AASLD Practice Guidance on Drug, Herbal and Dietary Supplement Induced Liver Injury

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Submitted for publication July 7, 2022

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Manuscript length= 10, 647 words (without references/ tables/ figures)

Abbreviations

AIH	autoimmune hepatitis
ALF	acute liver failure
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APAP	acetaminophen
AST	aspartate aminotransferase
DI-AIH	drug-induced AIH
DILI	drug-induced liver injury
DILIN	Drug-Induced Liver Injury Network
FDA	US Food and Drug Administration
GTE	green tea extract
HCV	hepatitis C virus
HDS	herbal and dietary supplement
HEV	hepatitis E virus
ICI	immune checkpoint inhibitor
IgM	immunoglobulin M
IMH	immune-mediated hepatitis
INR	international normalized ratio
irAE	immune-related adverse event

Submitted for publication July 7, 2022

NAC	*N*-acetylcysteine
NRH	nodular regenerative hyperplasia
SOS	sinusoidal obstruction syndrome
TB	tuberculosis
ULN	upper limit of normal
VBDS	vanishing bile duct syndrome

Statement of Conflicts of interest

Per American Association for the Study of Liver Diseases (AASLD) Governing Board requirements, all members of the writing group were required to submit a COI statement prior to and during the drafting of this guidance. Per AASLD COI policy, a majority of the authors were required to not have any stated COIs including the writing group chairs. AASLD does not consider research funds provided to a member's institution as a conflict of interest.

Submitted for publication July 7, 2022

Introduction

There are currently more than 1000 prescription medications available for use in the United States and more than 100,000 over-the-counter herbal and dietary supplements (HDS) available for purchase in retail stores and online. In addition, the average adult American receives more than six prescription medications per year.[1, 2] Many of these drugs and HDS products have been implicated as causes of drug-induced liver injury (DILI). Furthermore, DILI is a leading reason for regulatory actions regarding drugs in development as well as those in the marketplace.[1] Confidently establishing a diagnosis of DILI is difficult because of the need to exclude more common competing causes of liver injury, the protean clinical manifestations from an individual agent, and the lack of a validated diagnostic biomarker.[3–5]

This guidance was developed with the support and oversight of the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines Committee, who chose to commission a guidance, rather than a guideline, because of the paucity of randomized controlled trials on this topic. This document was developed by consensus of an expert panel and provides guidance statements based on formal review and analysis of the literature on the topics and questions related to the needs of patients with drug- and supplement-induced liver injury.

The aim of this practice guidance is to provide recommendations regarding the common clinical, laboratory, and histological features seen in patients with DILI based upon observational and epidemiological data reported in case series or DILI registries. In addition, expert opinion-based recommendations for patient management including risk stratification are provided to assist patients and practitioners.

DILI classification

DILI can be mechanistically classified as being either direct (i.e., dose dependent, intrinsic, and predictable) or idiosyncratic (largely dose independent, idiosyncratic, and unpredictable) (**Table 1**). Direct hepatotoxins such as acetaminophen (APAP) (*N*-acetyl-para-aminophenol) can cause liver injury in nearly all exposed individuals if a threshold dose or duration is exceeded. In contrast, idiosyncratic hepatotoxins are usually neither dose- nor duration-related but rather occur at varying times during or after drug administration.[6] Idiosyncratic DILI is uncommon, with most approved drugs, occurring in only one in 1000 to one in a million exposed individuals. Although most patients do not have rash, eosinophilia, or other hypersensitivity features at presentation, aberrant host immunity is implicated in most instances of idiosyncratic DILI.[3]

Submitted for publication July 7, 2022

A third mechanism of hepatotoxicity is called indirect DILI, which arises when the biological action of the drug affects the host immune system, leading to a secondary form of liver injury. Like idiosyncratic DILI, indirect hepatotoxins are generally independent of the dose of medication administered and have a latency of weeks to months with varying clinical manifestations. Examples of indirect hepatotoxicity include the immune-mediated hepatitis (IMH) observed with immune checkpoint inhibitors (ICIs) and reactivation of hepatitis B virus infection following rituximab infusions.[7, 8]

GUIDANCE STATEMENTS

- **1. Clinicians should be familiar with the three main types of hepatotoxicity when evaluating patients with suspected DILI.**
- **2. Direct hepatotoxins such as APAP can cause liver injury in nearly all exposed individuals once a threshold dose or duration of use is exceeded.**
- **3. Idiosyncratic DILI is largely independent of the dose and duration of medication use and characterized by a low incidence and variable drug latency and clinical and histological features.**
- **4. Idiosyncratic DILI is believed to arise from an aberrant adaptive host immune response to the drug and/or its metabolite(s).**
- **5. Indirect hepatotoxins are generally independent of the dose administered and have a variable latency and manifestations that arise from the biological action of the drug on the liver and/ or host immune system.**

Epidemiology of idiosyncratic DILI

Idiosyncratic DILI is uncommon, with an estimated annual incidence in the general population of 14 to 19 events per 100,000 inhabitants or 60,000 cases per year in the general United States population.[9, 10] The estimated incidence of idiosyncratic DILI also varies based upon the case definition as well as the methods used for case ascertainment. For example, the incidence appears to be higher in exposure-based studies using electronic

medical records: 32.8 per 100,000 adult patients who received one of the top implicated drugs in the United States and 40 per 100,000 patients at a pediatric hospital.[11, 12] The incidence of idiosyncratic DILI is even higher in hospitalized patients, being reported as high as 1.4% among medical inpatients.[13–16]

Results of ongoing DILI registry studies demonstrate that the spectrum of suspect drugs and demographics of afflicted patients substantially differ among countries and regions.[17–24] These observations likely reflect differences in case definitions as well as differences in medication use, health care systems, and sociocultural and medical attributes in the various populations. **(Table 2)**

Leading causes of idiosyncratic DILI worldwide

Although hundreds of medications can cause idiosyncratic DILI, several drug classes are more frequently implicated than others. For example, antimicrobials, central nervous system agents, immunomodulatory agents, and antineoplastic agents are more frequently implicated than antihypertensives.[17–24] Also, striking geographic differences exist among the specific implicated drugs. For instance, HDS products surpass pharmaceuticals in China, Korea, and Singapore, accounting for 27%–62% of their DILI cases.[22, 25, 26] In contrast, HDS products represent only a minority of cases in Japan, the United States, and Spain but with an increasing incidence over time.[23, 27–31] Amoxicillin-clavulanate is the most frequently implicated individual agent in many western countries, whereas anti-tuberculosis (TB) agents dominate in Asian countries (**Table 2**).

Submitted for publication July 7, 2022

Risk determinants: An individual's risk of developing idiosyncratic DILI is determined by complex interactions among host, drug, and environmental factors.[32]

i. **Drug properties:** Although idiosyncratic DILI typically is independent of the total dose or duration of medication administered, most implicated drugs are given at a daily dose of >50–100 mg per day.[33] More than 80% of DILI cases that resulted in liver transplantation in the United States were caused by medications with daily doses exceeding 50 mg.[34] In some instances, dose escalation may also increase the risk of developing idiosyncratic DILI as seen with azathioprine, whereas dose reduction or increasing the dosing interval may improve tolerability.[35–37]

Drugs with high lipophilicity and extensive metabolism in the liver (>50%) are associated with an increased hepatotoxic potential, especially in combination with a high daily dose (>100 mg daily).[38, 39] In addition, drugs that form reactive metabolites, exert mitochondrial toxicity, and inhibit bile acid transporters in in vitro test systems are associated with increased DILI risk in humans.[32] Concomitant administration of multiple hepatotoxic drugs has also been associated with an increased risk of DILI in several studies.[40–43]

ii. **Host age, sex, and race and ethnicity:** The impact of host age, sex, and race and ethnicity on DILI susceptibility is not well established because of the lack of large exposure-based epidemiological studies to compare DILI incidence with drug-treated controls. Although standardized DILI incidence increases with patient age, this may be explained, in part, by greater medication use with increasing age.[9] Noticeable differences also exist between sexes, with women experiencing more frequent and severe hepatotoxicity.[44, 45] A French population-based study showed that the standardized DILI incidence was more than two times higher in women than men older than 50 years, although no sex differences were noted under age 50.[9, 10] In addition, older subjects appear to be at increased risk of isoniazid and amoxicillin-clavulanate hepatotoxicity, whereas younger individuals are more prone to develop DILI from anticonvulsants and minocycline.[45, 46] Finally, case series demonstrate an

overrepresentation of women with diclofenac, macrolide, flucloxacillin, halothane, ibuprofen, interferon beta-1a, and nitrofurantoin hepatotoxicity. Similarly, men appear to be overrepresented with azathioprine, anabolic steroid, and amoxicillin-clavulanate hepatotoxicity.[45–47]

The Drug-Induced Liver Injury Network (DILIN) has demonstrated that trimethoprim-sulfamethoxazole is the most common suspect drug among African Americans, whereas amoxicillin-clavulanate is the leading cause in White populations. In addition, African Americans were more likely to have adverse outcomes and develop chronic DILI.[48, 49] In contrast, Asian Americans were more likely to experience a liver-related death or undergo liver transplant than the other racial groups.[48, 49] Because of the limited number of ethnic minorities included, additional studies are needed to confirm these data.

iii. **Medical comorbidities and environmental factors:** Obesity has been associated with an increased risk of tamoxifen-induced steatosis/steatohepatitis.[50] Being overweight, having diabetes, alcohol use, and chronic viral hepatitis have also been associated with progressive fibrosis in methotrexate-treated patients.[51, 52] However, the amount of alcohol consumed was not associated with clinical outcomes in consecutive patients enrolled in the DILIN Prospective registry.[53] Furthermore, there are limited data exploring the impact of diet, tobacco use, and coffee consumption on DILI susceptibility. The mechanism by which chronic liver disease (e.g., NAFLD, viral hepatitis) impacts DILI susceptibility remains unclear.[54] However, DILI caused by anti-TB therapy has been associated with abnormal baseline serum aminotransferases, showing a stronger dose-dependent association with the severity of liver enzyme elevation than older age.[55]

iv. **Host genetic risk factors:** Various host genetic factors related to drug-metabolizing enzymes and transporters have been reported as increasing DILI susceptibility.[56] (**Table 3)**. A missense variant (rs2476601) in PTPN22, which has been associated with

other autoimmune disorders, appears to be a risk factor for all-cause DILI across multiple racial and ethnic groups with an odds ratio of 1.4.[57, 58] Several genetic studies have also identified distinct HLA alleles as risk factors for specific drugs or HDS products. In general, the identified HLA alleles have low positive predictive value, because of the low incidence of DILI in the general population, but a high negative predictive value. Therefore, pretreatment HLA testing will likely not prove useful in most circumstances to prevent DILI, but HLA testing may be helpful in DILI diagnosis and causality assessment.[59, 60]

GUIDANCE STATEMENTS

- **6. The estimated annual incidence of idiosyncratic DILI in the general population is low (14–19/100,000) but higher in exposure-based studies using electronic medical record data (33–40/100,000).**
- **7. Antimicrobials, central nervous system agents, and anti-inflammatory agents are the most commonly implicated agents in DILI series worldwide. However, herbal and dietary supplements are most commonly implicated in some Asian countries and are increasingly implicated in western countries as well.**
- **8. The daily dose of a medication, its lipophilicity, and extent of hepatic metabolism influence the risk of causing DILI when comparing medications.**
- **9. Insufficient data exist to confirm subject age, sex, and race and ethnicity as reliable risk factors for DILI susceptibility. However, some drugs are more likely to cause DILI in older individuals (e.g., amoxicillin-clavulanate, isoniazid), whereas others are more commonly implicated in children (valproate, minocycline).**
- **10. Medical comorbidities such as obesity and diabetes are associated with increased incidence and severity of DILI with specific drugs. However, the role of alcohol, tobacco, and diet in DILI susceptibility is not established.**
- **11. Patients with pre-existing liver disease are at increased risk of developing liver injury with selected drugs (e.g., methotrexate, anti-TB therapy). In addition, subjects with pre-existing liver disease are at increased risk of poor outcomes with a DILI episode.**

- **12. A polymorphism in PTPN22 is a genetic risk factor across multiple drugs and major ethnic groups. Various HLA alleles have also been associated with increased susceptibility to individual drugs, but the clinical utility of HLA testing in DILI diagnosis has yet to be determined.**

Diagnostic approach to DILI

DILI is largely a clinical diagnosis of exclusion, relying upon a detailed medical history including medication exposure, the pattern and course of liver biochemistry tests before and after drug discontinuation, and exclusion of other causes of liver disease. The initial laboratory testing for DILI includes serum aminotransferases (aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total and direct bilirubin levels, whereas serum albumin and international normalized ratio (INR) levels are a marker of severity **(Figure 1**). Clinically significant DILI is commonly defined as any one of the following: (1) serum AST or (ALT) >5× upper limit of normal (ULN) or ALP > 2× ULN (or pretreatment baseline if baseline is abnormal) on two separate occasions at least 24 h apart; (2) total serum bilirubin >2.5 mg/dL along with elevated serum AST, ALT, or ALP level; or (3) INR >1.5 with elevated serum AST, ALT, or ALP.[30, 74] Although DILI may present with lower levels of laboratory abnormalities, up to 20% of individuals in the general population have mildly increased liver biochemistries because of NAFLD, alcohol, and other common conditions.[74]

Medication history

A detailed medication history, including the use of HDS products, is critical in all suspected DILI cases. This information should include start and stop dates of the suspect agent(s), dose change if any and when, prior use of the medication, dechallenge data (i.e., clinical course following drug discontinuation), and rechallenge results (i.e., response to re-exposure). Typically, DILI appears within 6 months of starting a new medication, although certain drugs have longer latency periods (e.g., nitrofurantoin, methotrexate). In contrast, hypersensitivity reactions can have very short latency periods of only 24–72 h. Although DILI is often attributed to repeated exposure to an oral agent, it is important to recognize that exposure to an intravenous agent, such as monoclonal antibodies, may also cause DILI. However, topical formulations of medications to the skin, eyes, or ears rarely, if ever, cause DILI because of the low dose of medication absorbed.

