CME

ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury

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Idiosyncratic drug-induced liver injury (DILI) is common in gastroenterology and hepatology practices, and it can have multiple presentations, ranging from asymptomatic elevations in liver biochemistries to hepatocellular or cholestatic jaundice, liver failure, or chronic hepatitis. Antimicrobials, herbal and dietary supplements, and anticancer therapeutics (e.g., tyrosine kinase inhibitors or immune-checkpoint inhibitors) are the most common classes of agents to cause DILI in the Western world. DILI is a diagnosis of exclusion, and thus, careful assessment for other etiologies of liver disease should be undertaken before establishing a diagnosis of DILI. Model for end-stage liver disease score and comorbidity burden are important determinants of mortality in patients presenting with suspected DILI. DILI carries a mortality rate up to 10% when hepatocellular jaundice is present. Patients with DILI who develop progressive jaundice with or without coagulopathy should be referred to a tertiary care center for specialized care, including consideration for potential liver transplantation. The role of systemic corticosteroids is controversial, but they may be administered when a liver injury event cannot be distinguished between autoimmune hepatitis or DILI or when a DILI event presents with prominent autoimmune hepatitis features.

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INTRODUCTION

The writing group was invited by the Board of the Trustees and the Practice Parameters Committee of the American College of Gastroenterology to develop a practice guideline regarding the diagnosis and management of idiosyncratic drug-induced liver injury (DILI). The writing group developed this practice guideline using an evidence-based approach. We used the following resources: (i) a formal review and analysis of the recently published world literature on the topic (MEDLINE search up to September 2020); (ii) the American College of Physicians' Manual for Assessing Health Practices and Designing Practice Guidelines (1); (iii) guideline policies of the American College of Gastroenterology; and (iv) the clinical experience of the authors and the external reviewers with regards to idiosyncratic DILI. This practice guideline is an update to the practice guideline published in June 2014 (2). The portions of the guideline document where there have been no new clinically important publications are not modified, and thus, some remain unchanged from the 2014 guideline document (2).

These recommendations, intended for use by physicians and other health care providers, suggest preferred approaches to the diagnosis and management of DILI (Table 1). They are intended to be flexible and should be adjusted as deemed appropriate when applied to individual patients. Recommendations are evidence-based wherever possible, and, when such evidence is not available, recommendations are made based on the consensus opinion of the authors. To more fully characterize the available evidence supporting the recommendations, the ACG Practice Parameters Committee has adopted the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) (3) system to evaluate the quality of supporting evidence (Table 2), with the GRADE process of evaluating quality of supporting evidence conducted by 2 formally trained GRADE methodologists (R.J.W. and K.G.). The quality of the evidence is graded from high to very low. High quality evidence indicates that further research is unlikely to change confidence in the estimate of effect, and that the true effect lies close to this estimate. Moderate quality evidence is associated with moderate confidence in the effect estimate, although further research could impact the confidence of the estimate. Low quality evidence indicates that further study is likely to have an important impact on the confidence in effect estimate and would likely change the estimate. Very low quality evidence indicates very little confidence in effect estimate, and the true effect is likely to be substantially different than the estimate of effect. A strong recommendation is made when the benefits clearly outweigh the negatives and the result of no action. A conditional recommendation is used when some uncertainty remains about the balance of benefits/potential harm. Key concepts are

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Table 1. Summary and strength of recommendations

1. In individuals with suspected hepatocellular or mixed DILI:
(a) Acute viral hepatitis (A, B, and C) and autoimmune hepatitis should be excluded with standard serologies and HCV RNA testing (strong recommendation, very low quality of evidence).
(b) Anti-HEV IgM testing may be considered in selected patients where there is heightened clinical suspicion (e.g. recent travel in an endemic area, DILI phenotype is atypical, or there is no readily identifiable culprit agent). However, it should be noted that the performance of the currently available commercial tests is not clear (conditional recommendation, very low quality of evidence).
(c) We recommend testing for acute CMV, acute EBV, or acute HSV infection be undertaken if classical viral hepatitis has been excluded or clinical features such as atypical lymphocytosis and lymphadenopathy suggest such causes (strong recommendation, very low quality of evidence).
(d) We recommend evaluation for Wilson disease and Budd-Chiari syndrome when clinically appropriate (strong recommendation, very low quality of evidence).
2. In individuals with suspected cholestatic DILI:
(a) We recommend abdominal imaging (ultrasound, computed tomography scan, and MRI) should be performed in all instances to exclude biliary tract pathology and infiltrative processes (strong recommendation, low quality of evidence).
(b) We recommend limiting serological testing for primary biliary cholangitis to those with no evidence of obvious biliary tract pathology on abdominal imaging (strong recommendation, low quality of evidence).
(c) We suggest limiting endoscopic retrograde cholangiography to instances where routine imaging including MRI or endoscopic ultrasound is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis, or pancreaticobiliary malignancy (conditional recommendation, very low quality of evidence).
3. When to consider a liver biopsy?
(a) We recommend performing a liver biopsy if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated (strong recommendation, low quality of evidence).
(b) We suggest performing a liver biopsy if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).
(c) We suggest performing a liver biopsy if peak ALT level has not fallen by >50% at 30–60 d after onset in cases of hepatocellular DILI or if peak Alk P has not fallen by >50% at 180 d in cases of cholestatic DILI despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).
(d) We suggest performing a liver biopsy in cases of DILI where continued use or re-exposure to the implicated agent is contemplated (conditional recommendation, very low quality of evidence).
(e) We suggest considering a liver biopsy if liver biochemistry abnormalities persist beyond 180 d, especially if associated with symptoms (e.g., itching) or signs (e.g., jaundice and hepatomegaly), to evaluate for the presence of chronic liver diseases and chronic DILI (conditional recommendation, very low quality of evidence).
4. We suggest using a prognostic model consisting of MELD, Charlson comorbidity index, and serum albumin in clinical practice for predicting 6-month mortality in individuals presenting with suspected DILI. A web-based DILI mortality calculator is available at http://gihep.com/calculators/hepatology/dili-cam/ (conditional recommendation, low quality of evidence).
5. We strongly recommend against re-exposure to a drug thought likely to have caused hepatotoxicity, especially if the initial liver injury was associated with significant aminotransferase elevation (e.g., >5xULN, Hy's law, or jaundice). An exception to this recommendation is in cases of life-threatening situations where there is no suitable alternative (strong recommendation, low quality of evidence).
6. We recommend promptly stopping suspected agent(s) in individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction (strong recommendation, low quality of evidence).
7. Although no definitive therapies are available either for idiosyncratic DILI with or without ALF, we suggest consideration of NAC treatment in adults with early stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients (conditional recommendation, low quality of evidence).
8. We suggest against using NAC for children with severe DILI leading to ALF (conditional recommendation, low quality of evidence).
9. There are no well-conducted studies to either recommend or refute corticosteroid therapy in patients with DILI. However, they may be considered in a subset of patients with DILI exhibiting AIH-like features (conditional recommendation, low quality of evidence).
10. We recommend encouraging patients to report use of HDS to their health care providers and be reminded that supplements are not subjected to the same rigorous testing for safety and efficacy as are prescription medications (strong recommendation, low quality of evidence).
11. We recommend applying the same diagnostic approach for DILI to suspected HDS-hepatotoxicity. That is, other forms of liver injury must be excluded through a careful history and appropriate laboratory testing and hepatobiliary imaging. Excluding other causes, the diagnosis of HDS-hepatotoxicity can be made with confidence in the setting of recent use of HDS (strong recommendation, low quality of evidence).
12. We recommend stopping all HDS in patients with suspected HDS-hepatotoxicity and continued monitoring for resolution of their liver injury (strong recommendation, low quality of evidence).
13. We recommend consideration of liver transplantation evaluation in patients who develop ALF and severe cholestatic injury from HDS-DILI (strong recommendation, low quality of evidence).

