirrhosis are important manifestations [43–45]. Using the Simplified Scoring System of the Autoimmune Hepatitis Group is also a helpful approach for DIAIH diagnosis [46]. Both idiopathic AIH and DIAIH have similar clinical symptoms, serological testing and histological patterns except that patients with DIAIH have no cirrhosis on histology and there is often the resolution of the injury after stopping the causative drug without a requirement of long-term immunosuppressive therapy [43]. Liver biopsy typically shows interface hepatitis with portal and periportal infiltrates of lymphocytes and plasma cells. Drugs that have been reported to cause DIAIH include nitrofurantoin, minocycline, methyldopa, statins, diclofenac, anti-tumor necrosis factor α, and herbal products [42, 47, 48].

Recommendation 3 Drug-induced autoimmune hepatitis is not uncommon entity and needs complete investigations including the Simplified Scoring System of the AIH group, serological testing and liver biopsy.

Grading of evidence: A. Grading of recommendation: strong (1).

Drug-associated fatty liver disease (DAFLD)

DAFLD is a rare form of DILI with less than 2% of non-alcoholic fatty liver disease (NAFLD) caused by drugs [49]. The pathogenesis of DAFLD is complex implicating many biological pathways of hepatocyte lipid metabolism. Patients with DAFLD usually present with chronic mild to moderate hepatitis resembling NAFLD and sometimes present with worsening of pre-existing NAFLD caused by the drug. Since NAFLD is common affecting 24% of the general population [50], a diagnosis of DAFLD is challenging and should be based on the recent elevation of serum aminotransferase or presence of hepatic steatosis. Liver biopsy shows macrovesicular or microvesicular steatosis and steatohepatitis depending on the mechanism of a specific lipotoxic drug. Medications that commonly cause fatty liver include methotrexate, tamoxifen, amiodarone, and 5-fluorouracil [24, 25, 51–53]. DAFLD is associated with dose and duration of the medication intake. The decision on whether to continue or stop the drug will depend on evaluating the benefits of therapy against the risks of liver disease progression.

Recommendation 4 Drug-associated fatty liver disease is an uncommon entity likely caused by specific drugs especially hormonal medications. These medications should be considered as risk factors for fatty liver; appropriate investigations to exclude other possible causes of liver disease should be pursued.

Grading of evidence: B. Grading of recommendation: strong (1).

Laboratory tests

There is currently no specific biomarker for the diagnosis of DILI. Diagnosis of DILI depends on serum liver biochemistry tests and laboratory or imaging tests to exclude other possible causes of liver diseases. Liver biopsy is not routinely performed in all suspected cases with DILI.

Serum amino transferases (alanine amino transferase-ALT, aspartate amino transferase AST), alkaline phosphatase (ALP), and serum total bilirubin (TB) are the hallmarks for determination, characterization, and severity grading for patients with DILI [10]. For these purposes, the first available blood test at the onset of the clinical presentation should be used since the serum chemistries may change overtime during disease progression [54]. ALT may be replaced by AST, when ALT is unavailable and when there is no concurrent muscle disease contributing to rise in AST [10]. The overall agreement of AST/ALP and ALT/ALP in determining the pattern of liver injury was 76% with 96% agreement on hepatocellular injury pattern [35, 55]. Gamma-glutamyl transferase (GGT) can't be used as ALP substitute due to low reliability [55]. In addition, laboratory assessment should include serum albumin and INR to evaluate the severity of liver damage. Prolonged INR > 1.5 indicates impending liver failure. The presence of hepatocellular DILI and jaundice without findings of cholestasis (AST or ALT > 3 × ULN, ALP < 2 × ULN) is related to ALF and leads to death or transplantation > 10% of patients (Hy's law) [34, 56, 57]. The degree of liver enzyme elevation alone may not reflect the severity of liver damages [10]. Some phenotypes of liver injury such as sinusoidal obstruction syndrome or liver tumors require imaging studies or liver biopsy as additional tools for diagnosis. Patients with DILI should be monitored serially with serum liver chemistry tests until complete normalization for diagnostic reassurance.

Recommendation 5 Serial ALT level measurement and assessment of serum albumin, INR, and bilirubin should be done being the standard tool to evaluate the severity of liver damage during the course of monitoring a patient with DILI.

Grading of evidence: C. Grading of recommendation: strong (1).

The pattern of liver injury provides useful guidance on diagnostic approach and further investigations. Patients with hepatocellular or mixed pattern of DILI should be investigated for acute viral hepatitis A, B, C and E (detection of anti-hepatitis A virus IgM, anti-hepatitis B virus core

protein IgM or hepatitis B surface antigen, detection of anti-hepatitis C virus antibodies, and detection of anti-hepatitis E virus IgM) and AIH (assessment of anti-nuclear antibodies, anti-smooth muscle antibodies, serum IgG levels, and/or liver biopsy). A history of significant alcohol use should be obtained. Testing for cytomegalovirus, Epstein–Barr virus, and herpes simplex virus infection should be undertaken when indicated or suspected especially in immunocompromised patients or extrahepatic manifestations such as rash, lymphadenopathy, splenomegaly, or herpetic lesions are present. Wilson's disease in patients younger than 40 years and Budd–Chiari syndrome in those with hepatomegaly with/without ascites should be considered in the differential diagnosis of DILI. In patients with DILI with cholestatic pattern of injury, imaging of abdomen should be performed to exclude biliary dilation or obstruction. In such patients, if abdominal imaging is normal, testing for antimitochondrial antibody (AMA) should be considered to exclude primary biliary cholangitis (PBC) in an appropriate clinical setting.

Recommendation 6 Testing for anti-HAV IgM, IgM anti-HBc HBsAg, anti-HCV, anti-HEV IgM as well as ANA, anti-smooth muscle antibodies and serum IgG levels should be done in all patients with a suspected diagnosis of DILI. This is particularly important when they have hepatocellular or mixed pattern of liver injury.

Grading of evidence: B. Grading of recommendation: strong (1).

Imaging

Ultrasonography of the abdomen should be done routinely in all patients with suspected DILI to exclude focal liver lesions and tumors, biliary dilation or obstruction, and pancreatic lesions. Additional investigations like CT, MRI, MRCP, or PET scan may be considered depending on the clinical situation. Secondary Sclerosing Cholangitis could be drug related. Chemotherapeutic agents occasionally can give imaging of sclerosing cholangitis [58, 59].

A detailed history along with a diagnostic non-invasive cholangiogram obtained by MRCP may be useful in such settings.

Recommendation Ultrasonography of the abdomen should be done routinely in all patients with suspected DILI. CT scan, MRI, MRCP, and PET scan may be considered if clinically indicated.

Grade B. Evidence 1.

Liver biopsy in DILI

The diagnosis of drug-induced liver injury (DILI) and herb-induced liver injury (HILI) is indeed challenging, because histopathological features may mimic any primary hepatic or biliary disease. This challenge is compounded by polypharmacy and comorbidities that affect the liver.

Histological pattern

A wide range of histopathological features of the liver has been described in numerous reports of DILI cases [60]. Hence the results of liver histology are considered non-specific and do not allow DILI diagnosis with the required certainty [10].

Acute hepatitis is the most common histological pattern of DILI. Overall, the histological features of acute hepatitis caused by DILI may be indistinguishable from other causes of acute hepatitis like acute viral hepatitis, initial presentation of autoimmune hepatitis, and Wilson disease. The presence of prominent eosinophilic infiltrates, granulomas, and sharply defined perivenular necrosis favors adverse drug reaction [61], but again, none of these features is DILI or specific.

Acute drug-induced cholestasis is another feature of DILI, with two different histological varieties; one showing bland cholestasis and the other one signs of an acute cholestatic hepatitis [60]. The histological pattern of the acute drug-induced cholestatic hepatitis may mimic obstructive biliary diseases and cholestatic forms of both autoimmune hepatitis and acute viral hepatitis, requiring thorough distinction. Drugs may also cause chronic cholestatic diseases including the vanishing bile duct syndrome with ductopenia, which should be differentiated from primary hepatobiliary diseases such as primary biliary cholangitis, primary sclerosing cholangitis, and other conditions causing chronic intrahepatic cholestasis.

The histological pattern of DILI also includes autoimmune hepatitis, granulomatous hepatitis, steatohepatitis, chronic hepatitis, cirrhosis, peliosis, vascular injury including the sinusoidal obstruction syndrome (SOS), Ito cell lipidosis, adenomas, and malignant tumors [60].