Initial laboratory assessment

A clinical pattern of liver injury that matches what has been previously reported for a particular medication or HDS product can be helpful in deciding whether an agent is likely the cause of the injury. The biochemical pattern of liver injury also guides the evaluation for competing causes of liver disease. (**Figure 1**) In general, the pattern of injury can be categorized as primarily hepatocellular, with a predominance of transaminase (ALT, AST) elevation; cholestatic, with a predominance of ALP elevation; or mixed. These patterns can be more precisely and quantitatively expressed through the R-value, defined as serum ALT/ULN divided by serum ALP/ULN. An R value greater than 5 identifies cases of hepatocellular liver injury, whereas an R value less than 2 categorizes cases of cholestatic liver injury, and an R value between 2 and 5 reflects a mixed liver injury pattern.[75, 76] The R-value is best calculated at the time of presentation, but the pattern of injury can change as the condition progresses.[77] Moreover, a given drug may be associated with more than one clinical profile.

Competing causes of liver injury

Testing for acute viral hepatitis is recommended for all patients with suspected DILI including hepatitis A immunoglobulin M (IgM), hepatitis B surface antigen, anti-hepatitis B core antibody IgM, and hepatitis C virus (HCV) RNA to exclude acute hepatitis C infection (**Figure 1**). In fact, 1.3% of adjudicated cases in the initial analysis of the DILIN cohort tested positive for HCV RNA.[30] Another mimicker of DILI is acute hepatitis E virus (HEV) infection, which is increasingly reported in developed nations because of exposure to HEV genotype 3 infections. Of note, anti-HEV IgM seroprevalence was 3% in adjudicated cases in the DILIN database. Although there are concerns regarding reliability of the commercially available serologic tests, testing for acute HEV infection should be considered in selected instances, including cases without a clear suspect agent or in cases with very high aminotransferase values arising in older adults.[78] All patients with suspected DILI should also undergo screening for sporadic autoimmune hepatitis (AIH), with testing for autoantibodies (e.g., antinuclear and anti–smooth muscle antibodies) and serum immunoglobulin levels, although there are some drugs which can manifest an AIH-like picture.[79–81]

Patients with recent hypotension, sepsis, or heart failure are at risk for ischemic liver injury, usually characterized by rapid and a marked increase in serum aminotransferase values followed by rapid decline with normal or near normal bilirubin levels. In younger patients, Wilson's disease can be considered using recommended testing.[3, 79] In cholestatic cases, testing for antimitochondrial antibody is recommended to assess for primary biliary cholangitis. In patients with a predominance of AST greater than ALT, alcohol-associated hepatitis should be considered, especially if

aminotransferase elevations are modest (e.g., AST generally <300 U/L) and associated with high gamma-glutamyl transpeptidase and erythrocyte macrocytosis. Furthermore, testing for serum creatinine phosphokinase (CPK)levels in this setting is recommended. All patients with suspected DILI should undergo some type of liver imaging, typically starting with an abdominal ultrasound to assess for presence of cirrhosis, biliary obstruction, or other focal liver changes. Additional imaging, such as computerized tomography or magnetic resonance cholangiography, may be used to assess for vascular abnormalities or pancreaticobiliary disease.[82]

Certain drugs have been associated with specific clinical and histologic phenotypes, also called "signatures," such as autoimmune-like hepatitis, granulomatous hepatitis, vanishing bile duct syndrome (VBDS), or sinusoidal obstruction syndrome (SOS).[80] These signature phenotypes are summarized in **Table 4.** However, DILI can present with a multitude of clinical and histological phenotypes from the same drug depending on host factors and timing of evaluation.

Finally, improvement of liver injury after drug discontinuation (dechallenge) is important in DILI diagnosis; resolution of injury after discontinuation helps confirm the causal relationship to the drug. Equally important is a comparison of the present suspect drug presentation with reported cases in public databases such as LiverTox (see https://www.ncbi.nlm.nih.gov/books/NBK547852).[5] The LiverTox website provides a brief synopsis of the clinical features of idiosyncratic DILI due to more than 1000 prescription drugs and 60 herbal and dietary supplements that are culled from the world's literature. In addition, LiverTox provides a likelihood scale summarizing how many reports of bona fide hepatotoxicity have been attributed to a product as follows: category A, 50 or more reports; category B, 12–49 cases; category C, 4–11 cases; category D, 1–3 plausible cases; category E, no reports of liver injury; and Category X for newly approved agents.

GUIDANCE STATEMENTS

- **13. Clinically significant DILI is typically defined as any one of the following: (1) serum AST or ALT >5× ULN, or ALP >2× ULN (or pretreatment baseline if baseline is abnormal) on two separate occasions; (2) total serum bilirubin >2.5mg/dL along with elevated AST, ALT, or ALP level; or (3) INR >1.5 with elevated AST, ALT, or ALP.**

- **14. The majority of hepatotoxic drugs cause liver injury within the first 6 months of use but occasionally have longer latency intervals or may even present after drug discontinuation (e.g., amoxicillin-clavulanate). Therefore, evaluation of a patient with suspected DILI should include a detailed medication and HDS history within the 180 days prior to presentation.**

- **15. Idiosyncratic DILI cases should be categorized by the R value at presentation (R = (ALT/ULN)/(ALP/ULN)) into hepatocellular (R ≥ 5), mixed (2 < R <5), and cholestatic (R ≤2) profiles, which can help guide the evaluation of alternative causes of liver injury.**

- **16. Excluding alternative causes of liver injury is required in all DILI cases, including testing for viral hepatitis, metabolic liver disease, AIH, and pancreaticobiliary disease.**

- **17. Certain drugs have been associated with specific laboratory and histologic phenotypes, termed signatures which may be useful in causality assessment.**

- **18. We recommend accessing the LiverTox website for a synopsis of the published literature on liver injury due to over 1000 prescription drugs and more than 60 herbal and dietary supplements.**

Liver Biopsy in suspected DILI

Although a liver biopsy is not necessary to diagnose DILI, it can be helpful in excluding other causes of liver disease and in increasing the confidence in a diagnosis of DILI in cases of clinical uncertainty.[83] Certain medications are associated with specific histological patterns of liver injury that can be confirmed on biopsy.[84] Biopsy can also be useful when the liver biochemistries or symptoms do not improve with drug dechallenge or the patient remains jaundiced and can be used to help assess the severity of liver injury.[84–86] Finally, a liver biopsy may help identify other causes of underlying or concomitant diseases that can confound the clinical or biochemical presentation.[86]

Approach to liver biopsy interpretation

The first step in the evaluation of a liver biopsy for a patient with suspected DILI is to determine the pattern of injury, as there are various histological presentations of DILI.[87, 88] Approximately one-

third to one-half of DILI cases will present with acute hepatocellular liver injury and accompanying necro-inflammatory type of histology, which includes acute or chronic hepatitis with or without accompanying mild cholestasis.[87] This histological pattern includes various degrees of lobular inflammation, portal inflammation, interface hepatitis, apoptosis, granulomas, coagulative necrosis, and confluent or bridging necrosis (**Table 4**).[87] A diagnostic challenge occurs when trying to distinguish idiopathic AIH from drug-induced AIH (DI-AIH). Histologic features typically observed in AIH, such as interface hepatitis, emperipolesis (the presence of an intact cell within the cytoplasm of another), and rosette formation, are also observed amongst DILI cases (89%, 34%, and 40%, respectively, in DILI cases) and are not pathognomonic for AIH.[89] DI-AIH may show more portal neutrophilic infiltrates and be accompanied by cholestasis, whereas sporadic AIH may show a chronic "hepatitis" pattern, and the interface hepatitis will be dominated by plasma cells.[89] The presence of fibrosis may aid in distinguishing AIH from DI-AIH.[90–94]

DILI ICIs, referred to clinically as immune-related adverse events (irAEs), have been increasingly reported. The predominant histological pattern in ICI DILI is hepatocellular injury, with approximately 70% showing pan-lobular hepatitis and approximately 20% with centrilobular coagulative necrosis on liver biopsy.[95–97] Unlike AIH, plasma cell infiltration is not predominant, and the inflammatory infiltrate is composed mostly of T lymphocytes, with CD8+ cells being greater in number than CD4+ cells. Sclerosing cholangitis is an uncommon manifestation of ICI DILI.[96, 97] Overall, jaundice and liver failure are rare in DILI because of ICI, and approximately a third of those with severe grades of DILI may even regress spontaneously.[97]

Cholestatic DILI histology includes acute cholestasis, chronic cholestasis, and acute cholestatic hepatitis. In the acute cholestatic type, cholestasis without accompanying inflammation (so-called bland cholestasis) may be the sole histological presentation and manifests as bile present in dilated canaliculi and within the hepatocyte cytoplasm.[98] Acute cholestatic hepatitis is the presence of cholestasis accompanied by more prominent lobular inflammation. In chronic cholestasis, the cholestasis persists and may have severe bile duct injury or progress to bile duct loss.[88] If bile duct loss exceeds 50%, the condition is then termed VBDS.[99]

Less common histological manifestations of DILI include fatty liver disease; drug-induced steatosis and drug-induced steatohepatitis. Steatosis may be purely microvesicular, which is primarily related to mitochondrial injury, mixed micro- and macrovesicular, or purely macrovesicular.[100] Of note, microvesicular steatosis usually does not lead to increased echogenicity on ultrasound, nor does it manifest with hepatomegaly, and only liver biopsy can confirm its presence.[101]

Submitted for publication July 7, 2022

DILI resulting in vascular injury may lead to the development of nodular regenerative hyperplasia (NRH), obliterative portal venopathy (OPV), and SOS (formerly known as veno-occlusive disease).[86, 88] NRH and OPV may clinically present insidiously, whereas SOS may manifest as either acute or chronic disease. Peliosis hepatis appears as blood-filled lacunar spaces, and its development is associated with androgens and oral contraceptive agents.[102]

Nonspecific histological features and minimal changes may be seen on a liver biopsy in a patient with suspected DILI. These changes may include activation of sinusoidal lining cells, ceroid-laden macrophages, and ground-glass-like cytoplasm of hepatocytes (also known as induction hepatocytes).[103] Induction hepatocytes are frequently noted in the setting of polypharmacy, or chronic intake of phenytoin and barbiturates.[103] Phospholipidosis is another form of DILI seen as hepatocytes with foamy granular cytoplasm. Similar to induction hepatocytes, phospholipidosis represents an adaptive response to cationic amphophilic drugs like amiodarone and antimalarial agents, via the inhibition of lysosome-specific phospholipase A2.[100, 101]

DILI severity and prognosis

A liver biopsy can provide helpful prognostic information. The degree of necrosis and presence of prominent ductular reaction are associated with poor outcome, whereas the presence of eosinophils and granulomas is associated with better outcome.[104] These observations were also noted in a meta-analysis of DILI case reports.[105] According to DILIN, chronic DILI is the perpetuation of liver damage after 6 months from DILI onset independent of the pattern of liver injury, whereas the Spanish DILI Group considers 1 year as the best cutoff point.[48, 106] In contrast, a liver biopsy defines chronic liver disease when there is significant fibrosis or even cirrhosis noted on histology.[104]

GUIDANCE STATEMENTS

- **19. Liver biopsy is not required to make a diagnosis of idiosyncratic DILI but may be useful in DILI cases with a severe or protracted course and in those with diagnostic uncertainty. However, a biopsy is usually not required in mild or self-limited cases.**
- **20. A liver biopsy can help identify the hepatotoxic drugs based on specific histological patterns and can exclude concurrent liver diseases.**

- **21. A broad spectrum of histological patterns has been reported in patients with DILI, and a given drug may be associated with more than a single histopathological signature.**

- **22. The presence of eosinophils and granulomas on a liver biopsy in a patient with suspected DILI is associated with a more favorable outcome, whereas those who have necrosis or fibrosis have poorer outcomes.**

- **23. A liver biopsy from a patient with DILI may help determine the mechanism of injury, as was seen with the mitochondrial toxin fialuridine that led to microvesicular steatosis and necrosis.**

Causality Assessment

Causality assessment provides an organized approach to determining the likelihood that a given drug or HDS is the cause of liver injury by reviewing the timing, laboratory, and clinical features following exposure and exclusion of other more common causes of liver injury.[107] A scoring system is then applied to the component data fields, and a summary causality score is generated that typically ranges from definite (highly probable) to excluded (unlikely).