Table 1. (*continued*)

14. As the diagnosis of DILI in patients with CLD requires a high index of suspicion, we recommend exclusion of other more common causes of acute liver injury including a flare-up of the underlying liver disease (strong recommendation, low quality of evidence).
15. The decision to use potentially hepatotoxic drugs in CLD patients should be based on the risk vs benefit of the proposed therapy on a case-by-case basis (conditional recommendation, low quality of evidence).
16. There are no data to recommend a specific liver biochemistry monitoring plan when a potential hepatotoxic agent is prescribed in individuals with known CLD. Often, information contained in the package inserts is incomplete or unhelpful. Patients should be advised to promptly report any new onset symptoms such as scleral icterus, abdominal pain/discomfort, nausea/vomiting, itching, or dark urine. In addition, it is reasonable to monitor serum liver biochemistries at 4–6 weekly intervals, especially during the initial 6 mo of treatment with a potentially hepatotoxic agent (conditional recommendation, very low quality of evidence).

ALF, acute liver failure; Alk P, alkaline phosphatase; ALT, alanine aminotransferase; CLD, chronic liver disease; CMV, cytomegalovirus; DILI, drug-induced liver injury; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HDS, herbal and dietary supplements; HEV, hepatitis E virus; HSV, herpes simplex virus; Ig, immunoglobulin; MELD, model for end-stage liver disease; NAC, *N*-acetylcysteine; ULN, upper limit of normal.

statements that are not amenable to the GRADE process, either because of the structure of the statement or because of the available evidence. In some instances, key concepts are based on extrapolation of evidence and/or expert opinion. Each recommendation statement has an associated assessment of the quality of evidence and strength of recommendation based on the GRADE process. Strengths of recommendations are not always contingent on GRADE quality of evidence, particularly when the population health benefits are obvious and/or there is a suspected large magnitude of effect.

Table 2. Grading of Recommendations, Assessment, Development, and Evaluation

Strength of recommendation	Criteria
Strong	Factors influencing the strength of the recommendation include the quality of the evidence, presumed patient-important outcomes, and cost. Strong recommendations are those where the benefits clearly outweigh the negatives and the result of no action.
Conditional	Conditional recommendations are made when some uncertainty remains about the balance of benefits/potential harm. For example, there may be variability in preferences and values, uncertainty about the study outcomes or quality of evidence, and higher cost or resource consumption.
Quality of evidence	**Criteria**
High	Further research is unlikely to change confidence in the estimate of the clinical effect.
Moderate	Further research may change confidence in the estimate of the clinical effect.
Low	Further research is likely to have an important impact on the confidence in clinical effect and would likely change the estimate.
Very low	There is very little confidence in effect estimate, and the true clinical effect is likely to be substantially different.

This is a practice guideline for clinicians rather than a review article, and we refer interested readers to several comprehensive reviews published recently (4–8). The identification and the management of DILI in clinical trials is an important clinical problem but is beyond the scope of this practice guideline document. We refer readers interested in DILI in clinical trials to a series of consensus reports published recently by the IQ-DILI Consortium (9–12). Some important aspects of DILI such as autoimmune DILI, DILI due to statins, and other lipid-lowering agents or chemotherapeutic agents are not specifically covered in this practice guideline. However, we draw the readers' attention to *LiverTox*, an up-to-date, unbiased, and practical resource for both health care providers and patients on hepatotoxicity caused by more than 1,200 specific medications and supplements (13).

DILI remains one of the most challenging disorders faced by gastroenterologists. The wide range of presentations and culprit agents and lack of objective diagnostic tests make its diagnosis and management particularly difficult. Despite its low incidence in the general population, gastroenterologists must always consider the possibility of DILI in patients with unexplained acute and chronic liver injury as well as when prescribing certain gastrointestinal medications (e.g., azathioprine, anti–tumor necrosis factor agents, and sulfonamides) (14–16). Many herbal and dietary supplements (HDS) can cause DILI, and thus, they must be considered as a cause for DILI (15,17,18). For the purposes of this guideline, the term DILI will refer to liver injury from HDS as well as prescription or the over-the-counter drugs.