Liver histology is commonly of little impact in establishing the diagnosis of DILI, and this shortcoming also applies to HILI. In rare instances of diagnostic uncertainty regarding alternative causes, liver biopsy may be considered as a final diagnostic approach, provided the patient will benefit from this procedure.

Recommendations 1. Liver biopsy may be considered only if an alternative diagnosis needs to be ruled out.

Grade 2, evidence C.

2. Liver biopsy may be considered when patients fail to respond after the withdrawal of suspected medicine or herb.

Grade 2, evidence C.

Causality assessment methods and scales

Causality assessment is a systematic evaluation of the strength of the relationship between drug(s) exposure to drugs and the adverse event(s). Clinicians utilize causality assessment tools routinely in patients care; assessments of adverse drug reactions without a validated method, however, leads to wide disagreements between assessors [62]. Missed diagnosis of DILI may result in serious harm to patients or lead to inappropriate withdrawal of an effective medication [63]. Similarly, causality assessments often used for signal detection related to medicines in clinical trials can significantly impact risk–benefit judgements made by regulatory authorities. The widespread adoption of standardized causality assessment methods not only provides objectivity and consistency to the assessment of suspected DILI but also enhance the accuracy of case definition for epidemiological studies.

Roussel Uclaf causality assessment method (RUCAM)

In collaboration with the Council of International Organizations of Medical Sciences (CIOMS), Roussel Uclaf, French pharmaceutical company developed this method [13, 64]. Seven domains related to suspected DILI event such as time to onset, course, risk factors, concomitantly used drugs, non-drug causes, previous information on drug hepatotoxicity potential, and response to drug re-administration are assessed. Based on the points obtained in each of these domains, an overall score is calculated to classify the likelihood of DILI as excluded (< 1 point), unlikely (1–2 points), possible (3–5 points), probable (6–8 points) or highly probable (> 8 points). Individual domains of the tool have been validated in relation to events when DILI was suspected at initial presentation and the final diagnosis was either DILI or alternative etiology. Interestingly, risk factors were not significantly different between two groups in this evaluation although this domain was included in the final tool [64]. Further validation of the performance of RUCAM was carried out utilizing cases where DILI diagnosis was strengthened by positive re-challenge. Recent American and European Guidelines have recommended the use of RUCAM as the preferred method of formally assessing the causal relation between drugs and liver injury [65, 66].

Clinical diagnostic scale (CDS)

CDS is a causality assessment tool postulated by Maria and Victorino [67]. The scale consists of five categories, temporal relationship between drug intake and the onset of clinical picture, exclusion of alternative causes, extrahepatic manifestations, intentional or accidental re-exposure to the drug and previously published report in the literature of cases of DILI associated with the drug [67]. Assessment is excluded for scores < 6, unlikely for scores 6–9, possible for scores 10–13, probable for scores 14–17, and definite for scores > 17. CDS differs from the RUCAM scale [13] in point values and timing of drug administration to the onset of clinical features, and CDS also allocates points for extrahepatic manifestations (which are not included in the RUCAM), such as rash, fever, arthralgia, eosinophilia (> 6%), and cytopenia [67]. Furthermore, CDS does not have a category of risk factors.

According to a comparison of the RUCAM scale and CDS using 215 DILI cases diagnosed by 3 experts [68], CDS was reported to have lower discriminative power and poorer assessment in reactions that have long latency periods, evolution to chronicity after withdrawal, or death, compared with the RUCAM scale [13]. Furthermore, Tillmann et al. pointed out that the maximum score of 20 in CDS in their report is not achievable [69].

Structured expert opinion process

The structured expert opinion process is a causality assessment postulated by the US Drug-Induced Liver Injury Network (DILIN) in 2010 [70]. In order to facilitate adjudication, the extensive database was summarized in an abbreviated case report form (CRF). In addition, the clinical narrative was completed by the study investigator who enrolled the subject. The CRF summary and clinical narrative were forwarded to three independent reviewers who assessed the likelihood of DILI as unlikely (< 25%), possible (25–49%), probable (50–74%), highly likely (75–95%) and definite (> 95%). Authors reported that the structured expert opinion process produced higher likelihood scores than the RUCAM scale in assessing causality [70]. This major disadvantage of this method is not externally validated and hence, not widely applicable.

Japanese criteria

Japanese criteria were proposed from a workshop held during Digestive Disease Week—Japan 2004, [71] It is a modification of the RUCAM scale [64], and is widely used in Japan. The scale consists of eight categories; time to onset, course, risk factors, search for non-drug causes, previous information on hepatotoxicity of the drug, eosinophilia, drug-lymphocyte stimulation test (DLST), and response to unexpected re-administration [71]. Assessment of likelihood is reported as a low possibility for scores ≤ 2, possible for scores of 3 and 4, and highly possible for scores ≥ 5. The major differences of this criteria from RUCAM scale are as follows: (1) a reaction that occurs more than 15 days after stopping the drug in the hepatocellular type, and more than 30 days after stopping the drug in the cholestatic or mixed

type, is scored as zero, instead of "unrelated" in the RUCAM scale; (2) Concomitantly used drug(s) is not used in the score; (3) Age is not included as a risk factor; (4) serological tests for CMV and EBV are included, while test for herpes virus was excluded; (5) the grading of previous information on drug hepatotoxicity potential is changed to + 1 and 0; and (6) scores of eosinophilia (≥ 6%) and drug-lymphocyte stimulation test (DLST) are added. According to the manual of the Japanese criteria, expert assessment has been assigned a priority consideration in the scale [72]. In addition, anti-HEV IgA antibody test result has been recommended to be included under the category of non-drug causes after it became a part of the national insurance coverage testing in Japan in 2011 [73]. This scale has been misunderstood to have not been published in English by some authors [69, 74]. A major problem of this scale is that DLST using freshly prepared lymphocytes is only available in Japan, the results of which are different when using frozen and thawed cells [75].

Recommendations

RUCAM/CIOMS scale is the preferred causality assessment method to guide the systematic and objective evaluation of patients suspected to have DILI. Grade C.

Evidence: Extrapolation from level 2b studies (exploratory cohort studies with good reference standards).

Rechallenge and recurrent DILI

When the causal agent is promptly withdrawn, 80% of DILI events resolve [76]. Re- exposure to the same drug can lead to the recurrence of DILI (referred to as positive re-challenge) in 11–51% depending upon the individual medication [77, 78].

Largest experience of re-challenge comes from a survey of Glaxo Smith-Kline database 1958–2007. Among 36,795 cases of hepatic adverse events, 1089 were re-exposed to the drug and 648 (59%) resulted in a positive re-challenge response based on the criteria that 1) initial episode was a DILI (defined as ALT > 2 times ULN), and when re-exposed to the medication again there was a further ALT elevation > 2 times ULN [79]. Time to onset of recurrence of DILI was shorter (mean 1 week) than the initial episode (mean 3 weeks).

In certain circumstances, risk–benefit ratio might favour the reintroduction of critical medications. Two intervention trials have addressed the reintroduction of anti-tuberculosis medication following DILI. In a 3-arm trial ($n = 175$) excluding patients aged > 65 years with all regimens containing pyrazinamide DILI recurrence rates were similar (8.6–13.8%) between the groups [80]. In another 2-arm trial ($n = 45$) without age restriction comparing the reintroduction of a pyrazinamide containing regimen vs one without, former was associated with DILI recurrence in 25% (95% CI 9–45%) compared to none in non-pyrazinamide containing arm [81]. A large National Institute for Health Research funded RCT will compare two regimens for the reintroduction of anti-tuberculosis therapy following drug-induced liver injury [82].

In phase 2 and 3 studies (involving over 2000 patients), 103 patients developing pazopanib (selective multitargeted Tyrosine kinase inhibitor) induced liver injury were re-challenged with a weekly monitoring of liver biochemistry. Positive re-challenge (ALT > 3 × ULN) occurred in 38% at a median period of 9 days with the older age group as a risk factor, but none developed jaundice [83].

Genetic testing

Since the introduction of genome-wide association studies (GWAS) [84], the quality of evidence that links genetic risk factors to the development of DILI has improved considerably. These lines of evidence converge to highlight the role of adaptive immune response in the pathogenesis of drug- and herb-induced liver injury [85]. Consistent with this, human leucocyte antigen (HLA) alleles or haplotypes have been associated with DILI related to over 15 currently used drugs [85, 86]. While genetic tests have been readily integrated into the management of inflammatory bowel disease and human immunodeficiency virus infection, their application in the diagnosis of DILI has been limited to specialist centres so far.