Models of causality assessment

Several clinical tools have been developed for DILI causality assessment (**Tables 5 and 6**).

1. **Structured causality assessment instruments:** Causality may be determined using various instruments with predefined points awarded to features from the patient's history (**Table 5**):

   a) The Roussel-Uclaf Causality Assessment Method (RUCAM), also known as the Council for International Organisations of Medical Sciences scale, was first published in 1993.[75, 77] It provides a score varying from −10 to +14 points and groups the scores into five likelihood categories with stratification by hepatocellular versus cholestatic/mixed injury. The updated RUCAM score

was published in 2016 and has several modifications that generates a score ranging from –9 to +14 points with the same five likelihood categories.[108]

b) The Maria-Victorino Clinical Diagnostic Scale (CDS)[109] uses similar variables to the RUCAM but excludes concomitant medications and includes points for extrahepatic manifestations. There are five likelihood categories, but the dynamic range of possible scores is more compressed compared with the RUCAM and the RECAM. The CDS is not widely used in clinical practice because it was shown to be inferior to the RUCAM.[110]

c) The Digestive Disease Week-Japan 2004 (DDW-J) score is a modification of the RUCAM with the inclusion of drug-lymphocyte stimulation test (DLST) results and peripheral eosinophilia.[111, 112] Scores range from −5 to +17 points. Although the DDW-J was shown to be superior to the original RUCAM in Japanese patients, it is not currently used outside of Japan because of the lack of widely available and reproducible DLST assays.[112]

d) The Revised Electronic Causality Assessment Method (RECAM) is currently available online. This semiautomated, computerized platform has a dynamic range of −6 to +20 points and performs at least as well as the RUCAM in independent datasets.[113] The RECAM removed several risk factors and has an expanded list of competing causes to exclude, and diagnostic testing is categorical and menu driven to reduce interobserver variability.

Generic causality assessment models include the World Health Organization Collaborating Centre for International Drug Monitoring system by the Uppsala Monitoring Centre, which have not gained traction in DILI research or clinical practice because of their lack of liver specificity.[114, 115]

2. **Structured Expert Opinion.** The semiquantitative scale developed by DILIN categorizes the likelihood of DILI into five probability groups that vary from less than 25% to greater than 95% probability (**Table 6)**.[74, 116, 117] Advantages of expert opinion include the ability to account for atypical cases, interrupted drug exposure, and synthesis of subtle clues including liver histology in relationship to published literature. This approach has been

shown to be as useful as the RUCAM, although expert opinion is rarely available in routine clinical practice.[117]

Limitations of Causality Assessment in DILI

There are several important challenges in DILI causality assessment, especially with the structured nonexpert opinion approaches. For example, patients may be taking multiple drugs or HDS products over the same time frame (e.g., multiple drugs for TB). In addition, compositional complexity and lack of label trustworthiness of HDS confounds assessment.[118, 119] An underlying chronic liver disease flare also is not accounted for by the current scales.[120, 121] Last, structured assessments do not take into account evolving knowledge of and experience with hepatotoxicity due to drugs and HDS over time, which will add confidence to decision making. Causality assessment by expert opinion addresses the unique clinical features of a particular patient along with knowledge of the hepatotoxic potential of the suspect agent versus other causes of liver injury.[122]

Limitations regarding the RUCAM include the relative weighting of its domain scores, which were developed using a set of cases with drug rechallenge and not by evidence-based or statistical weighting. Furthermore, consideration of other causes of liver injury may have been overlooked or unappreciated when the tools were first developed.[75, 118] For example, there is no requirement for testing for acute HCV or HEV infection, and there are few good data to justify inclusion of risk factors as listed in the RUCAM.[9, 29, 30] Some limitations of the original have been addressed in the updated RUCAM, which stratifies causality assessment by the R-value, expands the search for alternative diagnoses, specifies criteria for rechallenge, but still retains the risk factors of age and alcohol for all cases.[108, 119] The updated RUCAM also provides more specific guidance in ascertaining the hepatotoxicity profile of the suspect drug but is not intended for use in patients with chronic liver disease.

With RECAM now being available online, it is anticipated that this automated electronic platform may provide more rapid and reliable causality assessment using standardized, quantitative, and categorical data fields. Notwithstanding, RECAM has yet to be tested in regions of the world where the spectrum of DILI agents differs from that seen in the United States and Spain (**Table 2**) or in cases with more than a single suspect drug. Furthermore, the RECAM has not yet been tested in

herbal and dietary supplement induced liver injury cases and its inter and intrarater reliability needs to be determined.

GUIDANCE STATEMENTS

- **24. There are currently three commonly used causality assessment methods, and each has its own strengths and limitations.**
- **25. Structured causality assessment instruments incorporate the dose, duration, and timing of suspect drug and other concomitant drug or herbal and dietary supplement product use, an assessment of the laboratory, radiological and histological features at presentation, and exclusion of competing causes of liver injury.**
- **26. The semiquantitative expert opinion causality assessment scale developed by DILIN is frequently used in clinical practice and in prospective research studies, but the need for specialized expertise limits its generalizability.**
- **27. The updated RUCAM has improved user instructions and more complete diagnostic evaluation compared with the original RUCAM but retains risk factors of age, alcohol, and pregnancy that are of unclear value.**
- **28. The RECAM is a newly developed, computerized causality assessment instrument, which may prove more reproducible and reliable than RUCAM but further validation studies are needed.**
- **29. Intentional suspect drug rechallenge is rarely undertaken in clinical practice but, when available, may prove useful in causality assessment.**

Herbal and Dietary Supplement Hepatotoxicity

Herbal and dietary supplements are widely used around the world on a daily basis. For example, more than 50% of adults over the age of 20 used dietary supplements in the preceding 30 days in a 2017–2018 study.[123] Marketed supplements comprise single ingredient products as well as mixtures of many different ingredients that may be both natural and synthetic. Although herbals have been used for millennia by many different cultures for many purposes, contemporary herbal and dietary supplements commonly are multi-ingredient products that are marketed under the guise of delivering some improvement in appearance, performance, or sense of well-being.[124] Although the majority of marketed supplements are safe, many instances of harm resulting from individual and multi-ingredient products have been reported, including acute liver failure (ALF).

Submitted for publication July 7, 2022

Epidemiology of herbal and dietary supplement use and liver injury

American consumers spent more than $9.6 billion on herbal products in 2019.[125] Based upon DILIN Registry data, herbal and dietary supplements comprise approximately 20% of all cases of liver injury encountered in adults.[28] Regulation of products in the United States is minimal—manufacturers are not compelled to prove that their product is safe, and only need to attest to the product's safety based on historical use. The 1994 Dietary Supplement Health and Education Act provides the current regulatory framework for supplement manufacturing and distribution in the United States.[126] The regulatory environment in non-US markets varies, as summarized in a recent review.[127] For example, in the European Union, the allowance of a product on the market requires a demonstrated history of safe use, along with periodic chemical verification of the labeled ingredients.

Allegations of injury attributable to a dietary supplement can be reported by consumers and providers to the US Food and Drug Administration (FDA), through the MedWatch passive reporting system.[128] These reports are investigated by the FDA's Center for Food Safety and Applied Nutrition, and, when the veracity of a report is verified, regulatory actions can be taken against the manufacturer, including withdrawal of a product from the market in the most extreme circumstance.

Special considerations in the diagnosis of herbal and dietary supplement associated liver injury

Structured causality assessment tools are confounded by several factors unique to herbal and dietary supplements. First, it is well known that supplements are vulnerable to intentional or inadvertent inclusion of ingredients. Botanical ingredients include plant parts and other herbs that are not listed on the product label. Nonbotanical ingredients include chemicals, pesticides, and heavy metals. Intentional adulteration usually results from the inclusion of substances, usually pharmaceuticals, to achieve some pharmacodynamic effect in keeping with the supplement's marketed purpose for use. An example is the inclusion of sildenafil in products marketed for sexual performance. Second, the composition of herbal and dietary supplements may change over time as a result of varying growing conditions, leading to batch-to-batch variability. Third, latency of exposure to a product before the onset of injury can be quite variable because of the accumulation of product within the body. Finally, the lack of knowledge and awareness of potential liver injury from these widely used, over-the-counter supplements may cause the injury to go unrecognized by patients and providers.

Herbal and dietary supplement hepatotoxicity; susceptibility factors, and outcomes

Submitted for publication July 7, 2022

Many of the most prominent instances of hepatotoxicity from herbal and dietary supplements have resulted from multi-ingredient products such as Hydroxycut, Herbalife, and Oxy-Elite Pro.[129] However, dietary supplements are ever-changing, in that there is variability of ingredients that may come and go within the same supplement, such that the product sold with the same label at two time points could be substantially different. Furthermore, the DILIN has shown that supplements implicated in liver injury are frequently mislabeled.[130] DILIN's current efforts are being directed to understand the toxicity that may result from specific ingredients that are sold individually or as ingredients in product mixtures. (**Table 7)**

Through detailed analyses of hepatotoxicity due to specific ingredients, recognition of characteristic toxicity patterns arises. The polyphenolic catechins comprise the chemically active component of green tea extract (GTE). The polyphenolic backbone of the catechins is exploited for its antioxidant potential but is likely also responsible for liver injury. Several cases of liver injury due to GTE have been published, with the most convincing cases being those in which injury recurred following rechallenge.[131, 132] A focused analysis of GTE cases enrolled in DILIN has led to recognition of the typical presentation of GTE as being hepatocellular and sometimes fatal, with a strong genetic association with HLA-B*35:01.[72] This same HLA risk allele has also been associated with hepatotoxicity in Han Chinese individuals attributed to *Polygonum multiflorum*, a popular herbal taken to enhance hair color and improve fertility.[73]

Recent studies have shown that patients with herbal and dietary supplement hepatoxicity leading to liver failure are more likely to die or undergo transplantation compared with patients with drug hepatoxicity.[133, 134] This may be due to delayed recognition of the product as the cause of liver injury or reluctance of herbal and dietary supplement consumers to seek medical care.

GUIDANCE STATEMENTS

- **30. Herbal and dietary supplements are commonly used worldwide, with permissive standards of safety in the United States and other countries leading to the possibility of inaccurate labeling, adulteration, and contamination.**
- **31. Supplements can cause severe hepatotoxicity that can have variable clinical, laboratory, and histological phenotypes.**

- **32. Genetic polymorphisms in the HLA region and the conditions under which a product is consumed may influence the likelihood of an individual patients developing herbal and dietary supplement hepatotoxicity.**

- **33. HLA-B 35:01 has been associated with hepatotoxicity attributed to GTE in White populations and P. multiflorum hepatotoxicity in Asian populations.**

Natural history and management of idiosyncratic DILI

The majority of adults and children with idiosyncratic DILI present with a drug latency of 2–24 weeks, although some drugs have an ultrashort (<7 days) latency.[30] In multiple prospective registry studies, nearly 50% of patients have acute hepatocellular injury, whereas the remainder present with either an acute mixed or cholestatic injury pattern (**Table 2**). Once a diagnosis of idiosyncratic DILI is suspected, the suspect agent(s) should be immediately discontinued. Hospitalized patients with severe acute liver injury need to be carefully monitored for disease progression, and those with ALF (coagulopathy and encephalopathy) should be urgently referred to a liver transplant center because of their low likelihood (~25% chance) of spontaneous recovery.[34,143]

With drug discontinuation, the majority of patients with DILI (80%) fully recover without long-term sequelae.[30] However, up to 10% of patients with severe hepatocellular DILI with jaundice may be at risk of death because of their liver condition or underlying medical comorbidities. Multiple studies have also demonstrated that patients with higher total bilirubin and INR levels as well as lower serum albumin levels at presentation are at greatest risk for adverse outcomes.[143–146] In addition, recent prospective registries have demonstrated that patients with pre-existing liver disease are at greater risk of adverse hepatic outcomes.[30, 29] Per **Table 8**, a variety of prognostic indices and tools have been proposed to identify patients with DILI at increased risk of adverse hepatic outcomes. Similarly, some clinical features are associated with a greater likelihood of spontaneous recovery such as the presence of granulomas and eosinophils on liver biopsy.[88, 107]

Chronic DILI is typically defined as persistent elevation in serum liver biochemistries or the presence of radiological or histological evidence of ongoing injury 6–12 months after DILI onset.[29, 147] The incidence of chronic DILI in 598 subjects enrolled into DILIN was 21% at 6 months, with African Americans and patients with a cholestatic liver injury at presentation being at increased risk.[147] A minority of patients (i.e., <1%) may also experience progressive loss of intrahepatic bile ducts leading to VBDS that can be progressive and fatal.[100] Other reported phenotypes of chronic DILI include hepatic steatosis from tamoxifen and NRH due to azathioprine or oxaliplatin that may lead to complications of portal hypertension during long-term follow-up (**Table 4**).