One common and useful characterization of DILI is to separate them into intrinsic or idiosyncratic types. The former refers to drugs that are capable of causing liver injury predictably in humans or in animal models when given in sufficiently high doses. Acetaminophen (APAP) is perhaps the best-known and widely used drug to cause intrinsic DILI. Idiosyncratic DILI is less common, affects only susceptible individuals, has less consistent relationship to dose, and is more varied in its presentation. Although recent data have begun to blur the distinction between these 2 categories somewhat, they remain useful conceptual paradigms. APAP, while by far the most common cause of DILI, is the only agent in wide use that causes intrinsic DILI. Its clinical picture is relatively easy to recognize. Diagnostic and therapeutic guidelines for APAP hepatotoxicity are well established (19–22). Therefore, this guideline is limited to the wider array of idiosyncratic DILI that is more difficult to diagnose and treat. In addition, characterizing the injury by latency, pattern of injury (e.g., *R*-value), mortality risk (Hy's law) (23,24), and outcome

Table 3. Terminology and definitions

Term or concept	Definition
Intrinsic DILI	Hepatotoxicity with potential to affect all individuals to varying degrees. Reaction typically stereotypic and dose dependent (e.g., acetaminophen).
Idiosyncratic DILI	Hepatotoxicity affecting only rare susceptible individuals. Reaction less dose dependent and more varied in latency, presentation, and course.
Chronic DILI	Failure of return of liver enzymes or bilirubin to pre-DILI baseline, and/or other signs or symptoms of ongoing liver disease (e.g., ascites, encephalopathy, portal hypertension, and coagulopathy) 6–9 mo after DILI onset.
Latency	Time from medication (or HDS) start to onset of DILI.
Washout, resolution, or dechallenge	Time from DILI onset to return of enzymes and/or bilirubin to pre-DILI baseline levels.
Rechallenge or re-exposure	Readministration of medication or HDS to a patient who already had a DILI to the same agent.
Hy's law	Observation made by late Hyman Zimmerman suggesting ~10% mortality risk of DILI if the following 3 criteria are met: 1. Serum ALT or AST >3xULN; 2. Serum total bilirubin elevated to >2xULN, without initial findings of cholestasis (elevated serum alkaline phosphatase); 3. No other reason can be found to explain the combination of increased aminotransferases and bilirubin, such as viral hepatitis A, B, C, or other pre-existing or acute liver disease.
Temple's corollary	An imbalance in the frequency of ALT >3xULN between active treatment and control arms in a randomized controlled trial. This is used to assess for hepatotoxic potential of a drug from premarketing clinical trials. Although this is a sensitive marker, its specificity in predicting the DILI liability of a compound is limited.
R-value	ALT/ULN ÷ Alk P/ULN. Used to defined hepatotoxicity injury patterns: hepatocellular ($R > 5$), mixed ($R = 2–5$), and cholestatic ($R < 2$).
RUCAM	Diagnostic algorithm that uses a scoring system based on clinical data, pre-existing hepatotoxicity literature on the suspected agent, and rechallenge.

Alk P, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DILI, drug-induced liver injury; HDS, herbal and dietary supplements; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

(resolution vs chronic) is critical in evaluating and managing DILI in clinical practice. These topics and terms form the framework for this guideline and are defined in Table 3.

GENETIC AND NONGENETIC RISK FACTORS

Our understanding of genetic risk factors for DILI is still in its infancy; describing the known genetic associations with diverse drugs is beyond the scope of this clinical practice guideline (6). Nongenetic risk factors can be host-related because of environmental factors or compound-specific in nature (Table 4).

The causative agents for DILI in children and in adults vary, and they differ based on the indication for which the medications are prescribed. Age may confer susceptibility to DILI in a drug-specific fashion. For example, drugs that act on the central nervous system (e.g., anticonvulsants) and antimicrobials (e.g., minocycline) are the more common causes of DILI in children. Infants and children appear susceptible to liver injury caused by valproate and are at increased risk of Reye syndrome caused by aspirin. Although propylthiouracil (PTU) may cause DILI in all age groups, children are more susceptible to severe and fatal hepatotoxicity due to PTU (25,26). With increasing age, there is an increasing risk of liver injury because of many medications such as isoniazid, amoxicillin-clavulanate, and nitrofurantoin (27,28).

There is no evidence to suggest that women are at higher risk of all-cause DILI (i.e., DILI caused by any type of agent), but they seem to be at higher risk of liver injury caused by certain medications such as minocycline, methyldopa, diclofenac, nitrofurantoin, and nevirapine. The typical signature of DILI caused by minocycline, methyldopa, diclofenac, and nitrofurantoin is chronic hepatitis resembling autoimmune hepatitis (AIH) with female preponderance (6).

DILI is a rare cause of acute liver injury in pregnant women which could well be due to generally infrequent usage of prescription medications. There is no evidence to suggest that pregnancy by itself increases the susceptibility to DILI because of any agents other than tetracycline. Common causes of DILI in pregnant women are antihypertensive agents such as methyldopa and hydralazine, antimicrobials including antiretroviral agents, and PTU (29). Most liver injury episodes resolve spontaneously on stopping the suspected agent, but liver transplantation and maternal death have rarely been reported (29).

Although animal experiments show that diabetes mellitus increases susceptibility to toxic liver injury caused by certain compounds (e.g., APAP), there is no evidence to show that diabetes mellitus increases the risk of all-cause DILI in humans. Liver injury due to selected compounds such as methotrexate and antituberculosis (anti-TB) medicines may be increased in individuals with diabetes. A report from the US Drug-Induced Liver Injury Network (DILIN) showed that underlying diabetes mellitus was independently associated with death or liver transplantation (hazard ratio 2.3, 95% confidence interval [CI] 1.5–3.5) (30).

Although alcohol consumption is included as one of the elements for assessing causality in the Roussel Uclaf Causality Assessment Method (RUCAM) causality instrument (31,32), there is no evidence to suggest that chronic alcohol consumption is a risk factor for all-cause DILI. However, heavy alcohol consumption is a risk factor for causing DILI because of certain compounds such as APAP, methotrexate, and isoniazid. The package insert recommends that individuals with substantial alcohol consumption should not take duloxetine, although there are no published data to show that alcoholism increases the risk of

Table 4. Variables that may predispose individuals to idiosyncratic drug-induced liver injury

Host factors	Environmental factors	Drug-related factors
Age	Smoking	Daily dose
Sex	Alcohol consumption	Metabolic profile (lipophilicity and reactive metabolites)
Pregnancy	Infection and inflammatory episodes	Class effect and cross-sensitization
Malnutrition		Drug interactions and polypharmacy
Obesity		
Diabetes mellitus		
Comorbidities including underlying liver disease		
Indications for therapy		

duloxetine hepatotoxicity. A recent report from the DILIN observed that anabolic steroids were the most common cause of DILI among heavy drinkers (likely guilt by association) and that heavy drinking was not associated with worse outcomes in DILI, compared with non-DILI (33).

Drug-drug interactions and polypharmacy are often invoked as risk factors for DILI, although there is scant evidence to show that they increase the risk of all-cause DILI. However, drug interactions may potentially exacerbate the risk of DILI because of anti-TB agents and anticonvulsants such as valproate.