Considering the fact that a number of critical drugs such as antibiotics, anti-epileptics, monoclonal antibodies and anticancer agents are associated with DILI, it is important to accurately attribute adverse reaction to a particular drug. Presumptive withdrawal of the agent will interrupt effective care and deprive the patient of drug benefits; on the other hand, re-exposure to the drug has a potential to lead to a serious adverse event. Some of these HLA alleles have > 95% negative predictive value in predicting DILI occurrence [87]. Hence, genetic tests can be used to exclude the diagnosis of DILI or to exclude a specific drug as an etiological agent in clinical situations where more than one medication could have potentially caused DILI.

Exclusion of alternative causes is an important component of causality assessment in a suspected DILI. There are substantial overlaps between DILI and auto-immune hepatitis (AIH). Original International AIH Group score, a tool used for the diagnosis of AIH included carriage of HLA alleles DRB1*03:01 or *04:01 as one of the components [88] while the simplified score that is used more often has only 65% sensitivity [89]. When faced with a clinical decision to permanently withdraw an effective medication in a patient versus initiation of long-term immunosuppressive

regimen, it is justifiable to incorporate genetic tests into diagnostic workup to increase the accuracy and confidence in the diagnosis.

Recommendation

HLA genotyping should be utilised in selected clinical scenarios where genetic tests assist the accurate diagnosis and management of patients.

(Quality of evidence: A, strength of recommendation: weak).

New biomarkers

There is a critical need for DILI biomarkers that would improve (1) early identification of DILI during drug-development, (2) monitoring of DILI during clinical trials, (3) early diagnosis in clinical practice and (4) stratification of those who progress on to develop acute liver failure or develop chronicity in the longer term.

During drug development, organ or tissue specificity of a biomarker is important to identify drug-related adverse reactions and their outcome. Glutamate dehydrogenase (GLDH), located in mitochondria of centrilobular hepatocytes has been considered a liver-specific biomarker to confirm or rule out hepatocellular injury in cases where potential muscle origin of ALT makes latter an unreliable marker [90]. Additional enzymes sch as paraoxonase-1 (PON) malate dehydrogenase (MDH), and purine-nucleoside phosphorylase (PNP) may also address some of the limitations of ALT measurement in DILI.

Overall the outcome of idiosyncratic DILI appears to be worse than that of paracetamol overdose. In an international collaborative study, macrophage colony-stimulating factor receptor(MCSFR), cytokeratin 18 (K18) and osteopontin were identified as biomarkers that predict an unfavourable prognosis. Prediction of liver transplantation or death from liver failure among DILI patients using the Model for End-Stage Liver Disease was improved by incorporation of K18 and MCSFR levels [91]. MicroRNA-122 (miR-122) is a hepatocyte-specific miRNA and in patients with DILI relatively lower levels of serum miRNAs -122, -4463 and -4270 have been shown to be associated with mortality. A combination of low levels of serum albumin and miR-122 had 100% sensitivity for predicting death within 6 months.

Currently, TransBioLine, a consortium supported by the Innovations Medicines Initiative is investigating novel diagnostic, prognostic and mechanistic biomarkers in DILI [90].

Recommendation

Novel biomarkers should be validated to allow early detection and assessment of prognosis of idiosyncratic DILI.

Grade of evidence: C, strong recommendation.

Prognosis and natural history

A. Grading severity

As would be expected for diseases of low incidence including DILI, the prognosis and natural history are highly variable and difficult to determine at an individual patient level, even in severe cases. Outcomes vary from fatal, rapidly progressive disease (as with mitochondrial toxins) on the one hand, to rapid or sometimes gradual resolution and full recovery on the other. In national registries that are subject to recruitment bias towards more severe cases, outcomes of death and/or liver transplantation within 6 months has been reported at between 6 and 9% [34, 57, 92]. Predictors of poor outcomes in DILI include (a) an elevated bilirubin at presentation (b) hepatitis with hepatocellular injury (versus mixed or cholestatic injury) and (c) exposures to agents such as isoniazid, haloalkane anesthetics and sulfonamides are more likely to be associated with severe outcomes. The sentinel observation that hepatocellular injury accompanied by jaundice portends a serious hepatotoxic reaction was first noted by Zimmerman [9]. This landmark study in hepatology has stood the test of time. More recently, Hy's law has been defined as DILI with an ALT more than $3 \times$ ULN and total bilirubin TBL > 2XULN. In a 2014 report from the Spanish DILI consortium (771 patients), 32 developed acute liver failure [93]. Hepatocellular injury, female sex, high levels of TBL, and a high AST/ALT were independent risk factors for acute liver failure [93]. In that study, the authors suggested that at presentation, a TBL > 2ULN + an ALT or AST (whichever was higher $\times$ ULN)/alkaline phosphatase both expressed as multiples of ULN ≥ 5 had the optimal sensitivity and specificity for predicting acute liver failure (63% specificity, 90% sensitivity).

B. Chronic DILI

In contrast to cases of severe DILI, the prognosis and course in non-severe cases is much more variable with injury regressing over weeks, but in some cases years. The latter is exemplified by flucloxacillin hepatotoxicity for which cases have been reported that persist for over 7 years [94]. Given ascertainment and referral bias as well as frequent confounding by fatty liver disease and alcohol (two highly prevalent diseases in the community at large), the true incidence of chronic DILI is difficult to know. In one study from the Swedish DILI registry ($N = 685$), during a median follow-up of 11 years, 3.4% were diagnosed with liver disease at a subsequent hospitalization or at death. Of these, 1.4% had chronic DILI (as no other cause of the liver disease was

discerned) [95]. The true prevalence is likely to be higher if milder cases are included, but such cases are likely to be lost to follow up, or even when known, impacted by concomitant alcohol, metabolic associated fatty liver disease (MAFLD) or commonly used drugs such as statins. When chronic DILI is defined as persistent elevations in liver tests, the overall prevalence was reported at 5.7% in the Spanish registry [34] and up to 18% in the US registry at 6 months [76]. However, whether this represents true chronic DILI is uncertain. Overall, it has been suggested that up to 10% of patients with DILI develop severe disease resulting in death or transplantation, and a similar number is likely to have chronic DILI, while the remaining recover [96].

Treatment of DILI

General measures

The key principles for treating DILI are (1) timely diagnosis by a high index of suspicion, (2) identifying the offending agent(s), (3) prompt withdrawal before irreversible liver damage. Most DILI recovers spontaneously without active treatment after discontinuation of the offending agent(s) [97]. The patient should be educated and given alert card to avoid repeating the use of the offending agent or similar ones with known cross reactivity because continued exposure is associated with the development of severe or chronic liver diseases [44]. Antihistamines such as hydroxyzine or diphenhydramine and/or cholestyramine maybe used to control disturbing pruritus. The role of silymarin or glycyrrhizin in the treatment of DILI is uncertain. Admission is required for those with coagulopathy and/or hepatic encephalopathy indicating the presence of liver failure.

Specific therapies

Cholestyramine

Cholestyramine, a bile acid-binding resin has been used to treat a lethal leflunomide or teriflunomide-induced DILI which can be fatal. Cholestyramine interferes with enterohepatic recycling of leflunomide and its metabolite, thus accelerating its elimination. Cholestyramine is dosed at 8 g 3 times orally daily for 11 days [98].

L-Carnitine

L-Carnitine is an antidote for valproate-induced hepatotoxicity [99] and/or valproate-induced hyperammonemia with encephalopathy in acute overdoses or in therapeutic doses [100]. Early treatment with carnitine reverses encephalopathy [101, 102]. L-Carnitine is administered at 100 mg/kg intravenously over 30 min (but less than 6 g), followed by 15 mg/kg every four hours until clinical improvement [103].

N-Acetylcysteine (NAC)

NAC is a glutathione precursor and is an approved antidote for acetaminophen-induced hepatotoxicity. In a randomized trial intravenous *N*-acetyl cysteine was shown to improve transplant-free survival in non- acetaminophen-induced liver failure but only in early-stage encephalopathy [104]. In another study NAC together with prednisolone when used in cases of severe idiosyncratic DILI due to flupirtine (central acting non-opiod analgesic) showed a significant improvement in ALT, AST and INR within 2 weeks compared to those who were not treated with NAC [105]. NAC has also been used in other causes of DILI induced ALF [104, 106].