Submitted for publication July 7, 2022

Medical Management of idiosyncratic patients with DILI

General supportive care is recommended for all patients with acute DILI including the use of antiemetics, analgesics, antipruritics, and parenteral hydration as needed. Patients with severe nausea and vomiting, coagulopathy, mental status changes, or dehydration may require hospitalization for observation and monitoring (**Table 9**). A 3-day course of *N*-acetylcysteine (NAC) should be considered in adult patients with DILI-related ALF in light of improved 3-week outcomes in a large randomized controlled trial, particularly in patients with early stage encephalopathy.[148] Another randomized trial of 102 patients with antitubercular DILI also demonstrated a shorter length of stay but no survival benefit with NAC.[149] However, outcomes with a short course of parenteral NAC were poorer in children with non-APAP ALF, limiting enthusiasm for its use in children.[150] Corticosteroids at a dose of 1 mg/kg of methylprednisolone are frequently given to patients with severe immune-mediated hypersensitivity reactions, including the syndrome known as drug reaction with eosinophilia and systemic symptoms (DRESS).[151, 152] In some instances, a short course of corticosteroids (i.e., 1–3 months) with rapid tapering may be of benefit in patients with autoimmune features on biopsy as well as for patients with DILI from ICIs and tyrosine kinase inhibitors.[153, 154] (**Table 9**). Ursodeoxycholic acid may improve symptoms of pruritus and hasten DILI recovery, but large, randomized controlled trials are needed to determine the optimal dose and duration.[155]

In addition to general supportive care, drug-specific therapy may be recommended for selected scenarios. For example, there are uncontrolled data demonstrating clinical benefit with L-carnitine therapy for children with hyperammonemia due to valproate hepatotoxicity.[156] In addition, cholestyramine may be of value for patients with leflunomide hepatotoxicity because of its prolonged half-life and enterohepatic circulation.[157] Last, defibrotide is a complex mixture of single stranded polydeoxyribonucleotides derived from porcine intestine that has antithrombotic and profibrinolytic activity. Its use has been associated with improved survival in patients with severe SOS following hematopoietic cell transplantation compared to historical controls.[158]

GUIDANCE STATEMENTS

- **34. Most adults and children with idiosyncratic DILI present with an acute liver injury phenotype that may or may not be symptomatic but typically resolves within 6 months of onset without long-term sequelae in 80%.**

Submitted for publication July 7, 2022

- **35. In registry studies, 10% of patients with idiosyncratic DILI are at risk for adverse hepatic outcomes including ALF, liver transplantation, and death within 6 months of onset.**
- **36. Because of the low likelihood of spontaneous survival in idiosyncratic DILI-related ALF of only 25%, early transfer of these individuals to a liver transplant center is recommended.**
- **37. Chronic liver injury that persists beyond 6–12 months is observed in 10%–20% of patients with DILI and may be more commonly encountered in those with cholestatic DILI.**
- **38. Individuals at increased risk for adverse outcomes include patients with DILI with higher bilirubin and INR values and lower serum albumin at presentation as well as those with severe necrosis and fibrosis on liver biopsy and those with medical comorbidities and pre-existing liver disease.**
- **39. Discontinuation of the suspect drug along with supportive care of antiemetics, antipruritics, and hydration are the mainstay of idiosyncratic DILI management.**
- **40. A short course of intravenous NAC may be of benefit in hospitalized adult patients with DILI-related ALF, but this therapy is not recommended for children.**
- **41. Corticosteroids given for 1–3 months may be of benefit in selected patients with idiosyncratic DILI, including those with severe hypersensitivity features, DRESS, and autoimmune features on liver biopsy. However, the optimal dose and duration are unknown because of the lack of controlled clinical trials.**
- **42. Ursodeoxycholic acid is not an established therapy for patients with DILI but is presumably safe to administer.**
- **43. Defibrotide is a profibrolytic that is approved for use in adults and children undergoing hematopoietic cell transplantation with moderate to severe SOS.**
- **44. Rechallenge with the suspect drug should generally be avoided unless the anticipated benefit is high for a severe or life-threatening condition.**

APAP hepatotoxicity

APAP is widely used and a ubiquitous over-the-counter analgesic. In North America, APAP overdose is believed to result in 100,000 calls to poison control centers, 50,000 emergency room visits, and at least 500 deaths annually.[159] The annual number of ALF cases from APAP dwarfs the number of ALF cases associated with all idiosyncratic reactions combined.[160] The reason for this widespread toxicity is that, unlike drugs associated with idiosyncrasy, APAP is a dose-related hepatotoxin, with all mammalian species susceptible to liver injury in doses only two to three times therapeutic dosing.[161] Although APAP initially was noted to be a frequent cause of toxicity in attempts at self-harm, increasing recognition of inapparent or unintentional overdosing has become apparent.[162] Unintentional overdosing may occur in the setting of chronic pain or flu-like symptoms because of the lack of awareness of dosing limitations and/or the simultaneous use of multiple APAP containing products.[163] Other risk factors for APAP toxicity include fasting and malnutrition, which can lead to depletion of intrahepatic glutathione stores, as well as use of alcohol and other medications that can induce the cytochrome P-450 system and lead to enhanced production of the toxic metabolite, *N*-acetyl-p-benzoquinone imine.[164] Recent data suggest that APAP hepatotoxicity may occur even when therapeutic doses are used, but particularly in association with these other cofactors.[165] Histologically, APAP toxicity is characterized by a variable degree of pericentral necrosis.

A diagnosis of APAP overdose is based upon a history of ingestion of excessive doses (usually >4 g as a single time point) that can then lead to variable severity of acute hepatocellular liver injury with towering transaminase levels (often >1000 U/L) within the first 24 h of observation (**Table 10**). Measurement of a serum APAP level after a single time point ingestion can help identify the patients at greatest risk of developing liver injury.[161] More recently, detection of serum APAP-protein adducts has been proposed as a more specific means to make a diagnosis of APAP hepatotoxicity particularly in patients presenting late or with an unintentional overdose, but this assay is not commercially available.[166]

Management of APAP overdose

After a single time point APAP overdose, symptoms of nausea and vomiting ensue within 12–24 h, peaking at about 72 h, and resolving rapidly thereafter. The severity of necrosis is linked to the extent of excess dosing and can lead to hyperacute ALF because of its rapid onset. Administration of oral or intravenous NAC is an effective antidote given as a loading dose followed by maintenance doses over several days.[167] If NAC is administered within 12 h of ingestion, it virtually assures that the liver damage will be minimal. The characteristic laboratory profile of APAP hepatotoxicity include

very high aminotransferase levels with low bilirubin. The coagulopathy can be severe, and a prolonged INR is a bad prognostic sign.[168]

Management in the early h after an APAP overdose includes activated charcoal by ingestion or gavage, and certainly NAC, even if given more than 12 h after APAP ingestion.[169, 170] For unintentional cases, NAC is also given although its efficacy may be limited. Development of signs and symptoms of liver failure (encephalopathy, primarily) are concerning, and once they are present, nearly one-third of patients either die or require a liver transplant. The remaining patients make a full and complete recovery within 7days.

Prognosis

Several prognostic scores have been developed and evaluated including the King's College Hospital score, MELD score, and the Acute Liver Failure Study Group prognostic index.[167] In countries in which the over-the-counter sale of APAP has been restricted, the incidence of serious APAP toxicity has fallen. Outcomes have also generally improved over the past two decades, likely because of improvements in intensive care, with only 8% of patients undergoing transplantation.[168, 169]

GUIDANCE STATEMENTS

- **45. APAP is a dose-dependent hepatotoxin that leads to acute pericentral liver injury when doses exceeding 4 g are ingested within a 24-h period or excessive doses over several days.**
- **46. APAP overdose is the leading cause of ALF among adults in the United States.**
- **47. A diagnosis of APAP hepatotoxicity relies upon a history of excessive APAP ingestion, detection of an elevated serum APAP level following single time point ingestion, and exclusion of competing causes of acute hepatocellular liver injury.**
- **48. Gastric lavage and activated charcoal should be given to all patients presenting within 4 h of a single time point APAP overdose.**
- **49. Intravenous or orally administered NAC can prevent liver injury nearly completely if given within 12 h of ingestion but is also recommended for patients presenting later.**
- **50. The prognosis in APAP-related ALF is related to the degree of encephalopathy, coagulopathy, and acidosis.**

Early detection of DILI in clinical practice

The key to preventing clinically significant liver injury from DILI is early detection of the signal event before it becomes symptomatic or severe. Therefore, individuals taking a drug with a moderate to high likelihood of causing DILI should undergo laboratory and clinical monitoring using a validated surveillance program, but only a few bona fide protocols exist. Currently, the FDA advises practitioners to follow recommendations in the FDA product labels for a multitude of potential hepatic adverse events.[171] In addition, patients taking potentially hepatoxic medications are advised to report any new or untoward symptoms to their provider.

FDA-approved labels are available online and can be searched through the FDA database, Drugs@FDA (https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm). Substantial differences have been identified between US (FDA) and European Medicines Agency drug labeling recommendations regarding hepatoxicity.[172, 173] For example, 8.7% of the warnings for drug hepatoxicity and 21.3% of the contraindications for patients with liver disease were disparate in a recent study.[173]

Submitted for publication July 7, 2022

The package inserts of currently approved drugs may recommend (i) monitoring, with or without providing a schedule for testing or any instructions; (ii) therapy discontinuation if symptoms and/or signs of liver injury supervene; or (iii) medication discontinuation or interruption for specified laboratory abnormalities.[174, 175] **Per Table S1**, the specific recommendations vary substantially by agent. Although many medications have been associated with liver-related fatalities, only a minority carry a black box warning for hepatotoxicity. Some recently approved drugs and biological agents have concrete recommendations for monthly laboratory monitoring during the first 12 months of therapy to detect acute hepatocellular injury. In contrast, VBDS was observed during clinical studies of pexidartinib, a monoclonal antibody used to treat tenosynovial giant cell tumor.[176] To ensure prompt treatment modification or discontinuation in patients with early liver injury, a comprehensive risk evaluation and mitigation strategy has been instituted by the FDA for pexidartinib that requires the registration and clinical monitoring of all treated patients.[176]

Hepatotoxicity monitoring in routine clinical practice

A commonsense approach to monitoring is to target individuals who are taking medications that have a high likelihood of causing hepatotoxicity. Important considerations for liver biochemistry monitoring include (i) reference ranges for serum aminotransferase levels which may vary among laboratories, (ii) the presence of baseline elevations in patients with underlying liver disease, (iii) latency of enzyme elevations that may vary from days to months and, rarely, even years (e.g., with nitrofurantoin and minocycline), [81] and (iv) transient and self-limited aminotransferase elevations encountered with drugs like isoniazid (INH) and statins (**Figure 3**) that can resolve with continued dosing presumably because of metabolic and or immunological adaptation.[177, 178]

Monitoring strategies for four commonly used medications

Isoniazid

In the United States, an estimated 13 million individuals have latent TB, but less than 10,000 individuals are treated for active TB each year.[179] Although the incidence of severe DILI appears to be lower than previously appreciated,[180] isoniazid continues to be a leading cause of DILI-related ALF in the United States and worldwide (**Table 2**).[181–184] The recommended treatment for latent TB has recently changed from 6–9 months of isoniazid monotherapy to

regimens with a lower risk of hepatoxicity, including 3- to 4-month regimens of isoniazid with other agents.[185] Whereas the treatment for active TB still consists of isoniazid, rifamycin, pyrazinamide, and ethambutol, alternative strategies are now available that depend upon various individual patient characteristics.[186]