Key concepts

1. Although a number of host, environmental, and compound-specific risk factors have been described in the literature, there is no evidence to suggest that these variables represent major risk factors for all-cause DILI.
2. Certain variables such as age, sex, and alcohol consumption may increase risk of DILI in a drug-specific fashion.

DIAGNOSIS AND CAUSALITY ASSESSMENT IN DILI

DILI remains a diagnosis of exclusion based primarily on a detailed history and judicious use of blood tests, hepatobiliary imaging, and liver biopsy. Diagnostic algorithms available to the clinician are based on clinical scoring systems (31,32,34). Although they can help organize the clinician's history and testing by providing a diagnostic framework, they lack clarity and proven accuracy. Suggested minimum data required for the diagnosis of DILI have been published (Table 5) (35).

History and physical examination

The importance of a thorough history in DILI cannot be overemphasized. Accurate history of medication exposure and onset and course of liver biochemistry abnormalities is crucial. Usually, DILI events occur within first 6 months after starting a new medication, but there are exceptions. Some compounds have a propensity to cause DILI after a longer latency (e.g., nitrofurantoin, minocycline, and statins; Table 6) (15). History taking is greatly enhanced by knowledge of the most common and most rarely implicated DILI agents. The use of illicit drugs should also be noted because agents such as methylenedioxymethamphetamine have been linked to liver injury, and in some instances, acute liver failure (ALF) (36). Overall, antibiotics and antiepileptics are most commonly reported accounting for >60% of DILI overall, while antihypertensive and diabetic medications are less common (37–39). There are increasing reports of DILI because of HDS, and thus, close questioning regarding HDS consumption is crucial (18,40,41). Table 6 lists the best characterized as well as the most commonly prescribed agents associated with DILI including those used in gastroenterology. Typical latencies and patterns of injury are also provided. Certain drugs, sometimes but not always, have a signature presentation in terms of latency, biochemical pattern, and other characteristics (Table 6).

Harnessing knowledge of rare or newly reported cases of DILI is more daunting. The US Food and Drug Administration (FDA) approved an average of 90 drugs per year from 2007 to 2011 (42). Published case reports of DILI are spread across general medical, subspecialty, toxicology, pharmacology, and gastroenterology journals, and they are of varying quality (35). The National Institute of Diabetes and Digestive and Kidney Diseases and the National Library of Medicine has launched *LiverTox*, a free and helpful on-line DILI resource consisting of detailed information on more than 1,200 agents, and it is updated periodically (13,43).

DIAGNOSTIC EVALUATION: BLOOD TESTS AND IMAGING STUDIES

The diagnostic approach to DILI can be tailored according to the pattern of liver injury at presentation. The *R*-value is defined as serum alanine aminotransferase (ALT)/upper limit of normal (ULN) divided by serum alkaline phosphatase (Alk P)/ULN. By common convention, $R > 5$ is labeled as hepatocellular DILI, $R < 2$ is labeled as cholestatic DILI, and $2 < R < 5$ is labeled as mixed DILI. The pattern of liver injury provides a useful framework to allow one to focus on differential diagnosis and further evaluation. However, the same medication can present with varying laboratory profiles and clinical features in individual DILI patients.

The differential diagnosis for acute hepatocellular injury includes acute viral hepatitis, AIH, ischemic liver injury, acute Budd-Chiari syndrome, and Wilson disease. One should keep in mind that acute biliary obstruction may initially present with a hepatocellular pattern of injury but subsequently evolves into a cholestatic presentation.

Acute hepatitis C and acute hepatitis E infections are known masqueraders of DILI (44,45). The diagnosis of acute hepatitis C can be challenging because anti–hepatitis C virus (HCV) antibodies may be negative initially. In a recent report from the DILIN Prospective Study, acute hepatitis C infection masqueraded as DILI in 1.5% of cases, leading to the recommendation that acute hepatitis C infection should be excluded in patients with suspected acute hepatocellular DILI by HCV RNA testing (44). Another published report from the DILIN showed that 3% of individuals with suspected DILI tested positive for anti–hepatitis E virus (HEV) immunoglobulin (Ig)M, and it was concluded that serological testing for acute hepatitis E infection should be performed in individuals with suspected DILI, especially if clinical features are compatible with acute viral hepatitis (46). Although the diagnosis of acute hepatitis E can be made most readily by testing for IgM anti-HEV antibodies, the reliability of currently available tests is not high (47). Use of HEV serology may be best reserved for cases with obvious risk factors (e.g., travel to an endemic area) where the pretest probability may increase the test performance and predictive value. Acute cytomegalovirus, Epstein-Barr virus, and herpes simplex virus infection may sometimes present with elevations in liver

Table 5. Recommended minimal elements of a diagnostic evaluation in the work-up of suspected drug-induced liver injury

Element	Comments
Sex	Particularly pertinent for competing disorders (e.g., PBC)
Age	Particularly pertinent for competing disorders (e.g., HEV)
Race/ethnicity	Particularly pertinent for competing disorders (e.g., sarcoidosis, sickle cell–related biliary stone disease, and oriental sclerosing cholangitis)
Indication for use of drug or HDS	
Concomitant diseases	Particularly pertinent disorders may include sepsis, heart failure, hypotension episodes, recent general anesthesia, parenteral nutrition, and cancer
Presence of rechallenge	Give timing of rechallenge if performed
History of other drug reactions	Certain cross-reactivities may exist (e.g., antiepileptics)
History of other liver disorders	Chronic viral hepatitis, NAFLD, hemochromatosis, alcoholic liver disease, PSC, PBC, and liver cancer
History of alcohol use	Past vs present; estimated grams per day; sporadic vs binge drinking vs regular (daily or weekly)
Exposure time (latency)	Start and stop dates or total number of days, weeks, or months taken
Symptoms and signs	Presence or absence, time of onset, type (fatigue, weakness, abdominal pain, nausea, dark urine, icterus, jaundice, pruritus, fever, and rash)
Physical findings	Fever, rash, hepatomegaly, hepatic tenderness, and signs of chronic liver disease
Medications and HDS products	Complete list of medications or HDS products with particular attention to those started in the previous 6 mo
Laboratory results	Day of first abnormal liver biochemistry, liver biochemistries, and eosinophil counts at presentation
Viral hepatitis serologies	Anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV, and HCV RNA
Autoimmune hepatitis serologies	ANA, anti-smooth muscle antibody, and IgG level
Imaging	US +/− Doppler, CT, or MRI +/− MRCP
Histology if available	Timing of biopsy in relation to enzyme elevation and onset
Washout (dechallenge) data	Follow-up liver biochemistries
Clinical outcome	Resolution, transplant, death, and timing of each

ANA, antinuclear antibody; CT, computed tomography; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDS, herbal and dietary supplements; HEV, hepatitis E virus; Ig, immunoglobulin; MRCP, magnetic resonance cholangiopancreatography; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; US, ultrasound.
See ref. (179).

biochemistries, although patients with such acute infections often have characteristic accompanying systemic manifestations such as lymphadenopathy, rash, and atypical lymphocytes.