Ursodeoxycholic acid (UDCA)

Case reports and series suggested UDCA may improve cholestatic liver injuries associated with certain antimicrobials, steroid-resistant immune checkpoints inhibitors, in combination with prednisolone for anabolic steroids and others [107–111]. However, there is no controlled trial on the benefit of UDCA in DILI.

Steroids

Although controlled studies are lacking, oral or intravenous steroids have been shown to improve both hepatic and extrahepatic manifestations of injury in patients with hypersensitive adverse drug reaction such as in drug rash/reaction with eosinophilia and systemic symptoms (DRESS syndrome). Liver is the most common extrahepatic organ involved in severe DRESS syndrome [112]. Treatment with steroids may sometimes be prolonged and may have to be continued till the liver biochemical tests and/or symptoms return to near normal. Steroids have also been recommended in patients developing hepatotoxicity from immune check point inhibitors, biologicals, and in drugs-induced autoimmune like hepatitis but not in all cases [113–115].

Management of drug-induced acute liver failure (DILI-ALF).

Up to 10% of DILI progresses to ALF, a hepatology emergency [92, 93]. In Western countries, paracetamol induced hepatotoxicity is the etiology in 40% of ALF and 7.1% required liver transplantation within 7 days [116, 117]. In Asian countries, antituberculosis drugs and complimentary medicines are two common causes of DILI-ALF [97]. While idiosyncratic DILI accounts for 8–11% of ALF with overall mortality rates of 31–33% and low spontaneous recovery

rates at 27–35% [118, 119]. About 40% of idiosyncratic DILI-ALF requires liver transplantation [118, 119].

Treatments non-specific to DILI-ALF

Liver transplants for DILI-ALF result in 1 and 5 years survival benefits of about 70–80% [120]. Artificial and bioartificial liver support systems improve liver parameters but do not show survival benefits in randomized control trials. In the albumin dialysis study on ALF with 38% of the subjects had paracetamol-induced ALF, there were no survival benefits compared to standard medical therapy [121]. In the study on high volume plasma exchange (HVPE) in ALF which showed improvement in transplant-free survival, the authors reported similar survival for a subset of paracetamol-induced ALF compared to non-paracetamol ALF in both the control and HVPE arms [122].

Treatments specific to DILI-ALF

Activated charcoal within 1–2 h of ingestion reduces the absorption of paracetamol and NAC or methionine in those with potentially toxic overdose (defined as greater than 7.5 g to 10 g or 150 mg/kg to 200 mg/kg bodyweight or more or plasma paracetamol concentration above risk-line or abnormal liver enzymes or ALF) reduce morbidity and mortality [123]. Charcoal hemoperfusion did not show benefit [123].

For non-paracetamol ALF, randomized controlled trial of NAC (intravenous NAC at 150 mg/kg/h over 1 h followed by 12.5 mg/kg/h for 4 h then continuous infusion of 6.25 mg/kg for 67 h) showed improved outcome in adults with grades I–II hepatic encephalopathy resulting in higher transplant-free survival at 52% compared to 30% in placebo arm [104]. In this study the DILI-ALF subgroup ($n=45$) had the most beneficial effects, NAC improved transplant-free survival to 58% from 27% with placebo [104]. Subsequent studies showed NAC reduced IL-17 a cytokine implicated in hepatic encephalopathy and poor outcome [124] and ameliorates liver injury as measured by a decrease in ALT and bilirubin [125]. Unfortunately, similar studies in the pediatric population did not show benefit from NAC [126, 127].

High-volume plasma exchange has been tried in ALF across diverse etiologies with some success [122]. However, its role specifically in drug-induced acute liver failure is not clear, although its efficacy in improving outcome has been reported in anecdotal cases reports of toxic liver injury and drug-induced ALF.

Recommendations

1. Early diagnosis of DILI, prompt withdrawal and avoiding repeat use of the offending agent are important.
2. Cholestyramine is recommended in leflunomide-induced DILI to accelerate elimination (B,2).
3. L-Carnitine is an antidote for valproate-induced hepatotoxicity and/or valproate-induced hyperammonemia (B, 2).
4. NAC is an antidote for acetaminophen-induced hepatotoxicity. (A, 1) and used with prednisolone NAC improves liver biochemistries and function in flupirtine induced DILI (B, 1).
5. UDCA may improve liver enzymes in DILI with cholestasis, however, it is uncertain whether it helps in the liver injury (C, 2).
6. There is insufficient evidence to recommend cholestyramine, carnitine, NAC and UDCA for DILI beyond the above (C, 2).
7. DILI-ALF needs to be referred urgently for consideration for liver transplant (B, 2). Intravenous NAC is recommended in adults with DILI-ALF (A, 1).
8. High volume plasmapheresis may be an option in DILI-ALF particularly when liver transplantation option is not feasible or accessible (C, 2).

Preventing DILI

The value of liver test monitoring

The best treatment for DILI is diagnosing it early and stopping the offending drug in the pre-symptomatic phase because by the time signs and symptoms appear (particularly jaundice) significant injury would have occurred. Severity of DILI worsens when the insulting drug is continued after the initial onset of injury, which usually remains undetected for varying periods. Elevation in liver enzymes is the first sign to suspect and diagnose DILI. Individual measures of liver function tests should not be assessed in isolation or at one cross-sectional time point. Serial LFTs should be considered at a frequency depending on the level of evidence attributable to the drug in question [128]. Patients can either be a 'Tolerator' (without any derangement in LFT), an 'Adaptor' with transient transaminitis of around less than five times the upper limit of normal, or a 'Susceptible' to DILI with the onset of jaundice and other symptoms and signs of more severe DILI with continued drug use [41]. The idea of serial LFTs is to identify the persons susceptible to DLI at an earlier stage for the timely discontinuation of the offending drug. Pre-existing viral hepatitis or chronic liver disease or alcohol consumption or any other risk factor would necessitate increase in the frequency of monitoring. For example, with Isoniazid therapy, the guidelines suggest monitoring LFT once in two weeks in the initial 8 weeks and once in four weeks beyond that till completion of ATT. ALT elevation beyond three times the upper limit of normal along

with symptoms of fatigue, jaundice, nausea and/or abdominal pain or elevation > 5 times the ULN in the absence of the said symptoms would merit discontinuation of the drug [2].

Statement: LFT monitoring is advisable in case of prolonged prescription of a potential hepatotoxic agent like Isoniazid/combination anti-TB drugs and discontinuation of the drug should be considered in case of significant elevation of transaminases and/or alarming symptoms like jaundice, nausea, abdominal pain (level A evidence).

Class effect and cross reactivity

Certain groups of drugs pose a higher risk of development of DILI as a class antibiotics, anticonvulsants, NSAIDS, checkpoint inhibitors, biologicals such as TNF alfa inhibitors. Many reasons are proposed for this class effect. It may be that these drugs as a class are used more frequently. It may be the class or family effect because of the shared therapeutic targets (class effect) or shared structural features of the group (family effect) [129]. The class effect is responsible for drugs like checkpoint inhibitors, TNF alfa inhibitors, whereas the family effect is proposed as the major mechanism with respect to NSAIDS [130, 131]. Defective adaptation because of gut microbial changes is the suspected mechanism with respect to antibiotics [132]. The importance of knowing the class effect and cross-reactivity lies in the fact that whenever a patient develops DILI, choosing the second drug with the least potential for hepatotoxicity would be essential. The comprehensive database available in the LiverTox (http://www.livertox.nlm.nih.gov) [103] is very useful in selecting safer alternative treatment options, as developed and maintained by the United States National Institutes of Health and the National Institute of Diabetes and Digestive and Kidney Diseases, will be very useful in selecting alternative safer treatment options.

Statement: It is important to understand the class effect and cross reactivity while choosing alternative treatments for a patient who developed DILI (level A evidence).

APASL specific issues in DILI

Traditional and complementary medicine–traditional Chinese Medicine induced liver injury

In Asian countries, Traditional Chinese Medicines (TCMs) have a long history and are widely used to prevent and treat a variety of diseases. In China, TCM refer to Chinese traditional medical herbs and non-herbal substances, or prepared compounds composed of multiple herbs and/or non-herbal components produced under the guidance of TCM theories. In recent years, the global consumption of herbal and dietary supplements (HDS) products is growing rapidly. People may mistakenly believe these products are natural and, therefore, safe [133]. However, it is noteworthy that the evidence of hepatotoxicity associated with TCM/HDS is increasing not only in Asia but also in the West [15].