Over the past 40 years, various recommendations for laboratory monitoring while receiving INH have been proposed that begin with baseline liver assessments for all patients. However, this approach has not been shown to be better than assessing for clinical symptoms of hepatitis at detecting toxicity.[181–184] Although the specific details are left to individual local and state programs to adopt, monthly liver test monitoring is generally reserved for those with baseline liver test abnormalities, viral hepatitis, heavy alcohol use, use of other hepatotoxic medications, underlying liver disease, or HIV infection and current or recently pregnant women. Periodic liver tests can also be performed in those older than 35 years of age. Underreporting and poor adherence to American Thoracic Society guidelines are common in cases of INH hepatotoxicity and are associated with hospitalization, death, and liver transplantation.[187, 188] However, when patients are educated to self-monitor and stop drugs when symptoms occur, ALF and death can be averted.[189] Finally, reintroduction of INH after a DILI episode leads to recurrent liver injury in only 10% of patients but should only be done for patients with active, drug-resistant TB.[190]

Methotrexate

Long-term methotrexate (MTX) treatment can be associated with the insidious development of hepatic steatosis and fibrosis. Established risk factors for accelerated liver injury with MTX therapy include active alcohol consumption, pre-existing liver disease, diabetes, hyperlipidemia, and obesity.[191] Serial serum liver enzyme testing is part of all surveillance protocols devised by rheumatologists and dermatologists, and interval liver biopsy had previously been the mainstay to determine the extent and progression of fibrosis. When the liver biopsy guidelines in rheumatoid arthritis were relaxed, more frequent blood testing reduced the need for liver biopsies without sacrificing patient safety.[192, 193] The 2008 American College of Rheumatology guidelines for the treatment of rheumatoid arthritis advises laboratory monitoring at baseline and then every 2–4 weeks with the first 3 months, every 8–12 weeks for 3–6

months, and then every 12 weeks beyond 6 months of treatment.[194] The updated 2021 guidelines further restrict the use of MTX in patients with suspected NAFLD to those with normal liver tests without advanced hepatic fibrosis (stage 3 or 4), detected by noninvasive testing.[195] In contrast, the 2020 Academy of Dermatology guidelines for managing psoriasis recommends fibrosis-4 serologic testing and transient elastography at baseline and annually while on MTX therapy in patients with risk factors for hepatotoxicity.[196] Laboratory monitoring is recommended at baseline and every 3–6 months. Liver biopsy is reserved for those who have abnormal transient elastography results or those who have persistent liver test elevations. After 3.5–4.0 g of cumulative dose exposure, transient elastography and/or liver biopsy are recommended for all MTX recipients.

Statins

There are 7 HMG-CoA reductase inhibitors or "statin" drugs that are used on a daily basis by millions of patients with hyperlipidemia. In general, statins are safe to administer, but myalgias and myopathy may lead to early dose reduction or termination in up to 10% of treated patients.[197] Early on there was concern of self-limited serum aminotransferase elevations in up to 20% of patient receiving statins, but clinically significant hepatic dysfunction was very uncommon. In the DILIN study, only 22 of 1188 (1.8%) consecutively enrolled patients with DILI were attributed to a statin over an 8-year period.[93] Both acute cholestatic and hepatocellular injury were observed, as well as fewer patients with autoimmune features. Several randomized controlled trials have demonstrated no significant increase in the incidence of persistently elevated serum aminotransferase levels between statin and placebo therapy, including in patients with known chronic liver disease.[198–200] In addition, other studies have suggested that statins in patients with compensated chronic liver disease and cirrhosis may even reduce the risk of hepatocellular cancer and decompensation.[201] In 2012, the FDA altered the product labels of available statins so that baseline liver biochemistries be obtained but that on-treatment liver biochemistry monitoring is not required unless clinically indicated.[202] Therefore, we do not recommend checking liver biochemistries in patients receiving statins unless there are new or unexplained symptoms of hepatitis. However, statins should be avoided in patients with decompensated cirrhosis due to their hepatic metabolism, but low doses can be considered on an individual basis after assessing overall risk versus benefit.

Immunotherapy

Immune check point inhibitors (ICIs) are monoclonal antibodies given alone or in combination with other cancer treatments every 2–4 weeks that are prescribed to more than 50% of oncology patients with advanced solid organ tumors.[8, 203] The severity of IMH and other irAEs has been stratified into five grades according to common terminology criteria for adverse events. The incidence of IMH ranges varies from 1% to 15% in clinical trials and observational studies, respectively.[204] The majority of patients with IMH develop asymptomatic injury in the first 6–12 weeks of treatment. Patients who receive cytotoxic T-lymphocyte-associated protein 4 CTLA-4 antagonists particularly in combination with programmed cell death 1 and programmed cell death receptor ligand 1 inhibitors are at greatest risk of developing IMH. Recent studies suggest that bona fide DILI is only responsible for 30% of cases of demonstrable liver injury in patients with advanced cancer, whereas hepatic metastases, sepsis, and other causes of liver disease account for the remainder emphasizing the importance of contrast enhanced CT and MRI scanning in evaluation of these patients.[205] Liver biopsy typically demonstrates lobular or periportal hepatitis and is generally not recommended unless patients have persistent grade 3 hepatotoxicity or jaundice despite corticosteroids.[206]

Monitoring for IMH and other irAEs begins with baseline clinical assessment and laboratory testing before each treatment cycle. For patients with grade 1 liver injury (ALT >1–3× ULN and/or total bilirubin >1–1.5× ULN), continued therapy with more frequent laboratory monitoring is advisable. For patients with an ALT 3 to 5 x ULN and/or total bilirubin 1.5–3× ULN (grade 2 liver injury), the ICI should be withheld and consider oral prednisone 0.5–1.0 mg/kg per day (**Table 9**). For patients with grade 3 or higher hepatotoxicity (ALT 5–20× ULN and/or bilirubin 3–10× ULN or symptomatic liver dysfunction), the ICI should be permanently discontinued, and IV steroids at a dose of 1–1.5 mg/kg per day along with hospitalization for patients with jaundice should be considered. Mycophenolate mofetil or azathioprine can be used for steroidrefractory disease. After tapering of immunosuppression, the liver tests should continue to be monitored every 2–4 weeks because of the risk of rebound hepatitis. Fatalities arise in <1% of patients with IMH and almost exclusively occur in those with jaundice.[207] Rarely, ICI related sclerosing cholangitis can present with a cholestatic pattern of liver test elevations.

GUIDANCE STATEMENTS

- **51. Early detection of DILI is best achieved by educating patients to report untoward symptoms to their providers along with prospective clinical and laboratory monitoring with certain high-risk drugs like the ICIs, isoniazid, and methotrexate.**
- **52. All practitioners are encouraged to voluntarily report instances of suspected DILI to the FDA via the MedWatch system at https://www.fda.gov/safety/medwatch.**
- **53. Transient elevations of serum liver enzymes can be seen with drugs such as isoniazid that are self-limited despite continued dosing presumably because of metabolic and immunological adaptation.**
- **54. The FDA and LiverTox websites are a rich resource for information about drug hepatotoxicity and provide informative relevant documents and recommendations for surveillance that may be accessed online, including drug labeling and package inserts.**
- **55. Recommendations for hepatotoxicity monitoring vary in detail, according to the background information available. Often, common sense must be applied and/or experts consulted.**
- **56. Recommended monitoring for isoniazid hepatotoxicity includes patient education to report new symptoms suggestive of hepatitis. Monthly laboratory monitoring has not been shown to reduce the incidence of clinically significant liver injury and can lead to premature discontinuation of therapy in many patients. However, many specialty societies advise baseline and on-treatment laboratory monitoring in high-risk individuals.**
- **57. Annual measurement of liver elastography is recommended as a noninvasive means to monitor the hepatotoxicity of drugs like methotrexate that tend to cause silent fibrosis but is not likely applicable to most other drugs that cause DILI.**
- **58. Predosing liver biochemistries are recommended for all patients initiating statin therapy. However, routine on-treatment monitoring of liver biochemistries is not recommended because of the low risk of hepatotoxicity including in patients with liver disease.**
- **59. Patients with known compensated chronic liver disease and cirrhosis can and should receive statins as clinically indicated. However, use of statins in people with decompensated cirrhosis should be individualized based upon assessment of risk versus benefit.**

- **60. Predosing and on-treatment laboratory monitoring is the standard of care for oncology patients receiving ICIs with a series of steps to withhold the drug, increase laboratory monitoring, and use corticosteroids based upon the severity of liver injury.**

Summary/ Future Directions

Areas of unmet need in DILI clinical care include the need for improved diagnostic and prognostic biomarkers, accurate and reliable causality assessment instruments, and studies of the epidemiology of DILI. International Classification of Diseases, Tenth Revision codes and natural language processing algorithms may help identify DILI cases from administrative databases, but further refinement is needed.[208, 209] In addition, improved understanding of the molecular pathogenesis of DILI is needed to minimize future morbidity and mortality and identify therapeutic targets for intervention.

DILI biomarkers

Currently available serum markers of liver injury (i.e., AST, ALT, ALP) are neither sensitive nor specific enough to detect early DILI, nor are they able to reliably predict clinical outcomes. DILI biomarkers in development broadly fall into four categories: (A) dynamic liver injury markers that quantify the extent or severity of hepatocyte damage; (B) mechanistic biomarkers that aim to elucidate the intracellular pathways of liver injury; (C) prognostic biomarkers; and (D) diagnostic biomarkers including single nucleotide polymorphisms. Currently, glutamate dehydrogenase and micro-RNA-122 show promise as being more sensitive and specific biomarkers for liver injury compared with ALT from clinical studies in patients with APAP overdose (**Table 12**).[210, 211] The apoptotic index, which incorporates full-length serum cytokeratin 18 (CK18) and caspase-cleaved CK18 levels, may also be more sensitive than serum ALT in detecting liver injury and also be of prognostic value.[212, 213] Release of damage-associated molecular patterns (DAMPs) that activate immune cells to release cytokines and chemokines are believed to be important in DILI pathogenesis. In this regard, high-mobility group box 1, a DAMP that can be detected in the serum in various isoforms, ,as well as MCSFR and osteopontin, demonstrate promise as prognostic biomarkers.[210, 214–216]

To improve DILI diagnosis, several groups have proposed to include the results of in vitro lymphocyte proliferation assays wherein lymphocytes from the index patient are incubated with the suspect drug. (**Table 4)**.[111, 112] The DILIN tested a multiplex lymphocyte proliferation assay but did not obtain informative results.[217] Other groups are exploring the development of in vitro test systems derived

from circulating macrophages and human liver organoids, but further validation is needed.[218, 219] To facilitate DILI biomarker discovery and research, collection of biological samples using standardized protocols is strongly recommended along with use of consistent case definitions and adjudication both in clinical trials and registry studies.[5]

The early intracellular events and mechanisms that lead to DILI are not well understood. Studies of infiltrating lymphocytes in the livers of patients with DILI have demonstrated unique cellular profiles, but further studies are needed to improve our understanding of the immunopathogenesis of DILI with the hope of preventing disease progression and identifying targets for therapeutic intervention.[220]

GUIDANCE STATEMENTS

- **61. Currently available serum markers of liver injury such as serum AST, ALT, and ALP levels are not sensitive or specific enough to detect early DILI.**
- **62. DILI research continues to be hampered by the lack of an objective, reliable laboratory test to confirm a particular drug as the correct suspect agent.**
- **63. DILI biomarkers in development are currently being directed toward improved DILI diagnosis and prognosis as well as to provide mechanistic insight into DILI pathogenesis.**
- **64. DILI registries worldwide should use standardized methods and protocols for clinical and biological sample collection and causality assessment to facilitate studies of DILI epidemiology, outcomes, and treatment.**

Acknowledgements

The authors are grateful for the valuable contributions of the AASLD Practice Guideline Committee (PGC), particularly Matthew J. Stotts, MD. Members of the PGC include Elizabeth C. Verna (chair), George Ioannou, (chair), Rabab Ali, Scott W. Biggins, Roniel Cabrera, Henry Chang, Michael F. Chang, Po-Hung Chen, Kathleen Corey, Archita Parikh Desai, Albert Do, David S. Goldberg, Saul J. Karpen (board liaison), W. Ray Kim (board liaison), Lindsay King, Cynthia Levy, Jeff McIntyre, Jessica L. Mellinger, Anthony J. Michaels, Andrew Moon, Mindie H. Nguyen, Nadia Ovchinsky, Anjana A. Pillai, Daniel S. Pratt,

Ashwani K. Singal, Elizabeth Rand, Hugo R. Rosen, Adrienne Simmons, Matthew J. Stotts, Christopher J. Sonnenday, Puneeta Tandon, and Lisa B. VanWagner. The authors would like to thank the AASLD staff and particularly Audrey Davis-Owino for assistance in developing this guidance document.