AIH should be considered in the differential diagnosis of all cases of DILI, and, in fact, it is well known that some medications have high propensity to cause autoimmune-like DILI (e.g., minocycline and nitrofurantoin). Serum autoantibodies (antinuclear antibody and anti-smooth muscle antibody) and IgG levels should be routinely obtained, and a liver biopsy may be considered in selected cases. Low levels (e.g., titers less than 1:80 dilutions) of such autoantibodies are of little help in differential diagnosis because ~30% of adults, especially women, may have such positive autoantibodies (48). A rapidly emerging entity is the liver injury associated with immune-checkpoint inhibitor (ICI) use. This is often a diagnosis made in the appropriate clinical context and traditional autoimmune marker elevations are absent and histology does not necessarily mirror that seen in idiopathic AIH. A more in-depth discussion on ICIs is provided subsequently in this guideline.

Although rare, one should screen for Wilson disease with a serum ceruloplasmin level particularly in patients younger than 40 years; however, there are reports of Wilson disease in older individuals (49). In general, a normal or high level will end further pursuit of this diagnosis, but ceruloplasmin is an acute-phase reactant and may be falsely normal or elevated during an acute hepatitis. When suspicion remains or ceruloplasmin level is low, other tests such as 24 urine collection for copper, slit-lamp eye examination for Kayser-Fleischer rings, serum copper levels, and genetic testing of the *ATP7B* gene are indicated as outlined in diagnostic guidelines for diagnosing Wilson disease (50). Budd-Chiari syndrome may sometimes mimic DILI, and thus, it should be considered, especially if tender hepatomegaly and/or rapid onset of ascites is evident.

Competing etiologies in individuals with suspected cholestatic DILI are pancreaticobiliary in nature and can be extrahepatic or intrahepatic. Extrahepatic etiologies such as choledocholithiasis or malignancies (e.g., pancreatobiliary or lymphoma) can be readily identified with abdominal imaging tests such as ultrasonography, computed tomography, or magnetic resonance imaging. However, various intrahepatic etiologies mimicking DILI must be excluded based on careful history and physical examination (sepsis, total parenteral nutrition, or heart failure), serological testing (antimitochondrial antibody for primary biliary cholangitis [PBC]), or imaging (liver metastases, paraneoplastic syndromes, or sclerosing cholangitis). The role of endoscopic retrograde cholangiography in individuals with suspected DILI is largely limited to instances where routine imaging is unable to exclude impacted bile duct stones or primary sclerosing cholangitis (PSC) with certainty.

DIAGNOSTIC EVALUATION: LIVER BIOPSY

Liver biopsy is not mandatory in the evaluation of DILI. Of the DILIN registry's first 300 cases, fewer than 50% had a liver biopsy (26). The DILIN cases have more severe injury due to referral biases and inclusion criteria. Presumably, cases of less severe injury will have an even lower biopsy rate. Nevertheless, biopsy findings can be helpful and even diagnostic in some cases of suspected DILI. A detailed review of the plethora of histologic DILI findings is beyond the scope of this guideline. However, a

Table 6. Most common or well-described drug-induced liver injury agents and the patterns of their liver injury

	Latency[a]	Typical pattern of injury/identifying features
Antibiotics		
Amoxicillin/clavulanate	Short to moderate	Cholestatic injury, but can be hepatocellular; drug-induced liver injury onset is frequently detected after drug cessation
Isoniazid	Moderate to long	Acute hepatocellular injury similar to acute viral hepatitis
Trimethoprim/sulfamethoxazole	Short to moderate	Cholestatic injury, but can be hepatocellular; often with immunoallergic features (e.g., fever, rash, and eosinophilia)
Fluoroquinolones	Short	Variable—hepatocellular, cholestatic, or mixed in relatively similar proportions
Macrolides	Short	Hepatocellular, but can be cholestatic
Nitrofurantoin		Hepatocellular
Acute form (rare)	Short	Typically hepatocellular; often resembles idiopathic autoimmune hepatitis
Chronic form	Moderate to long (months–years)	Hepatocellular
Minocycline	Moderate to long	Hepatocellular and often resembles autoimmune hepatitis
Antiepileptics		
Phenytoin	Short to moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (e.g., fever, rash, and eosinophilia) (anticonvulsant hypersensitivity syndrome)
Carbamazepine	Moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Lamotrigine	Moderate	Hepatocellular often with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Valproate		
Hyperammonemia	Moderate to long	Elevated blood ammonia and encephalopathy
Hepatocellular	Moderate to long	Hepatocellular
Reye-like syndrome	Moderate	Hepatocellular, acidosis; microvesicular steatosis on biopsy
Analgesics		
Nonsteroidal anti-inflammatory agents	Moderate to long	Hepatocellular injury
Diclofenac		Hepatocellular injury with autoimmune features
Immune modulators		
Interferon-beta	Moderate to long	Hepatocellular
Interferon-alpha	Moderate	Hepatocellular, autoimmune hepatitis–like
Anti-TNF agents	Moderate to long	Hepatocellular. Can have autoimmune hepatitis features
Azathioprine	Moderate to long	Cholestatic or hepatocellular, but can present with portal hypertension (veno-occlusive disease and nodular regenerative hyperplasia)
Immune-checkpoint inhibitors		
Ipilimumab (CTLA-4 inhibitor) Nivolumab, pembrolizumab, and cemiplimab (PD-1 inhibitors) Atezolizumab, avelumab, and durvalumab (PDL-1 inhibitors)	Under 12 wk	Initially mixed pattern, but evolves primarily into hepatocellular pattern, without significant autoantibodies
Miscellaneous		
Methotrexate (oral)	Long	Fatty liver, fibrosis
Allopurinol	Short to moderate	Hepatocellular or mixed. Often with immune-allergic features. Granulomas often present on biopsy
Amiodarone (oral)	Moderate to long	Hepatocellular, mixed, or cholestatic. Macrovesicular steatosis and steatohepatitis on biopsy

Table 6. (*continued*)