In most countries, herbs are not included in the drug regulatory system, therefore, the source, contents and quality of the TCM/HDS products are not guaranteed. Therefore, it is difficult to identify the exact ingredients of herbal preparations. In fact, the real ingredients of many herbal products currently in use are complex and usually unclear, particularly in multicompound products. Due to a lack of strict standards and supervision, herbs may be sourced from the substitution of alternate plant species. These may be intentionally or accidentally adulterated with heavy metals, pesticides, herbicides, microorganisms, which could also contribute to hepatotoxicity. Thus, even a safe herbal product may also be contaminated by toxic compounds causing hepatotoxicity.

Besides TCM/HDS products itself, improper use of the medication and host-related factors are also the risk factors. Recent studies indicated that HLA-B*35:01 gene was potentially associated with the susceptibility for polygonum multiflorum-induced liver injury [134]. A panel of metabolomic biomarkers that characterized susceptible individuals were also identified [135].

Epidemiology

The real incidence of TCM/HDS-induced liver injury (TCM/HDS DILI) is unknown because it is almost impossible to know the number of people who use them. The current epidemiological data on TCM/HDS DILI only reflect its proportion among all in DILI patients. In the West, data from DILIN registry indicated that the proportion of HDS DILI cases increased from 7% total during the first 2 years to 20% 10 years later [6], [32]. Another nationwide study from Iceland demonstrated that 16% of DILI cases were attributable to HDS [7].

In Asia, herbal medicine is often the main cause of DILI. A prospective study from Korea indicated that herbs were associated with 27.5% of 371 DILI cases [8]. In Japan, dietary supplements and Chinese herbal medicines accounted for 9% and 6% of cases respectively in a prospective study [136]. In China, a nationwide study including 25,927 DILI cases indicated that 26.81% cases were associated with TCM/HDS products [4].

Several Chinese herbal medicines have been reported to cause liver injury, such as Radix polygon multiflora, Psoralea corylifolia, Epimedium brevicornu, Tripterygium wilfordi, Xanthate, Ligustrazine, Ephedra, Lycopodium serratum, Xiao-Chai-Hu-Tang, etc. Products containing pyrrolizidine alkaloids deserve attention, such as Gynura segetum (Tu-san-qi), Heliotrpium, Symphytum offificinale, Crotalaria and senecio. Many DILI cases are reported to be related to ‘‘Tusanqi” which

is a traditional preparation containing pyrrolizidine alkaloids. The main type of liver injury induced by pyrrolizidine alkaloids is sinusoidal obstruction syndrome (SOS)/hepatic sinusoidal occlusion syndrome (HSOS) [137, 138].

Regulation

Different countries may have different regulatory strategies for TCM/HDS.

In China, TCM is under control by the Chinese regulatory authority. To ensure the supervision on the whole life cycle of TCM, including the whole process from approval, application to post-market evaluation, the China's State Food and Drug Administration (CFDA) released a special guidance in 2018 [139]. The guidance also elaborates on the recognition and collection of risk signals as well as causality assessment for TCM. However, in many countries, TCM/HDS products do not need to undergo preclinical toxicology testing, nor clinical trials for safety or efficacy, and can be marketed without the approval of the regulatory authority.

Causality assessment

In clinical practice, RUCAM scoring is recommended for DILI causality assessment [65, 66, 140]. In the case of HDS hepatotoxicity, we have to realize that current commonly used causality assessment processes were not created specifically for TCM/HDS hepatotoxicity. In the RUCAM, the presence of a labeled warning of hepatotoxicity increases the score. However, warnings usually do not exist on TCM/HDS labels, thus, total score could be reduced. Since expert opinion allows assessors to consider all available clinical information, ACG guidelines prefer to select the expert opinion process for HDS hepatotoxicity [65].

Considering the complexity of TCM/HDS, the evidence-chained method is proposed in the guidance drafted by CFDA for causality assessment [139]. However, this method has not been validated, and its effectiveness and practicability in clinical practice are not clear.

Clinical presentation and diagnosis

Like liver injury caused by conventional medicines, current evidence suggested that TCM/HDS can lead to all patterns of known liver injury, including some special phenotypes [135]. The clinical manifestations are nonspecific and varied, ranging from asymptomatic with an elevation of liver enzymes to acute liver failure.

The diagnosis is extremely challenging. Herbal medications are often used concomitantly with conventional medicines in a clinical setting, which makes it difficult for causality assessment. Since most patients don't actively report the history of TCM/HDS use, carefully asking leading questions for the medical history and obtaining the information of TCM/HDS use is the key to establishing the diagnosis.

The diagnosis strategy is the same as that of liver injury caused by conventional medicines. In general, based on the comprehensive information of TCM/HDS use history, clinical manifestations, physical examination, laboratory, imaging and even liver histology examination, the diagnosis could be finally established by excluding other etiologies of liver injury. There are no specific diagnostic biomarkers for TCM/HDS DILI to date. However, pyrrole-protein adducts detected in the blood may be a potential diagnostic biomarker for pyrrolizidine alkaloids induced liver injury [141].

Management

The preventing management of TCM/HDS DILI includes a series of specific measures, such as improving public awareness of the potential risk of liver injury caused by TCM/HDS products, regular liver biochemical testing for those who use potential risk products for early detection of the signal of liver injury and developing regulatory strategies for the potential hepatotoxicity of TCM/HDS products by regulatory authorities. These regulations could include the issuance of a safety communication, require the need for close observation, specific recommendations for discontinuing treatment, issuing amendments and warning on the product label, a restricting and/or discontinuing of its commercial use of the herbal supplement, etc.

Whether the liver injury is caused by TCM/HDS or conventional medicines, the treatment principle is the same. Timely discontinuation of the suspected TCM/HDS is the most important strategy [140]. Except NAC are recommended in adults with acute liver failure, there is no available drug for the treatment of DILI. However, in China, Magnesium isoglycyrrhizinate (MgIG) which is a glycyrrhizic acid preparation, has been approved by the Chinese FDA for the treatment of acute hepatocellular injury from DILI, after it was shown that it can effectively and safely treat acute DILI in a randomized, controlled clinical trial [142]. It is necessary to monitor the liver injury until its resolution.

Comparison of TCM/HDS injury in China and the West

The most remarkable difference of TCM/HDS DILI between China and the West is the reason for the use/abuse of the causative agents. In the West, HDS DILI is mainly caused by dietary supplements, especially the body building agents [57]. However, in China, most cases were attributed to herbal medicines [4].

Both in China and the West, it seems TCM/HDS DILI may result in worse outcomes than the liver injury caused by conventional medicines. In China, a single-center study

suggested that mortality was higher in the herbal medicine group [143]. In the West, data from DILIN indicated that non-bodybuilding HDS causes more severe liver injury and has a higher liver transplantation rate than medications [32]. Study from Spain also indicated that HDS DILI had a higher incidence of ALF than conventional medicines [144].

APASL consensus on DILI-TCM

Summary

TCM/HDS products are not always safe, increasing evidence suggested that they could induce all patterns of liver injury, including some special phenotypes.

In some countries, herbs are not included in the drug regulatory system. Developing regulatory strategies for the potential hepatotoxicity of TCM/HDS products by regulatory authorities is important for risk management.

Risk factors for TCM/HDS-induced liver injury include TCM/HDS product itself, improper use and host-related factors.

RUCAM may not be the best choice for causality assessment of TCM/HDS hepatotoxicity. In a clinical setting, evidence-chained method proposed by China need to be further validated.

TCM/HDS DILI may result in a worse outcome than the liver injury caused by conventional medicines likely due to late diagnosis.

Recommendations

When making the diagnosis of TCM/HDS DILI, taking a thorough medical history and obtaining the information of TCM/HDS use is important (1C).

The diagnostic strategy of TCM/HDS DILI is mainly by the exclusion of other possible causes, the same as that of liver injury caused by conventional medicines (1C).

Patients with TCM/HDS DILI should have the suspected products discontinued immediately. Monitoring is necessary until recovery of liver injury (1C).

In China, Magnesium isoglycyrrhizinate (MgIG) is an available drug approved by CFDA for the treatment of acute hepatocellular injury including DILI (1A).