Financial Support: Funding for the development of this Practice Guidance was provided by the American Association for the Study of Liver Diseases.

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Tables

Figure Legends

Figure 1. Proposed diagnostic algorithm for patients with suspected drug-induced liver injury (DILI). A diagnosis of DILI relies upon careful elicitation of clinical history and drug exposures along with exclusion of other more common causes of liver injury. A1AT, alpha-1-antitrypsin; ALP, alkaline phosphatase; ALT alanine aminotransferase; AMA, anti-mitochondrial antibody; ANA, antinuclear antibody; ASMA, anti-smooth muscle antibody; AST, aspartate aminotransferase; CK, creatine kinase; CMV, cytomegalovirus; CT, computerized tomography; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; INR, international normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; T3, triiodothyronine; T4, thyroxine; TB, total bilirubin; TSH, thyroid stimulating hormone; TTG, tissue transglutaminase; ULN, upper limit of normal.

Figure 2 Examples of histological injury attributed to DILI. (a) Nodular regenerative hyperplasia can be seen with azathioprine and oxaliplatin. Reticulin stain highlights a nodular architecture with nodules made up of hyperplastic hepatocytes characterized by two-cell-thick plates that are bordered by atrophic hepatocyte plates. Note that the portal tract (arrow) is in the center of the nodule, termed reverse lobulation (original magnification ×10, reticulin stain). (b) Hepatocytes with ground-glass like cytoplasm are characterized by smooth homogeneous light pink color as opposed to the typical grainy eosinophilic cytoplasm of normal hepatocytes. These hepatocytes are typically found in zone 3. The development of these is often due to polypharmacy (original magnification ×10, hematoxylin and eosin stain). (c) This photomicrograph shows dilated canaliculi containing bile but no inflammatory infiltrates are present and very rare hepatocytes are noted to be undergoing feathery degeneration. This pattern of injury is reported with drugs such as trimethoprim-sulfamethoxazole (original magnification ×40, hematoxylin and eosin).

Figure 1.

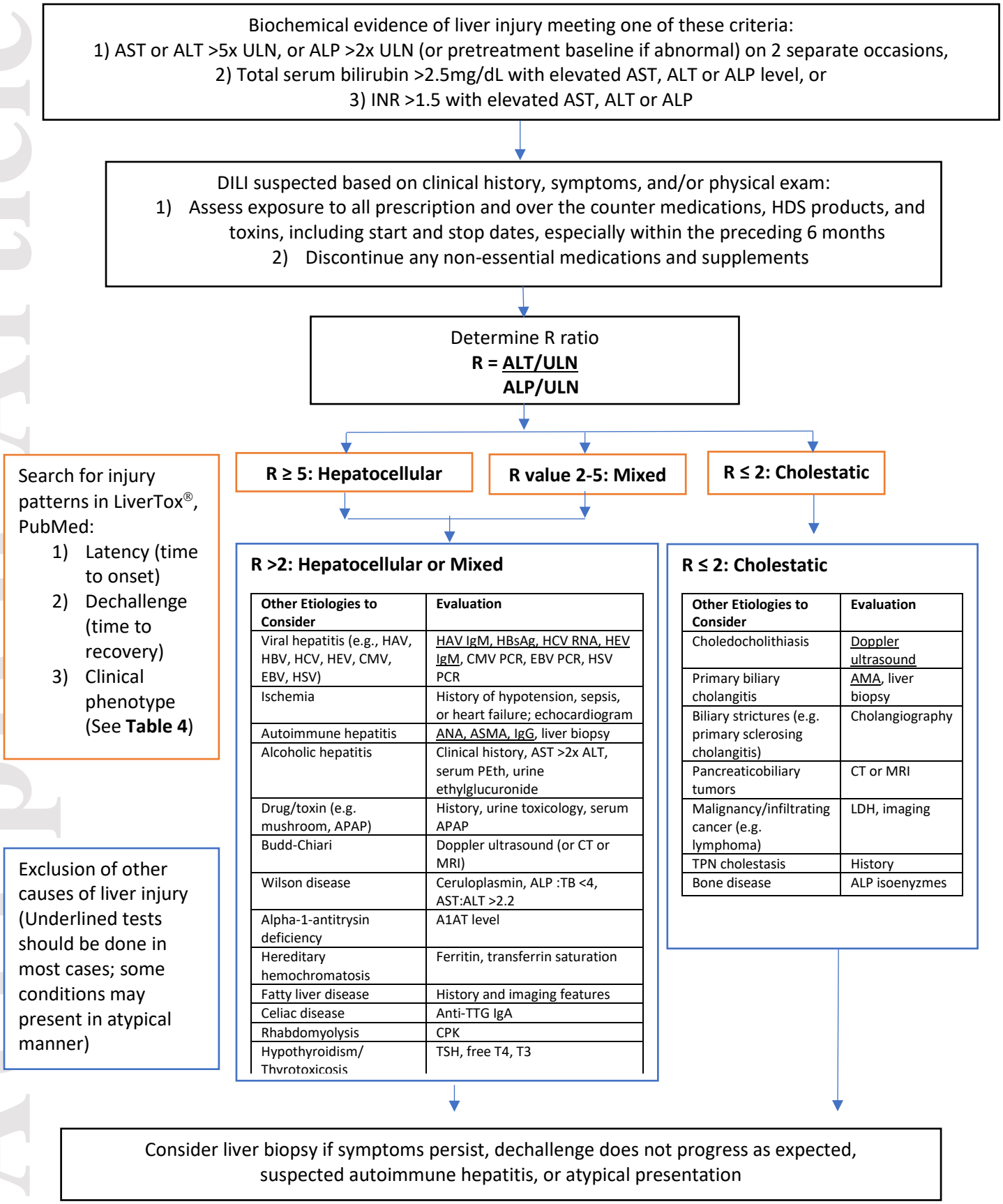

Figure 2a: Nodular Regenerative Hyperplasia (NRH). 10x reticulin stain.