	Latency[a]	Typical pattern of injury/identifying features
Androgen-containing steroids	Moderate to long	Cholestatic. Can present with peliosis hepatis, nodular regenerative hyperplasia, or hepatocellular carcinoma
Inhaled anesthetics	Short	Hepatocellular. May have immune-allergic features +/− fever
Sulfasalazine	Short to moderate	Mixed, hepatocellular, or cholestatic. Often with immunoallergic features
Proton pump inhibitors	Short	Hepatocellular; very rare

CTLA-4, cytotoxic T-lymphocyte antigen-4; PD-1, programmed cell death receptor-1; PDL-1, programmed cell death receptor-ligand 1; TNF, tumor necrosis factor.
[a]Short = 3–30 days; moderate = 30–90 days; long >90 days.

recent report from the DILIN Prospective Study provides extensive characterization of biopsies from a large cohort of patients with well-defined DILI (51). Other descriptions are also available (37,39,52). However, the frequency with which a liver biopsy makes a definitive DILI diagnosis is low. A biopsy usually supplements the work-up by suggesting another diagnosis or ruling out a competing one, rather than revealing a textbook description of DILI injury.

There are instances where biopsy can be strongly recommended such as to help discern between AIH and DILI (53). Current diagnostic algorithms for AIH include histology (54). AIH is typically responsive to immunosuppressive therapy, but commitment to therapy is often long term and has risks and side effects (55,56) Therefore, a biopsy is recommended if AIH remains on the differential and certainly if immunosuppressive therapies are contemplated. In this regard, it is important to recall that, in some patients, drugs seem to trigger the development of AIH. In most such instances, immunosuppressants can eventually be stopped without inciting a flare-up of AIH, whereas in idiopathic AIH, most patients will experience flare-ups when immunosuppressants are stopped (57). Recent data have suggested that early ALT response to corticosteroid therapy may help to distinguish DILI from AIH (58).

In general, persistence of biochemical abnormalities lowers the threshold for liver biopsy. Most DILI cases show steady decline in liver biochemistries after the presumed causative agent is stopped. This observation is often referred to as washout or dechallenge and is a major factor in DILI diagnostic scoring algorithms (31,32,34). Persistence of elevations weakens the case for DILI thereby strengthening the possibility of other diagnoses such as PSC, AIH, PBC, cancer, or granulomatous hepatitis. Typically, cholestatic DILI takes longer to resolve than the hepatocellular DILI. The decision on how long to wait before a biopsy is performed on a case-by-case basis. Some experts consider a less than 50% decline in the peak ALT value 30 days after stopping the suspected agent as reducing the likelihood of a DILI diagnosis (31,32). Others place the cutoff time for significant fall in ALT at 60 days (34). For cholestatic injury, the lack of a significant drop in AP or bilirubin (>50% drop in peak ULN or drop to <twice ULN) at 180 days is considered significant. There are no prospective studies examining yield of biopsy based on these cutoffs. However, considering a biopsy at 60 days for unresolved acute hepatocellular and 180 days for cholestatic DILI is reasonable. Earlier consideration of a biopsy is certainly justified, if there is continued rise in liver biochemistries particularly when any signs of liver failure develop. Conversely, if liver biochemistries are trending down, albeit slowly, then delaying liver biopsy is justified. DILI may also lead to chronic injury including a vanishing bile duct syndrome. If one suspects this possibility, a liver biopsy is indicated for diagnostic and prognostic purposes.

Occasionally, a liver biopsy may be necessary when continued use or contemplated rechallenge with a suspected medication is clinically necessary. Guidelines for considering a liver biopsy for patients receiving chronic methotrexate have been published (59,60). The clinical need for other medications (e.g., isoniazid and chemotherapeutic agents) can also be high, and a biopsy can help define the risk of re-exposure. For methotrexate-induced fibrosis and fatty change, the Roenigk Classification System is the recognized histologic grading system (61). For other agents, risk stratification is typically based on assessment of the degree of necrosis and fibrosis. The presence of hepatic eosinophils and lesser degree of necrosis have been associated with a greater likelihood of recovery in DILIN and other case series (51,62). A unique population in which biopsy may also be warranted to establish a diagnosis of DILI are those who have received a previous liver transplant, as competing pathologies such as rejection must be excluded (63).

There is growing interest to develop serum biomarkers for diagnostic and prognostic purposes (64). Serum glutamate dehydrogenase and miRNA-122 appear promising candidates for identifying DILI whereas keratin18, osteopontin, and macrophage colony-stimulating factor receptor may be helpful for predicting prognosis during an acute DILI event (65). However, this field is not sufficiently advanced, and these biomarkers are not routinely available for clinical implementation.

An algorithm for evaluating an individual with suspected DILI is shown in Figure 1.

Key concepts

1. Accurate clinical history related to medication exposure and the onset of liver test abnormalities should be obtained when DILI is suspected.
2. DILI is a diagnosis of exclusion, and thus, appropriate competing etiologies should be excluded in a systematic fashion.
3. Based on the *R*-value at presentation, DILI can be categorized into hepatocellular, cholestatic, or mixed types. This categorization allows testing for competing etiologies in a systematic approach.
4. Liver biopsy can support a clinical suspicion of DILI, provide important information regarding disease severity, and also help exclude competing causes of liver injury.