Traditional Complementary Medicine: Ayurveda, Yoga, Unani, Siddha, and Homeopathy (AYUSH)-induced liver injury

Epidemiology

The purported efficacy and safety of herbal drugs and the growing antipathy towards evidence-based conventional medicine have led to an increase in the use of complementary and alternative medicines (CAMs) in India, mostly, the Ayurveda system. There is a growing body of information in the form of reports and series on the toxicity associated with classical (practiced by a trained and regulated physician) and traditional (healers, folk-medicine), Ayurvedic and allied herbal medications (AHM) [145]. These AHMs can be non-proprietary /traditional /classical (i.e., the contents, formula, methods of preparation and indications are as per fixed principles stated in an accepted Ayurvedic text) or proprietary (i.e., patended medicines where formula, components, methods of preparation, dosing and indications are decided by the manufacturing company [146]. Until recently, the presumption that both classical and proprietary AHMs are safe and without organ toxicity has been held high among the general and patient population. The incidence, distribution, and determinants of Ayurveda, Yoga, and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) based systems associated with drug-induced liver injury (DILI) and outcomes remain sparsely studied. A National Sample Survey Office study in 2014 and 2016 found that only 6.9% of the Indian population favored AYUSH over conventional medicine, with the urban population more supportive of AYUSH forms of treatment compared to their rural counterparts [147]. A recent Indian national study on DILI found AHM comprised about 13% of all causes of DILI [148]. In a multicenter study on 3,132 patients with acute on chronic liver failure (ACLF), the Asian Pacific Association of Study of Liver (APASL) ACLF Research Consortium (AARC) implicated drugs as precipitating factors in 10.5% patients, and CAMs, inclusive of AHM and dietary supplements, were the most common causes accounting for 71.7% of DILI-related ACLF [149]. In one study, Philips et al. found that approximately 3% of patients presenting to the outpatient and emergency departments had possible or probable AHM-related DILI as with one-third of the patients ingesting CAMs from traditional Ayurvedic healers, mainly for gastrointestinal symptoms [150]. A single-center study demonstrated that 68% of cirrhosis patients had used CAM, and among them, 35.7% presented with CAM-related DILI leading to acute on chronic liver failure (ACLF) with an overall mortality of 53% [151].

Regulation of over-the-counter AHMs, homogeneity in good manufacturing practices and quality assurance, need for oversight in clinical efficacy and safety studies and post-marketing pharmacovigilance are current challenges faced by the AYUSH system in India and elsewhere [152].

Causality assessment

Determining AHM as the causative agent for DILI is the first important step toward diagnosis. The RUCAM, a widely used assessment tool to support a diagnosis of DILI is a structured, standardized, validated, and liver toxicity-specific

causality assessment method [13]. The RUCAM is also regarded as a well-established tool for qualitative assessment of causality even in cases of suspected herb-induced liver injury even though the exact causative agent/component is unlikely to be found from among polyherbal Ayurvedic medications. The RUCAM, conceived primarily for idiosyncratic DILI, excludes cases with onset of liver injury before the start of AHM, can be used prospectively, calculated individually for each co-administered product. It is utilized for acute liver injury and is not validated for use among patients with pre-existing chronic liver disease (CLD). Nonetheless, CLD could be considered a risk factor for the development of AHM-DILI [149, 151]. Pre-clinical studies on the potential hepatotoxicity of herbs and associated components are lacking. This is further complicated by the dissimilar organic and chemical composition in different parts of a medicinal plant. Therefore, the use of whole plants or parts these may have a differential impact on the pharmacokinetics and pharmacodynamics characteristics in humans. This feature is highlighted by reports and series on the liver toxicity and myriad liver injury presentations of certain Ayurvedic herbs such as ashwagandha (*Withania somnifera*), aloe vera, guggul (*Commiphora wightii*), puncturevine (*Tribulus terrestris*), turmeric, gotu-kola (*Centella asiatica*), bakuchi (*Psoralea corylifolia*), senna (*Cassia angustifolia*), noni juice (*Morinda citrifolia*), Malabar tamarind (*Garcinia gummi-gutta*), and gurmar (*Gymnema sylvestre*) are available in the literature [69, 151, 153–155]. It is important to attribute DILI to AHM by following the requisite minimum number of critical elements that are needed to assess causality as laid by expert consensus and where possible, the implicated AYUSH medicine(s) should be retrieved and analyzed for potential toxins, adulterants, and hepatotoxic heavy metals which could add toward prognostic valuation [150, 156, 157].

Clinical presentation and diagnosis

Clinically, an AHM-DILI patient can be asymptomatic with abnormal liver tests, symptomatic presenting as fatigue, anorexia, and abdominal pain or acute or chronic hepatitis thereby mimicking the complete spectrum of liver disease including drug-induced autoimmune hepatitis [155]. As with any other drug or dietary supplement induced liver injury, the diagnosis of AHM-DILI is one of exclusion and identifying the actual herb/herbal component is difficult especially in the presence of combinations of multiple herbal medication or polyherbal formulations which may contain adulterants and contaminants. A liver biopsy should be performed, particularly to rule out close competing causes, or ascertain the presence of underlying chronic liver disease, and identify the histologic patterns of liver injury associated with poor prognosis such as hepatocyte necrosis [150, 155].

Management

The first step in the management of AHM-related DILI is to discontinue the suspected/implicated herbal agent. Even though factors predictive of recovery are not well-defined, a majority of patients do improve spontaneously with the cessation of the offending agent. Those presenting with clinical features of acute liver failure, acute decompensation, and ACLF need hospitalization.

There are no specific or recommended therapies for AHM-related DILI; management is often supportive. This includes the use of ursodeoxycholic acid and cholestyramine with or without plasma-exchange or other extracorporeal liver support for those with cholestatic hepatitis, corticosteroids for those with features of hypersensitivity or immune-mediated liver injury biopsy or liver cell necrosis on histopathology. Other supportive off-label measures such as intravenous or oral *N*-acetylcysteine and nutritional therapy may also be administered, even though quality studies on the safety and efficacy of such interventions in AHM-related DILI are lacking. Patients presenting with ALF or ACLF or advanced disease may require early workup and listing for liver transplantation [149, 158–160].

Comparison of traditional and complementary medicine injury in India and the West

A vast majority of complementary medicine-related DILI in the West is due to herbal and dietary supplements (HDS), particularly in the USA and Europe. HDS related DILI in the West has female preponderance, severe forms of liver disease that is predominantly hepatocellular type of liver injury, when compared to the conventional prescription drugs. In Asian countries such as China and Korea, herbal drug-induced liver injury is more common than conventional drugs. The relative prevalence of DILI from traditional medicines and dietary supplements was shown to be 17.1% in Japan, 18.6% in China, 71% in Singapore, and 72.7% in Korea [161]. In India, DILI from the use of AHMs, accounts for 13% of all cases of DILI [148]. In patients with underlying alcoholic hepatitis, exposure to the Ayurvedic system of medication resulted in a poor 6-month survival compared to conventional prescription-based treatment (18% versus 52% respectively) [162]. There is, however, a need for multicenter studies with strict definitions and inclusion criteria [149, 150, 163].

Summary: recommendations

Prevalence of AHM use and incidence of AHM related DILI in general and patient populations remain unknown in the absence of public–private sector, and industry partnered surveys and pharmacovigilance.

Evidence B

The RUCAM, along with systematic and objective clinical and investigational assessment requires a minimum number of elements for reporting DILI, and can be used to assess causality among patients suspected to have AHM-related liver injury.

Evidence B, recommendation 2

AHM-related DILI presents with variable symptoms and signs in isolation or otherwise. Patients may be totally asymptomatic, or present as mimickers of acute and chronic hepatitis, autoimmune-like hepatitis, cholestatic hepatitis, granulomatous hepatitis or sinusoidal obstruction syndrome either as de novo or in the presence of an underlying chronic liver disease.

Evidence B

AHM-related DILI is a diagnosis of exclusion, strengthened by temporal association and causality even though identification of the actual agent or a component or their interactions that lead to liver injury may be difficult to prove especially with multiple herbal drugs combination or polyherbal formulations.

Evidence B, recommendation 2

The diagnosis of AHM-DILI does not require a liver biopsy but is recommended whenever possible, along with retrieval and analysis of the herbal agent(s), to rule out competing causes and to identify underlying chronicity and allow prognostication. Retrieval and analysis of the herbal agent(s) is ideal.