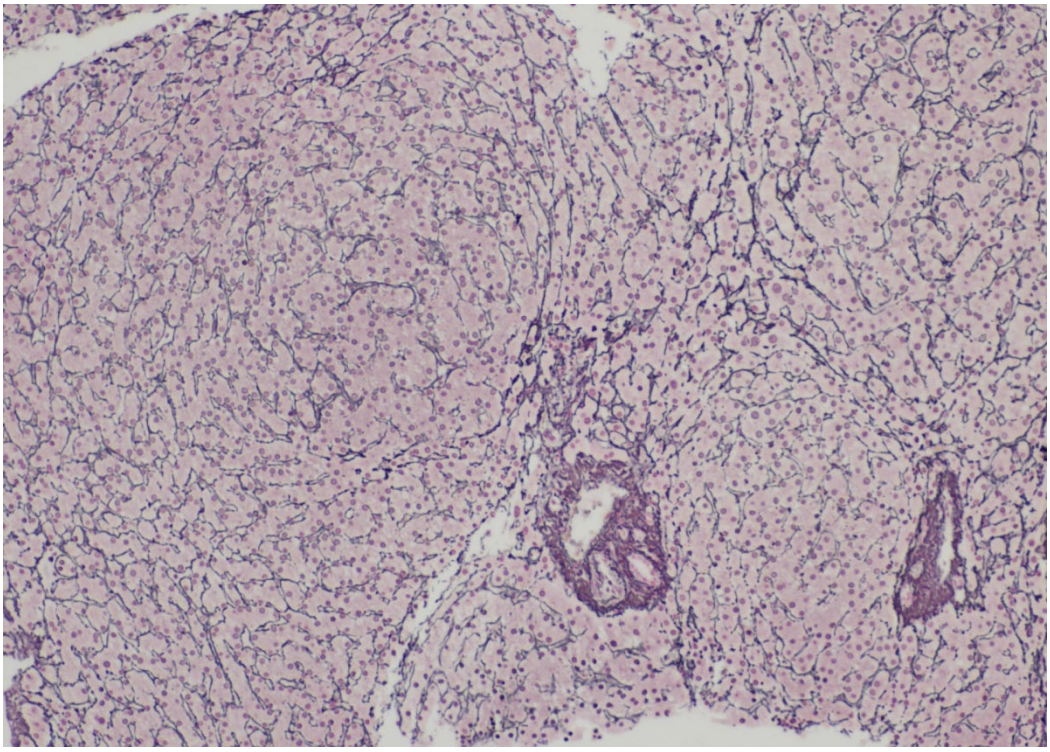

Figure 2b: DILI Ground Glass Cytoplasm

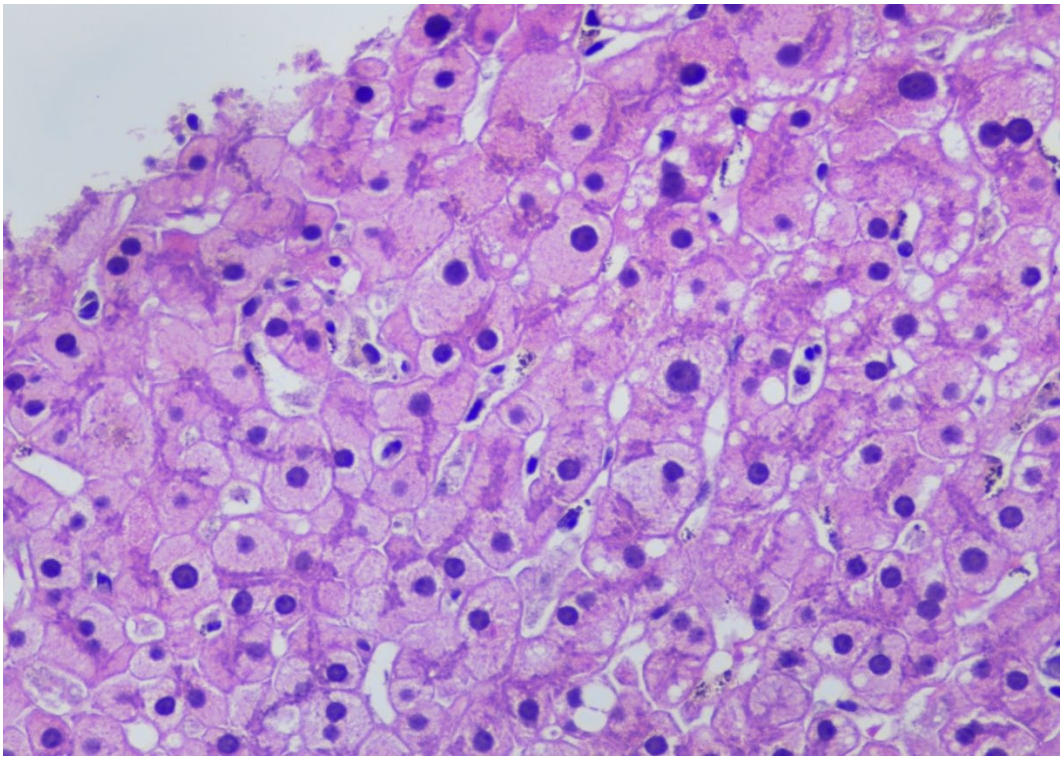

Figure 2c: Bland Cholestasis

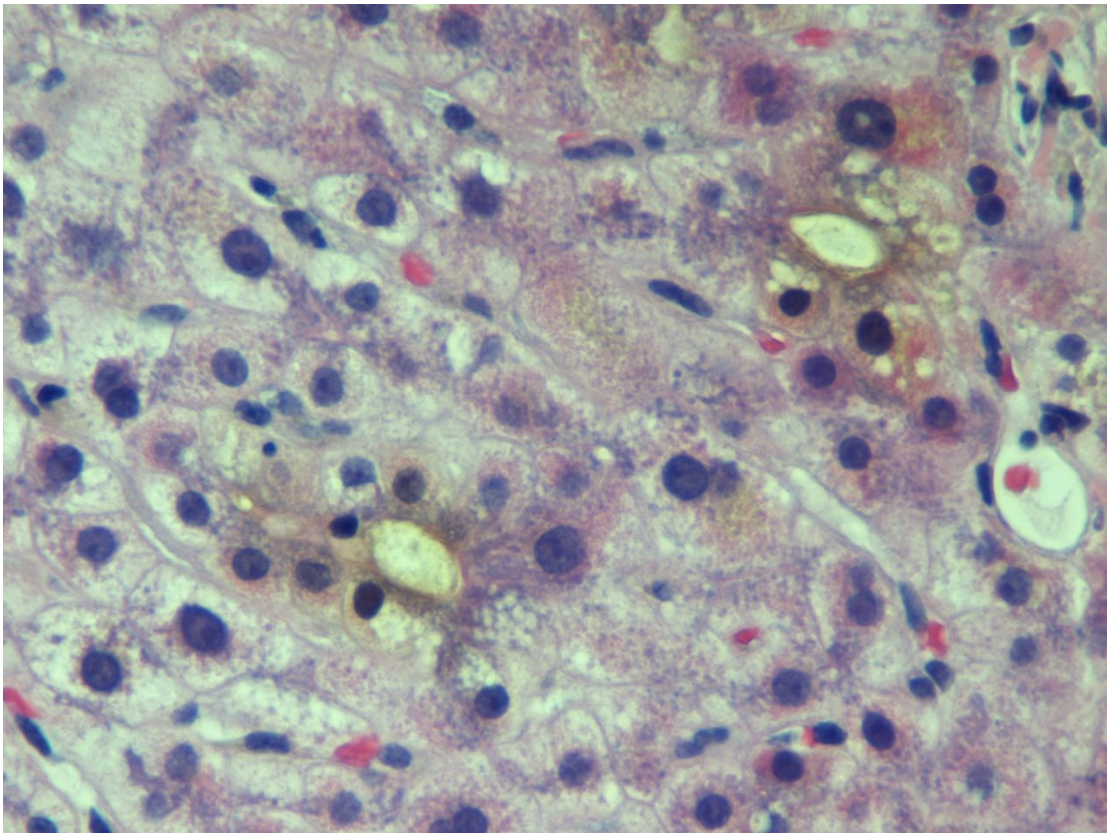

TABLE 1 Proposed classification of drug-induced liver injury

Mechanistic Classification	**Direct hepatotoxicity**	**Idiosyncratic hepatotoxicity**	**Indirect hepatotoxicity**
Incidence	Common	Rare	Intermediate
Dose relatedness	Yes	No	No
Predictable	Yes	No	Partially
Reproduced in animal models	Yes	No	Not usually
Latency	Rapid (days)	Variable (days to years)	Delayed (months)
Phenotypes of injury	Serum AST, ALT, or ALP elevations, hepatic necrosis, acute fatty liver, nodular regeneration	Mixed or cholestatic hepatitis, bland cholestasis, chronic hepatitis	Immune mediated hepatitis, fatty liver, chronic hepatitis
Examples	Acetaminophen, niacin, intravenous methotrexate	Amoxicillin-clavulanate, cephalosporins, isoniazid, nitrofurantoin	Immune checkpoint inhibitors, anti-CD20 monoclonal Ab, protein kinase inhibitors
Touted mechanism of injury	Intrinsic hepatotoxicity that is dose dependent	Idiosyncratic host metabolic or immune reaction	Indirect effect on liver or host immunity

Adapted from Björnsson et al.[5]

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

TABLE 2 Etiologies and outcomes with drug-induced liver injury in different countries

Country	**United States/ DILIN, *n* = 899**	**Spain, *n* = 843**	**Iceland, *n* = 96**	**Latin America, *n* = 311**	**China, *n* = 25, 927**	**India, *n* = 313/1288**
Study design	Prospective registry[30]	Prospective registry[29]	Prospective, population-based[9]	Prospective registry[18]	Retrospective case series[22]	Prospective case series[21, 31]
Publication year	2015	2021	2013	2019	2019	2010/2021
Age distribution, year	49 ± 17	54 (11–91)	55¥ (16–91)	50 (11–91)	43% (40–59 years)	39 (12–84)/43 (1–86)
% Female	59	48	56	61	49	42/48.6
% Liver- and non-liver-related fatality	Liver-related: 3.0; non-liver-related: 3.2	Liver-related: 2.1; non-liver-related: 1.7	Overall fatality: 1	Overall fatality: 4.9	Liver-related: 0.28*; non-liver-related: 0.11*	Overall fatality: 17.3/12.3
% Liver transplant	3.7	1.5	0	0	0.01	0
Top 3 implicated drug classes	Antimicrobials, HDS, cardiovascular agents	Anti-infectives, CNS drugs, musculoskeletal drugs (including NSAID)	Antibiotics, immuno-suppressants, psychotropic drugs	Antibiotics,** NSAIDs,** antitubercular**	TCM or HDS, antitubercular, antineoplastic or immune-modulators	Antitubercular, HDS, antiepileptics
Top 10 implicated agents	HDS, amoxicillin/ clavulanate, isoniazid, nitrofurantoin, trimethoprim-sulfamethoxazole, minocycline,	Amoxicillin/ clavulanate, antitubercular, HDS, ibuprofen, anabolic androgenic steroids,	Amoxicillin/ clavulanate, diclofenac, infliximab, nitrofurantoin, isotretinoin, atorvastatin,	Amoxicillin/ clavulanate, nitrofurantoin, diclofenac, RIP + INH + PIZ, nimesulide, ibuprofen, cyproterone,	Natural medicine, rifampicin, TCM, isoniazid, pyrazinamide, He Shou Wu, methimazole, propylthiouracil	Antitubercular, phenytoin, dapsone, olanzapine, carbamazepine, cotrimoxazole, NSAIDs, atorvastatin, leflunomide, ayurvedic

	cefazolin, azithromycin, ciprofloxacin, levofloxacin	flutamide, isoniazid, atorvastatin, diclofenac, ticlopidine	doxycycline, azathioprine	carbamazepine, methyldopa, atorvastatin	, atorvastatin, methotrexate	

The duration of follow-up varied among studies.

Age distributions are presented as ¥median (range), mean ± SD, or most prevalent age group (%).

Abbreviations: CNS, central nervous system; DILIN, Drug-Induced Liver Injury Network; HDS, herbal and dietary supplement; INH, isoniazid; NSAID, nonsteroidal anti-inflammatory drug; PIZ, pyrazinamide; RIP, rifampin; TCM, traditional Chinese medicine.

*The case fatality rates (liver-related vs. non-liver-related) were computed based on the cause of death in individual fatal cases: liver-related (72 deaths due to drug-induced liver injury [DILI] + 1 cirrhosis/DILI case) and non-liver-related (20 DILI-contributing death + 9 nonrelated death).

The table follows the classification/terminology used in the individual manuscripts, except for the Latin America study (**), to which categories were assigned based on the listed drugs.

TABLE 3 Genetic polymorphisms associated with drug-induced liver injury susceptibility

Drug	HLA group	Genetic variants	Odds ratio	MAF in controls*
Multiple drugs[58, 61]	Non-HLA	PTPN22 (rs2476601)	1.4	0.08
		rs72631567 (Chromosome 2)	2.0	0.03
Mixed /cholestatic	HLA-I	A*33:01/rs114577328$^{\Delta}$	5.0	0.01
		A*33:01/B*14:02/C*08:02.	5.6	0.009
Hepatocellular	Non-HLA	rs28521457 (chromosome 4/LRBA)	2.1	0.04
Amoxicillin-clavulanate[62, 63]	HLA-I	A*02:01 (rs2523822)	2.3	0.28/0.28**
		A*30:02	6.7 (HC)	0.029
		B*18:01	2.9 (HC)	0.096
	HLA-II	DRB1*15:01/DQB1*06:02 (rs3135388)	2.8	0.14/0.05**
		rs9274407	3.1	0.15/0.081**
		rs9267992	3.1	0.14/0.063**
	Non-HLA	PTPN22 (rs2476601)	1.6	0.08

Flucloxacillin [64, 65]	HLA-I	B*57:01	36.6	0.04
		B*57:03	79.2	0.0003
Minocycline[66]	HLA-I	HLA-B*35:02	29.6	0.006
Trimethoprim-Sulfamethoxazole[67]	HLA-I	A*34:02 (EUR)	47.5	0.001
		B*14:01 (EUR)	9.2	0.009
		B*27:02 (EUR)	13.5	0.002
		HLA-B*35:01 (AA)	2.8#	0.087
Isoniazid-containing antitubercular treatments[61, 68]	Non-HLA	rs72631567 (Chromosome 2)	5.8	0.03
		rs117491755 (ASTN2: EUR)	4.4	0.037
		NAT2*6/*6, *6/*7, or *7/*7 (ultraslow) (EUR/IND)	2.0/1.8	0.10/0.19
	HLA-I	C*12:02 (EUR)	6.4	0.006
		B*52:01 (EUR)	6.4	0.007
		B*52:01-C*12:02 (EUR/IND)	6.7/1.8	0.01/0.07
	HLA-II	DQA1*03:01(IND)	2.6	0.06
Terbinafine[69]	HLA-I	A*33:01/rs114577328Δ	40.5	0.01–0.03
		A*33:01/B*14:02/C*08:02	49.2	0.009

Valproate[70]	Non-HLA	mitochondrial DNA polymerase γ (POLG)	23.6##	
		p.Q1236H		≤0.086
		p.E1143G		≤0.04
Allopurinol[71]	HLA-I	HLA-A*34:02 (AA)	8.0/4.5###	0.033/0.057***
		HLA-B*53:01 (AA)	4.1/2.5###	0.120/0.184***
		HLA-B*58:01 (AA)	5.6/13.3###	0.046/0.020***
Green tea[72]	HLA-I	B*35:01	6.8	0.06
		C*04:01	3.7	0.12
Polygonum multiflorum[73]	HLA-I	B*35:01	30.4	0.027

Abbreviations: AA, African American; ASNT2, astrotactin 2; EUR, European descendants; IND, Indian; HC, hepatocellular injury; LRBA, LPS-responsive vesicle trafficking, beach and anchor containing gene; MAF, minor allele frequency (presented as fractions).

*Controls used in the analyses varies among the studies. Allele frequencies significantly varies among racial groups; thus, provided allele frequencies should be interpreted cautiously.

**Northwestern European/Spanish controls.

***The Charles Bronfman Institute for Personalized Medicine BioMe, National Center for Biotechnology Information database of Genotypes and Phenotypes (phs000925.v1.p1)/non-allopurinol drug-induced liver injury cases at Drug-Induced Liver Injury Network.

#Unadjusted odds ratio due to the limited size of the cohort.

##Combined odds.

###Computed based on the reported data.

ΔA proxy marker of HLA-A*33:01.

TABLE 4 Clinical and Histological Phenotypes of idiosyncratic DILI

Clinical Phenotype	**Histological phenotype**		
	Pattern	**Characteristic histology**	**Examples of associated drugs**
Hepatocellular	Acute hepatitis	Spotty necrosis, apoptosis, lobular inflammation, with or without portal inflammation and interface hepatitis	Phenytoin, dapsone, para-aminosalicylate, isoniazid, sulfonamides
	Panlobular hepatitis	Spotty or focal necrosis, acidophil bodies scattered throughout the lobule, hepatocytes with degenerative changes and lytic necrosis, lymphocytic infiltrates	Immune checkpoint inhibitors (e.g., ipilimumab, nivolumab)
	Zonal or nonzonal (confluent) necrosis	Coagulative necrosis in zone 3 or panlobular involvement with either submassive or massive necrosis	Acetaminophen, halothane, CCL4, cocaine, ferrous sulfate
	Granulomatous hepatitis	Noncaseating granulomas accompanied by significant inflammation; fibrin-ring granulomas	Sulfonamides, sulfonylurea, phenytoin, carbamazepine, quinidine, hydralazine, interferon-α, etanercept, ipilimumab
	Chronic hepatitis	Similar to chronic viral hepatitis or autoimmune hepatitis with portal inflammation, interface hepatitis, fibrosis, or cirrhosis	Atorvastatin, HDS, methotrexate, vinyl chloride
	Drug-induced autoimmune hepatitis	More prominent portal neutrophils than plasma cells along with cholestasis concurrently with the typical AIH histology of portal inflammation, interface hepatitis, rosette formation	Nitrofurantoin, diclofenac, α-methyldopa, hydralazine, minocycline, HMG-CoA reductase inhibitors, TNF inhibitors