Recommendations

1. In individuals with suspected hepatocellular or mixed DILI:
(a) Acute viral hepatitis (A, B, and C) and AIH should be excluded with standard serologies and HCV RNA testing (strong recommendation, very low quality of evidence).
(b) Anti-HEV IgM testing may be considered in selected patients where there is heightened clinical suspicion (e.g., recent travel in an endemic area, DILI phenotype is atypical, or there is no readily identifiable culprit agent). It should however be noted that the performance of the currently available commercial tests is not clear (conditional recommendation, very low quality of evidence).
(c) We recommend testing for acute cytomegalovirus, acute Epstein-Barr virus, or acute herpes simplex virus infection be undertaken if classical viral hepatitis has been excluded or clinical features such as atypical lymphocytosis and lymphadenopathy suggest such causes (strong recommendation, very low quality of evidence).
(d) We recommend evaluation for Wilson disease and Budd-Chiari syndrome when clinically appropriate (strong recommendation, low quality of evidence).
2. In individuals with suspected cholestatic DILI:
(a) We recommend abdominal imaging (ultrasound, computed tomography scan, and MRI) be performed in all instances to exclude biliary tract pathology and infiltrative processes (strong recommendation, low quality of evidence).
(b) We recommend limiting serological testing for PBC to those with no evidence of obvious biliary tract pathology on abdominal imaging (strong recommendation, low quality of evidence).
(c) We suggest limiting endoscopic retrograde cholangiography to instances where routine imaging including MRI or endoscopic ultrasound is unable to exclude impacted common bile duct stones, PSC, or pancreaticobiliary malignancy (conditional recommendation, very low quality of evidence).
3. When to consider a liver biopsy?
(a) We recommend performing a liver biopsy if AIH remains a competing etiology and if immunosuppressive therapy is contemplated (strong recommendation, low quality of evidence).
(b) We suggest performing a liver biopsy if there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).
(c) We suggest performing a liver biopsy if peak ALT level has not fallen by >50% at 30–60 days after onset in cases of hepatocellular DILI or if peak Alk P has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent (conditional recommendation, very low quality of evidence).
(d) We suggest performing a liver biopsy in cases of DILI where continued use or re-exposure to the implicated agent is contemplated (conditional recommendation, very low quality of evidence).
(e) We suggest considering liver biopsy if liver biochemistry abnormalities persist beyond 180 days, especially if associated with symptoms (e.g., itching) or signs (e.g., jaundice and hepatomegaly), to evaluate for the presence of chronic liver diseases (CLDs) and chronic DILI (conditional recommendation, very low quality of evidence).

CAUSALITY ASSESSMENT

Causality assessment methods include the RUCAM (31,32), Maria and Victorino system (Clinical Diagnostic Scale—CDS) (34), and the Digestive-Disease-Week Japan 2004 scale (DDW-J—published only in Japanese literature but used in the English literature publications) (66) to facilitate the causality attribution for suspected DILI. Although these instruments perform reasonably well in comparison with the gold standard of expert consensus opinion, the RUCAM (Table 7) seems to be used more widely by some clinicians, the pharmaceutical industry, and the regulatory agencies. It was intended for use at the bedside or in clinic (31). It yields a summed score from −10 to 14, higher scores indicating higher likelihood of DILI. Scores are grouped into likelihood levels of "excluded" (score ≤0), "unlikely (1–2), "possible" (3–5), "probable" (6–8), and "highly probable" (>8). This score card system is divided into hepatocellular injuries vs cholestatic or mixed injuries. Points are given or taken away based on timing of exposure and liver biochemistry washout, risk factors for DILI, competing medications, competing diagnoses, and rechallenge information (Table 7). There are some ambiguities on how to score certain sections of the RUCAM as well as suboptimal retest reliability (reliability coefficient of 0.51, upper 95% confidence limit 0.76) (67). Furthermore, the concordance between RUCAM and the DILIN causality scoring system, which is based on expert consensus opinion, is modest ($r = 0.42$, $P < 0.05$) (68). The DDW-J and CDS scoring systems are modifications of RUCAM with differences in number of assessment categories and variability in weightage attributed to drug or patient characteristics, while CDS is more stringent in attributing causality as "probable" with a tight numerical score range (34,66). Notwithstanding these limitations, it can be an adjunct to clinical impression, particularly for clinicians who do not see DILI frequently. Perhaps its greatest utility is in providing a framework on which the clinician can organize history taking and tests. It reminds the clinician of the important areas of a DILI history and requires precision in recording exposure times and latency (31,32,68).

Key concepts

1. Scoring systems that include RUCAM should not be used as a sole diagnostic tool in isolation because of their suboptimal retest reliability and lack of robust validation, but they can be used by the clinicians as a diagnostic framework for excluding competing etiologies when evaluating a patient with suspected DILI.
2. Consensus expert opinion after a thorough evaluation for competing etiologies is the current gold standard for establishing causality in individuals with suspected DILI, but this approach is not widely available and therefore cannot be recommended for clinical practice.
3. If uncertainty persists after thorough history and evaluation for competing etiologies, clinicians should consider seeking expert consultation to ascertain the diagnosis of DILI and to attribute causality to a suspected agent.

PROGNOSIS/PROGNOSTIC FACTORS

Patients with acute DILI generally recover spontaneously within 6 months from onset on stopping the suspected agent(s). However, in some individuals, DILI may cause ALF or chronic liver injury. Among 899 patients enrolled in the DILIN Prospective Study with definite, probable, or