Evidence B, recommendation 2

Management of AHM-related DILI begins with the withdrawal of implicated agent(s), providing supportive and targeted symptomatic care, identifying clinical factors predicting poor prognosis, and importantly early recognition of patients with ALF or ACLF requiring listing for liver transplantation.

Evidence C, recommendation 1

Anti-tuberculosis drug-induced liver injury

Epidemiology and burden

The use of 3 of 4 drugs (i.e. isoniazid, rifampicin and pyrazinamide) with a potential for hepatotoxicity places a huge burden on patients exposed to first-line anti-TB drugs. The incidence of hepatitis is variable depending on the definition used to define DILI and varies from 3.4% [164] to 7.3% [165]. Clinically significant or jaundice is ~ 1% in controlled settings but may be higher in real-life situations [164]. Although three-fourths of clinically significant hepatitis occur in the first 2 months of treatment, the risk for hepatotoxicity persists throughout the course of treatment of tuberculosis [166].

Anti-TB DILI is the most common cause of DILI and drug-induced acute liver failure in many Asian countries [97, 148, 167–170]. It is the second most common cause of drug-induced acute on chronic liver failure in Asia [149]. Roussel Uclaf Causality Assessment (RUCAM) should be used for causality assessment. It is impossible to tease out the inciting drug during combination therapy. Thus, it is challenging to apply RUCAM for individual drugs and as per working group the combination drugs are implicated as a single entity without deduction of points [10]. During reintroduction of first line anti-TB drugs, the last drug introduced may be implicated as a cause of DILI when it occurs. Fortunately, most individuals tolerate reintroduction of drug combinations without recurrence of DILI [80].

Acute viral hepatitis is common in many Asian countries; hepatitis B in China and hepatitis E in northern India [171]. The occurrence of de novo jaundice or elevated liver tests whilst on anti-TB drugs may pose a diagnostic dilemma. A default diagnosis of DILI for any episode of jaundice while on anti-TB drugs may incorrectly lead to cessation of therapy. In one study, acute hepatitis E was responsible for jaundice in 15% of subjects receiving anti-TB drugs highlighting the importance of excluding alternative causes as confounding factor in individuals that develop hepatitis on anti-TB drugs [171].

Hepatic tuberculosis itself may cause mild alteration of liver tests and rarely as clinical jaundice. This may be secondary to liver parenchymal infiltration or biliary obstruction form enlarged lymph nodes. In such instances, the liver biochemical test pattern is that of biochemical cholestasis (raised alkaline phosphatase with minimal elevation of transferases); these generally improve after the administration of first-line anti-TB drugs.

TB in HIV needs to be included.

Guidelines for monitoring hepatotoxicity

Clinical features and diagnosis of anti-TB-DILI

The most common serious adverse reaction to the first-line anti-tuberculosis therapy (ATT) i.e. isoniazid, rifampicin and pyrazinamide is drug-induced hepatitis leading to anti-tuberculosis drug-induced liver injury (AT-DILI). Patients may be asymptomatic or may experience a prodrome of fever and constitutional symptoms followed by nonspecific symptoms such as nausea, vomiting, anorexia, lethargy and abdominal pain which are otherwise unexplained [2, 172].

The diagnosis of anti-TB DILI has been elucidated as per the guidelines laid by the American Thoracic Society [2]. The guidelines formulated by APASL are shown in Tables 3 and 4 and compared with guidelines laid down by ATS, British Thoracic society and WHO. The most up to date are the NICE guidelines https://www.nice.org.uk/guidance/ng33). Overall the diagnosis of hepatotoxicity is similar to the working group criteria [10].

Although in the past the degree of elevation of transaminases was used as a criterion for predicting the severity of anti-TB DILI, emerging evidence suggests that the height of transaminases alone may not predict outcome but depends more on the presence of clinical jaundice, coagulopathy, ascites and encephalopathy [10, 166]. Other causes of abnormal liver biochemistry tests must be excluded before diagnosing AT-DILI. Although a positive re-challenge test is considered as the gold standard for diagnostic confirmation of DILI, most patients with anti-TB DILI tolerate reintroduction of first-line drugs. A positive rechallenge test is characterized by an elevation of more than twofold rise in serum AST or ALT with the reintroduction of the suspected offending TB medication, followed by a fall in ALT on discontinuation [2].

There is a clear need for further research on identifying better diagnostic markers. Two recent studies have elucidated the role of leucocyte telomere length [173] and combined 5-hydroxymethylcytosine (5-hmC) contents of human leucocyte antigen (HLA)-B and HLA-DQB1 as diagnostic biomarkers of AT-DILI [174]. These are promising approaches, however, more data is needed to incorporate these into general recommendations. A recent study found a small but increased risk of TB drug-related DILI in those carrying the *HLA-B*52:01* allele. Although the *N*-acetyltransferase 2 (NAT2) contribution is complex, ultraslow

Table 3 Anti-TB DILI: overview of monitoring advice

	American Thoracic Society (2006; updated 2016)	British Thoracic society (1998)	WHO (2010)	APASL (2021)
Baseline LFT	Yes	Yes	Not mentioned	Yes[a]
Baseline viral markers	–	–	HIV	HBsAg Anti-HCV HIV
Monitoring LFT—(if baseline Normal)	Not recommended unless symptoms arise	Not recommended unless symptoms arise	–	Not recommended unless symptoms arise
Monitoring of LFT (If baseline abnormal)	Yes Frequency: 2–4 weeks	Yes Frequency: Weekly If ALT > 2 UNL 2 weekly if ALT < 2 UNL	–	Initially weekly for 2 weeks and later 2 weekly for 2 months
Liver Disease	Weekly for 2 months Monthly thereafter. Plus Clinical Monitoring	Weekly-LFT Clinical monitoring frequent (frequency: not mentioned)	Yes—baseline Monitoring frequency: not mentioned	Yes, baseline and 1–2 weekly LFT with INR

[a]If serum albumin is < 3.5 mg/dl, get full liver biochemical tests, and ultrasound to exclude underlying chronic liver disease

Table 4 Overview of Management of anti-TB DILI

	American Thoracic Society (2006: updated 2016)	British Thoracic Society (1998)	WHO (2010)	APASL (2021)
Stopping TB (Hepatotoxic) drugs if clinical or symptomatic hepatitis	Yes	Yes	Yes	Yes
When to restart TB drug	ALT return to < 2 × ULN	ALT return to < 2 × ULN	LFT return to normal and clinical Symptoms resolve	AST/ALT < 2 × ULN Bilirubin < 1.5 × ULN
What TB drug to restart (To be started sequentially)	RIF ± EMB full dose After 3–7 days, INH full dose PZA (restart only if mild DILI)	INH → RIF→PYZ (Dose titration every 2–3 days)	RIF → 1st INH → (after 3–7 days) PZA—avoid	RIF →INH. → (start low dose of each drug and titrate dose upwards every 3 days) Continue EMB full dose PZA (Restart only if Mild DILI without jaundice)
Recommended LFT monitoring in rechallenge	Check ALT 3–7 days after INH rechallenge	Daily Monitoring of LFT	LFT Monitoring (No recommendation on frequency)	Monitor LFT and INR every 3–7 days, earlier if symptoms arise

metabolisers of NAT 2 (NAT2*6 and NAT2*7 variants) are at increased risk to develop AT-DILI [175].

Guidelines for monitoring hepatotoxicity of anti-TB-DILI

Although there are differences in biochemical monitoring practices for ATDILI with no standardized strategy, there is an agreement that monitoring begins at home and in the clinic. Patients should be educated for signs of ATDILI such as nausea, loss of appetite, vomiting, dark urine, and right upper abdominal pain followed thereafter by clinical assessments by the health care provider. Patients should be advised not to take alcohol or any other hepatotoxic medications and to maintain a record of their alcohol intake if any [2, 16].

Monitoring patients with risk factors versus no risk factors

Baseline and follow-up liver biochemistry in patients on ATT helps detect the early onset of hepatotoxicity. While AST and ALT levels indicate hepatocellular injury, the severity is assessed by monitoring serum bilirubin and serum alkaline phosphatase. Synthetic function is monitored by periodic measurement of prothrombin time and INR especially in those with jaundice, severe disease and preexisting liver disease.