Cholestatic	Acute cholestasis/bland cholestasis	Bile accumulation in hepatocytes and/or bile canaliculi with little or no inflammation or hepatocyte injury	Anabolic and oral contraceptives
	Chronic cholestasis	Bile accumulation, possibly bile duct loss/ductopenia, cholate stasis	Amoxicillin-clavulanate, flucloxacillin, enalapril, antifungal terbinafine
	Acute cholestatic hepatitis Mixed hepatocellular/cholestatic	Bile accumulation in hepatocytes and/or bile canaliculi with more prominent inflammation and hepatocyte injury	Antibiotics (erythromycin, amoxicillin-clavulanate), ACE inhibitors, phenothiazine neuroleptics
	Sclerosing cholangitis	Bile duct injury with intraepithelial lymphocytic infiltration and periductal fibrosis	Nivolumab
Fatty liver (drug-induced steatosis, drug-induced steatohepatitis)	Pure microvesicular	Numerous small droplets, foamy cytoplasm, hepatocyte nuclei retained in the center	Acetylsalicylic acid (Reye syndrome), valproic acid, glucocorticoids, aspirin, NSAIDS, tetracycline, NRTI, cocaine
	Macrovesicular	Medium- or large-sized fat droplets with hepatocyte nuclei displaced to the periphery	Glucocorticoids, methotrexate, NSAIDs, metoprolol, chlorinated hydrocarbons (e.g., CCL4 and chloroform), 5-fluorouracil, cisplatin, irinotecan, tamoxifen
	Mixed macro- and microvesicular	Combination of small and large droplet	Amiodarone, valproic acid, methotrexate
	Steatohepatitis	Presence of ballooning, inflammation, Mallory-Denk hyalines, and fibrosis, in a background of steatosis	Amiodarone, methotrexate, 5-floururacil, cisplatin, irinotecan, tamoxifen

Vascular	Sinusoidal obstruction syndrome	Sinusoidal congestion with hepatocyte necrosis, red blood cells trapped in Disse spaces, perisinusoidal fibrosis, fibrous obliteration of terminal hepatic venules; sloughing of endothelial cells	Busulfan, cyclophosphamide, plants containing pyrrolizidine alkaloids
	NRH and OPV	Small (1 mm) hyperplastic nodules bordered by atrophic hepatocyte plates (NRH); may require a reticulin stain. OPV will show either dilated and herniated portal veins or sclerotic lumina	Arsenic, copper sulfate, azathioprine, methotrexate, 6-mercaptopurine, oxaliplatin, didanosine, stavudine
	Peliosis hepatis	Blood-filled sinusoidal spaces	Androgens and oral contraceptives
Chronic DILI	Fibrosis/cirrhosis	Progression of fibrosis similar to chronic viral hepatitis	Methotrexate, valproic acid, HDS, oral contraceptives, isoniazid, trimethoprim-sulfamethoxazole, nitrofurantoin, methotrexate, diclofenac, fenofibrate, amoxicillin-clavulanate
Miscellaneous	Ground-glass cytoplasm (induction hepatocytes), Lafora body-like inclusions	Homogeneous light pink cytoplasmic inclusions with displacement of the nuclei	Barbiturates, phenytoin, polypharmacy; immunosuppressive agents, antibiotics
	Phospholipidosis	Enlarged, granular or foamy cytoplasm; may require electron microscopy to check for lamellar bodies	Antibiotics, antipsychotic, antidepressants, antianginal, antimalarial, antiarrhythmic, cholesterol lowering agents; amiodarone
	Pigment deposition	Ceroid-containing macrophages; lipofuscin	6-mercaptopurine, phenothiazine, aminopyrine, phenacetin,

Neoplastic	Hepatocellular adenoma	All subtypes possible, most common are inflammatory and HNF-1-alpha mutated	Oral contraceptives, anabolic and male hormone steroids, danazol

Abbreviations: ACE, angiotensin-converting enzyme; AIH, autoimmune hepatitis; CCL4, carbon tetrachloride; DILI, drug-induced liver injury HCA, hepatocellular adenoma; HDS, herbal and dietary supplement; HNF, hepatocyte nuclear factor; NRH, nodular regenerative hyperplasia; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; OPV, obliterative portal venopathy; TNF, tumor necrosis factor.

Table 5 Data fields in the RUCAM, CDS, and RECAM causality assessment instruments

Data field	**Updated RUCAM[108] score**	**CDS[109] score**	**RECAM[113] score**
1. Chronology (latency)			
1a. Drug start to liver injury onset*	+1 to +2	+1 to +3	−6 to + 4
1b. Drug discontinuation to liver injury onset*	+1	−3 to +3	−6 to 0
2. Dechallenge**	−2 to +3 hepatocellular; 0 to +2 cholestatic/mixed	0 to +3	−6 to +4
3. Competing causes of liver injury	−3 to +2	−3 to +3	−6 to 0
4. Rechallenge	0 to +3	+3	0 or + 6
5. Track record of drug/HDS hepatotoxicity	0 to +2	−3 to +2	0 to + 3
Risk factors	0 to +1	N/A	N/A***
6. Concomitant medication	−3 to 0	N/A	N/A^

7. Extrahepatic manifestations	-	0 to +3	-
Range of scores	−9 to +14	−6 to 17	−6 to +20
DILI likelihood categories			
Definite	≥9	>17	Highly likely/ high probable ≥8
Probable	6–8	14–17	4–7
Possible	3–5	10–13	−3 to +3
Unlikely	1–2	6–9	Unlikely/ excluded, <−4
Excluded	≤0	≤6	

Abbreviations: CDS, clinical diagnostic scale; HDS, herbal and dietary supplements; NA, not applicable; RECAM, Revised Electronic Causality Assessment Method; RUCAM, Roussel-Uclaf Causality Assessment Method.

Note: Only scores from the updated RUCAM are shown and are composites derived from hepatocellular and mixed/cholestatic categories (110).

*Only 1 of those 2 (i.e., only 1a or 1b) is counted.

**Stratified by hepatocellular vs. mixed/cholestatic in early version.

***In RECAM, risk factors were not assigned scores.

^RECAM was developed only for single drug cases and does not account for concomitant medications.

TABLE 6 Drug-Induced Liver Injury Network expert opinion scoring categories

Causality Score	**Likelihood, %**	**Description**
1. Definite beyond any reasonable doubt	>95	
2 Highly likely	75–95	Clear and convincing data, but not definite
3. Probable	50–74	Majority of data supports causal relationship
4. Possible	25–49	Majority of data suggests no causal relationship, but possibility remains
5 . Unlikely	<25	Causal relationship very unlikely with alternative etiology more likely
6. Insufficient data	determinable	Missing key data

Adapted from Fontana et al.[74]

TABLE 7 Herbal and dietary supplement products and ingredients implicated in hepatotoxicity

Ingredient	Chemical structure	Common uses	Hepatotoxicity phenotype	Expected outcome
Ashwagandha,[135] *Withania somnifera*	Steroidal lactone	Neuroprotection, anti-inflammatory	Cholestatic or Mixed	Recovery expected
Green Tea extract[72, 132]	Catechin-Polyphenol	Weight loss	Hepatocellular	Most recover, liver failure, transplant, death reported
Garcinia cambogia[136]	(-)-hydroxycitric acid	Weight loss	Hepatocellular	
Polygonum multiflorum[73, 137]	Stilbenes and anthraquinones	Antiaging, intestinal function	Hepatocellular or Mixed	Most recover, fatalities reported
Chinese skullcap, *Scutellaria baicalensis*; *Scutellaria lateriflora*	Flavonoid	Anxiety, insomnia, neurological disorders	Hepatocellular	Recovery typical
Kratom,[138] *Mitragyna speciosa*	Tetracyclic indole and pentacyclic oxindole alkaloids	Anxiety, opiate effect or withdrawal	Mixed	Recovery typical
Anabolic steroids[139]	Steroid backbone	Bodybuilding, performance enhancement	Cholestasis	Prolonged jaundice, full recovery
Turmeric/curcumin[140, 141, 142]	Polyphenol	Anti-inflammatory, weight loss, anticancer, cardiovascular disease	Hepatocellular	Recovery expected, one case of autoimmune hepatitis reported

TABLE 8 Prognostic Indices for patients with idiosyncratic drug-induced liver injury

Model/parameter	Model components	Proposed thresholds for liver transplant/death	Comments
MELD score[143]	Bilirubin, INR, and creatinine	**AUROC = 0.83**	Developed for cirrhosis patients
Hy's law[145]	ALT > 3× ULN and bilirubin >2.5 mg/dL	**PPV = 8%–20%**	ALP should be <2× ULN; not applicable to mixed/cholestatic cases
Modified Hy's law[144]	R-value >5 and bilirubin >2.5 mg/dL	**PPV = 12%; AUROC =0.73**	
Charlson comorbidity index and labs[146]*	**MELD score, Albumin, Charlson >2**	**AUROC = 0.89**	Discovery and validation cohort used for 6-month mortality

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AUROC, area under the receive operating curve; INR, international normalized ratio; MELD, model for end-stage liver disease; PPV, positive predictive value; ULN, upper limit of normal.

*Web-based mortality calculator available at http://gihep.com/calculators/hepatology/dili-CAM/.

TABLE 9 Recommended interventions for patients with idiosyncratic DILI

Intervention	Target population	Dosing	Comments
General intervention			
Acetaminophen analgesics	Mild to moderate pain	2 g maximum per day in divided doses	Consider short acting opiates if moderate-severe pain
Antiemetics	Moderate nausea/vomiting	Per package insert	
Ursodeoxycholic acid	Severe pruritus	10–15 mg/kg in divided doses	Prospective efficacy data lacking, likely safe
Hospitalization	Dehydrated, coagulopathic, encephalopathic patients	NA	Transfer to transplant center if ALF
N-acetylcysteine	Hospitalized with ALF	See APAP Table for dosing; 72-h duration in studies	IV requires cardiac monitoring; greatest benefit in early stage ALF
Corticosteroids	Severe hypersensitivity reactions; DRESS; checkpoint inhibitor with ALT >5× ULN; histology showing AIH-like features	1 mg/kg per day of methylprednisolone equivalents for ICI cases; 40–60 mg of prednisone for others	Optimal dose and duration not established but frequently can be tapered in 1–3 months
Drug-specific interventions			
L-carnitine	Valproate with hyperammonemia (hospitalized children)	100 mg/kg load followed by 50 mg/kg every 8 h	Short-term use
Cholestyramine	Leflunomide cases with persistent cholestasis	1 packet every 6–8 h for 14 days	Taper once cholestasis/pruritus resolves; give separate from other medications
IV penicillin/silymarin and dialysis	Amanita mushroom toxicity	Hospitalized patients or ALF	Short-term use to remove enterohepatic toxin

IV defibrotide	Hematopoietic cell transplant recipients with severe sinusoidal obstruction syndrome	6.25 mg/kg every 6 h for >21 days up to a maximum of 60 days	Shown to improve survival in children and adults compared with historical controls

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; APAP, acetaminophen; DILI, drug-induced liver injury; DRESS, drug reaction with eosinophilia and systemic symptoms; ICI, immune checkpoint inhibitor; IV, intravenous; NA, not applicable; ULN, upper limit of normal.

TABLE 10 Diagnosis and management of acetaminophen hepatotoxicity

Recommendation	Intentional overdose	Unintentional overdose
Diagnostic approach		
Time of ingestion	Single time point	Several days of repeated use
Dose	Supratherapeutic (typically >4 g over 24 h)	Repeated therapeutic (up to 4 g per day) or supratherapeutic dosing
Presence of coingestants	Diphenhydramine and other sedatives can lead to central nervous system depression	Opioids often used in combination
Liver injury parameters	From time of ingestion: 24–72 h: rapid rise in ALT to >1000 IU/L associated with variable rise in INR. Total bilirubin is typically <10 mg/dL. 72–96 h: biochemical elevations peak, and can progress to acute liver failure or rapid and full recovery	Presentation is often delayed, but still see rapid rise in ALT to >1000 IU/L, associated with rise in INR. Comorbid conditions, such as alcohol use, can affect total bilirubin levels. Eventually, liver injury can progress to acute liver failure or recovery
Serum acetaminophen level	Use modified Rumack-Matthew nomogram to estimate risk of hepatotoxicity	Often undetectable at initial presentation. APAP-protein adducts useful but assay not commercially available
Excluding other causes of acute liver injury	Review clinical history to exclude risk factors for hepatic ischemia and perform tests for acute viral hepatitis	
Management		
GI decontamination	Activated charcoal (1g/kg, max dose 50 g) if within 4 h of ingestion. Gastric lavage also utilized in some cases[175]	Usually not helpful nor recommended
N-acetylcysteine	Oral dosing: 140 mg/kg load followed by 70 mg/kg every 4 h; antiemetics as needed. Intravenous dosing (176): Preferred if intolerant of oral intake/ ileus or pregnant; telemetry monitoring recommended 150mg/kg load over 15–60 min, followed by 50 mg/kg (12.5 mg/kg/h) over the next 4 h then 100mg/kg (6.25 mg/kg/h) over 16 h thereafter (total 300 mg/kg over 24 h). For those with evidence of liver injury,	

	treatment is extended at 6.25mg/kg/h until ALT is decreasing and INR is <2
Evidence of acute liver failure (coagulopathy and encephalopathy)	Close monitoring in intensive care unit and consider prompt referral to a liver transplant center

Abbreviations: ALT, alanine aminotransferase; APAP, acetaminophen; GI, gastrointestinal; INR, international normalized ratio.