Early detection of AT-DILI, by close monitoring is associated with lower mortality and better prognosis [160]. It may enable faster recovery and normalization of transaminases, making such patients more likely to tolerate first-line ATT without a change of regimen as compared to those detected later.

Recommendations for monitoring in absence of risk factors

Patients without risk factors and who are being initiated ATT need a baseline documentation of serum transaminases, bilirubin, alkaline phosphatase, creatinine, and a blood platelet count. Thereafter, investigation for AT-DILI is prompted by new onset of symptoms that are otherwise unexplained. If at any point ALT and AST levels are consistent with hepatotoxicity, all hepatotoxic drugs are stopped and serial serum ALT, AST, serum bilirubin and prothrombin time or international normalized ratio (INR) estimations are followed until levels return to baseline. Additionally, all patients need screening for viral hepatitis (HAV, HEV and reactivation of HBV), autoimmune hepatitis and enquiry on the use of other hepatotoxic /CAM drugs. A liver specialist is consulted if the clinical or laboratory status continues to worsen [2, 159].

For latent TB infection (LTBI), in absence of risk factors, no baseline testing is recommended and investigation is prompted upon developing AT-DILI symptoms that are otherwise unexplained.

Monitoring in presence of risk factors

Comprehensive documents have listed risk factors that have been associated with AT-DILI. These include chronic use of alcohol, underlying chronic hepatitis B, hepatitis C, or HIV infection, concomitant use of medications with hepatotoxic potential, and baseline elevations of transaminases [2]. A baseline liver biochemistry that includes ALT ± AST, and bilirubin is recommended under these circumstances with a Q2 to 4 weekly retesting. In the absence of the above-stated risk factors and patients aged > 35 years, baseline testing is done on the physician's discretion with retesting either Q4–8 weekly or at 1, 3, and 6 months interval if on a 9-month regimen.

A comparison of monitoring guidelines of different bodies including from APASL expert opinion consensus is presented in Tables 3 and 4.

A study comparing the ATS recommendations of monitoring on a risk factor basis with a standard monitoring protocol at 2 weeks after treatment initiation found the ATS criteria to have only 66% sensitivity and 65% specificity for predicting the development of early AT-DILI [165]. The study argues towards the usefulness of standard 2-week ALT measurement in all patients regardless of risk factor status being treated for active TB (as opposed to testing over a range of 2–4 weeks for risk factor positive patients only according to ATS) to enable prompt identification of a subgroup of patients who develop AT-DILI at an early time point. The study also suggested "ATS-factor positive" patients should all have 2-week ALT check, but if this is normal, 2–4 weekly measurement may be unnecessary, as very few of these patients will go on to develop late DILI [165].

Notably, previous to ATS recommendations, one expert opinion recommended regular monitoring of liver function, weekly for two weeks and then two weekly for the first 2 months for patients with known chronic liver disease. Like ATS, routine monitoring for patients without risk factors was not recommended [176]. Another study recommended liver function testing every 2 weeks for the first 2 months and monthly thereafter in all patients on ATT [177]. These recommendations have not been tested and have limitations given the costs and logistics involved in the process.

In conclusion, many previous guidelines including ATS recommend regular monitoring for patients with risk factors although the timing of monitoring during a patient's treatment course varies over the years and from one expert opinion to another. However, most agree that for those patients without risk factors, routine monitoring after acquiring baseline liver functioning tests is not needed unless symptoms develop [2, 176, 177].

APASL recommendations

Based on a synthesis of the above-mentioned guidelines, and the fact that liver disease from hepatitis B is prevalent in Asia–Pacific, we recommend the following to be the most pragmatic steps to monitor AT-DILI:

- Baseline HBsAg, anti HCV and liver biochemical tests and ultrasound of the abdomen should be done on all patients before starting ATT. Grading of evidence B, Grade of recommendation 1
- Routine monitoring of liver biochemistry during treatment is not recommended in patients with no risk factors for AT-DILI unless symptoms develop. Grading of evidence A, Grade of recommendation 1
- For patients with risk factors, monitoring liver biochemistry tests every 2 weeks for the first 8 weeks. Monthly liver biochemistry tests may be carried out thereafter till the end of therapy particularly in individuals with risk factors for the development of drug-induced hepatitis. Grading of evidence B, Grade of recommendation 2

Management

Anti TB DILI management

First-line Anti TB drugs other than ethambutol are potentially hepatotoxic. The prescriber needs to be alert and must inform the patient regarding the drugs' potential for hepatotoxicity. Drug interactions and the host susceptibility are important considerations. Isoniazid and Pyrazinamide are the main drugs leading to liver injury. Early recognition of toxicity is the key to management which depends on effective monitoring of liver biochemical tests; early cessation is the key to a good outcome.

Isoniazid, rifampicin and pyrazinamide must be stopped at the early signs of toxicity such as elevation of 3-times or 5-times elevation of ALT or AST in the presence or absence of symptoms respectively. Ethambutol must be continued together with other second line non-hepatotoxic anti-TB drugs unless ATT was started for empirical reasons. Acute liver failure due to ATT should be managed in line with ALF in the intensive care with availability of Liver transplant if the clinical condition deteriorates. Use of *N*-acetylcysteine (NAC) [104] should be tried at the early stage of liver failure. The use of GCSF and stem cell therapies need more data for a recommendation in anti-TB DILI. Listing for liver transplant is mandatory if the clinical condition deteriorates and patient is progressing to a rapid drug-induced liver failure.

Recommendations

Anti TB treatment must be closely monitored with scrupulous attention to clinical symptoms and estimation of liver biochemistry tests from the start of treatment and periodically thereafter until the end of treatment. Most hepatotoxicity occurs especially in the first 2 months of starting the treatment.

Grading of evidence A, grade of recommendation 1

DILI in NAFLD and CLD

Few drugs have a potential to cause de novo NAFLD or chronic liver disease. Amiodarone and methotrexate are 2 prime examples. Development of clinically significant fibrosis leading to CLD and liver transplantation following MTX is rare and contentious [51]. Chronic liver disease may also occur following an episode of DILI leading to vanishing bile duct syndrome [107].

Patients taking anti-psychotics tend to gain weight. This may be complicated by the elevation of liver enzymes raising the possibility of NASH [178]. When patients are taking multiple medications, is difficult to tease out the contribution of individual drugs in causing fatty liver or elevated enzymes.

Tamoxifen has also shown increased risk of developing NASH eightfold but only in those who were overweight or obese and taking the drug for over 5 years. Presence of associated risk factors such as hypercholesterolemia and hypertension also plays a contributing role [24]. Transaminases normalize in a majority after cessation of tamoxifen.

Mechanisms and examples of drugs causing steatohepatitis include drugs causing increased insulin resistance (stavudine, glucocoticosteroids, tacrolimus), de novo free fatty acid synthesis (tamoxifen, efavirenz, and glucocorticoids), impaired lipophagy (amiodarone, chlorpromazine, fluoxetine), mitochondrial dysfunction either from impaired beta oxidation of fatty acids or oxidative phosphorylation (methotrexate, amiodarone, valproic acid, [179].

There are other drugs listed as causing NASH. Much of the evidence comes from experimental studies in animals and conclusive proof in humans are lacking [179].

There is an ongoing debate on the risk of developing drug-induced acute liver injury in patients with NAFLD or CLD. Population-based studies have not shown a heightened risk of DILI in the presence of obesity or metabolic syndrome [6, 7]. However, 2 studies, one prospective by Tarantino et al. [180] and another retrospective by Lammert et al. [181] showed a fourfold increased risk of DILI in middle-aged patients. The drugs implicated include antibiotics and anti-secretory drugs.

Individuals with CLD from hepatitis B and C virus infection and those with HIV are at increased risk to develop DILI [182]. Individuals with chronic liver disease are at increased risk of dying from DILI compared to those without risk factors [15]. Whether the risk is similar in NAFLD patients is unknown. However, the presence of obesity, (a surrogate marker for NASH) appears to increase the risk of odds of transplantation or odds of dying after transplantation in individuals with ALF [183].

Statement: Some drugs such as amiodorone, methotrexate, and tamoxifen have the potential to produce fatty liver disease and chronic liver disease.

Grading of evidence: B. Grade of recommendation: 1

There is an increasing recognition of the predisposition of patients with chronic liver disease to develop de novo drug-induced liver injury.

Grading of evidence B. Grade of recommendation 2.

Risk of death is increased in patients with underlying liver disease (Grading of evidence B, grade of recommendation 1).

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