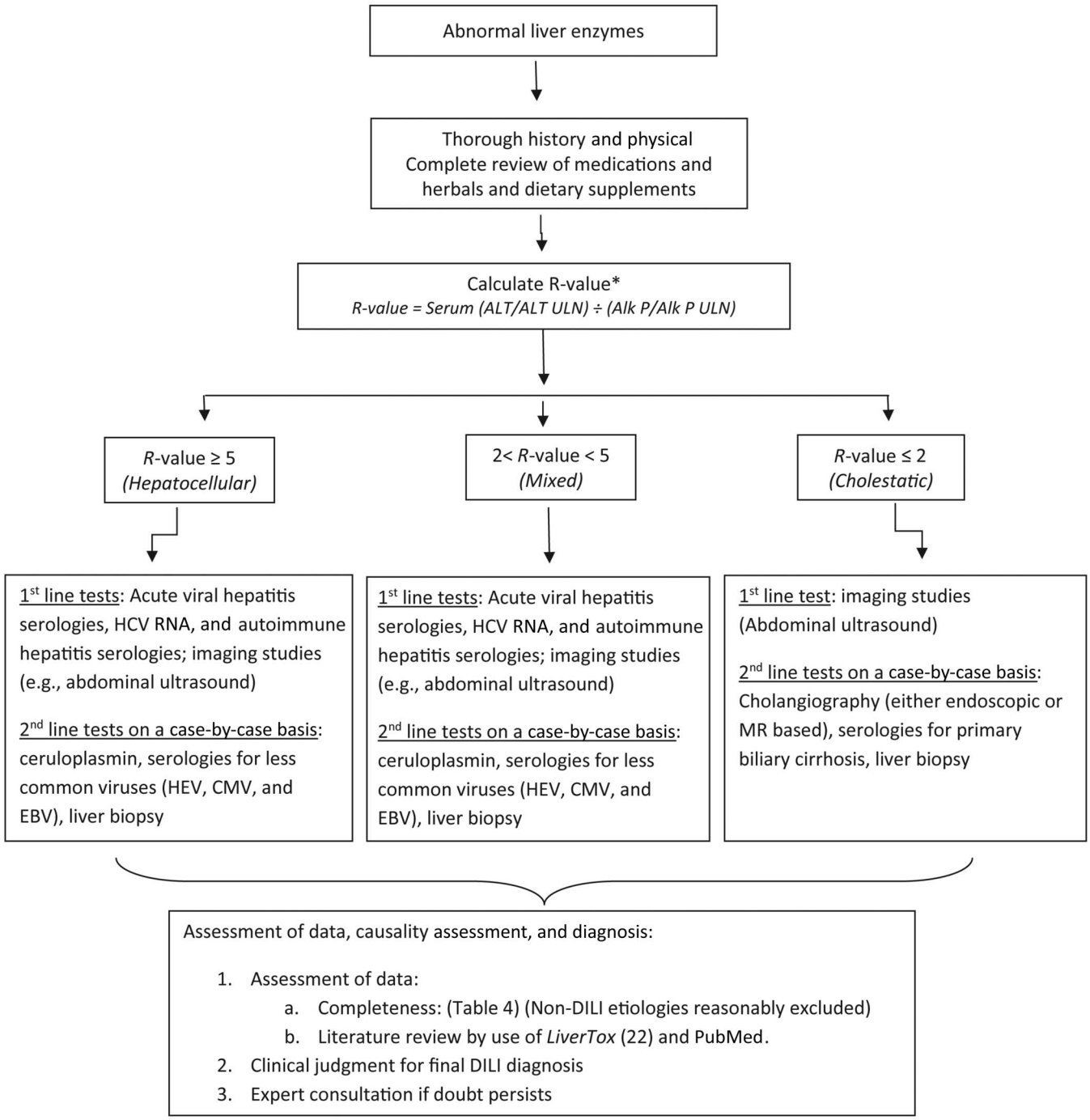

Figure 1. An algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI). The *R*-value cutoff numbers of 2 and 5 serve only as a guideline. Which tests and their order must be based on the overall clinical picture including risk factors for competing diagnosis (e.g., recent travel to HEV endemic area), associated symptoms (e.g., abdominal pain and fever), and timing of laboratory tests (i.e., the *R*-value may change as the DILI evolves). Alk P, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HCV, hepatitis C virus; HEV, hepatitis E virus; HSV, herpes simplex virus; ULN, upper limit of normal.

possible DILI, 69% recovered, 17% developed chronic liver injury (defined as elevated liver tests more than 6 months after onset), and 10% died or undergone liver transplantation (15). In a population-based study, 23% of patients with DILI were hospitalized and the most common symptom was jaundice (16).

Among clinical characteristics, age, race, and sex have been studied for their association with more severe liver injury. In a study of 99 patients with DILI, those with persistent liver injury were older compared with those who resolved (mean age of 52 years vs 43.7 years, $P = 0.01$) (69). Compared with whites, African Americans developed more severe liver injury, had

Table 7. Roussel Uclaf Causality Assessment Method

Criteria	RUCAM					
Enzyme pattern	Hepatocellular			Cholestatic or mixed		
Exposure	Initial exposure	Subsequent exposure	pts	Initial exposure	Subsequent exposure	pts
Timing from						
Drug start	5–90 d	1–15 d	+2	5–90 d	1–90 d	+2
	<5, >90 d	>15 d	+1	<5, >90 d	>90 d	+1
Drug stop	≤15 d	≤15 d	+1	≤30 d	≤30 d	+1
Course	**Difference between peak ALT and ULN value**			**Difference between peak Alk P (or bili) and ULN**		
After drug stop	Decrease ≥50% in 8 d		+3	Decrease ≥50% in 180 d		+2
	Decrease ≥50% in 30 d		+2	Decrease <50% in 180 d		+1
	Decrease ≥50% in >30 d		0	Persistence or increase or no information		0
	Decrease <50% in >30 d		−2			
Risk factor	Ethanol: yes		+1	Ethanol or pregnancy: yes		+1
	Ethanol: no		0	Ethanol or pregnancy: no		0
Age	≥50 yr		+1	≥50 yr		+1
	<50 yr		0	<50 yr		0
Other drugs	None or no information		0	None or no information		0
	Drug with suggestive timing known hepatotoxin w/ suggestive timing		−1	Drug with suggestive timing known hepatotoxin w/suggestive timing		−1
	Drug w/other evidence for a role (e.g., + rechallenge)		−2	Drug w/other evidence for a role (e.g., + rechallenge)		−2
			−3			−3
Competing causes	All group I[a] and II[b] ruled out		+2	All group I[a] and II[b] ruled out		+2
	All of group I ruled out		+1	All of group I ruled out		+1
	4–5 of group I ruled out		0	4–5 of group I ruled out		0
	<4 of group I ruled out		−2	<4 of group I ruled out		−2
	Nondrug causes highly probable		−3	Nondrug causes highly probable		−3
Previous information	Reaction in product label		+2	Reaction in product label		+2
	Reaction published; no label		+1	Reaction published; no label		+1
	Reaction unknown		0	Reaction unknown		0
Rechallenge	Positive		+3	Positive		+3
	Compatible		+1	Compatible		+1
	Negative		−2	Negative		−2
	Not performed or not interpretable		0	Not performed or not interpretable		0

Causality grading: ≤0, excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; and ≥9, highly probable.
Alk P, alkaline phosphatase; ALT, alanine aminotransferase; CMV, cytomegalovirus; EBV, Epstein-Barr virus; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.
[a]Group I: HAV, HBV, HCV (acute), biliary obstruction, alcoholism, and recent hypotension (shock liver).
[b]Group II: CMV, EBV, and herpes virus infection.

higher hospitalization rates, higher rates of liver transplantation or liver-related death, and more likely to develop chronic liver injury. The most frequently identified drugs in African Americans and whites were trimethoprim-sulfamethoxazole and amoxicillin-clavulanic acid, respectively (69). Women account for 56%–70% in large studies of DILI, suggesting women are a greater risk of idiosyncratic DILI and possibly an increased risk of more severe injury (15,16,70).

Prognosis is partly determined by the pattern of liver injury. Patients with cholestatic DILI are more than twice as likely to develop chronic liver injury compared with patients with hepatocellular DILI. By contrast, hepatocellular injury is more likely to be fatal or result in liver transplantation, albeit both events are rare. In most instances, the hepatocellular DILI phenotype leading to ALF evolves more slowly unlike where ALF due to APAP develops rapidly (71).

Data from studies support the 10% rule that was initially observed by Zimmerman in 1978 and more recently codified as "Hy's

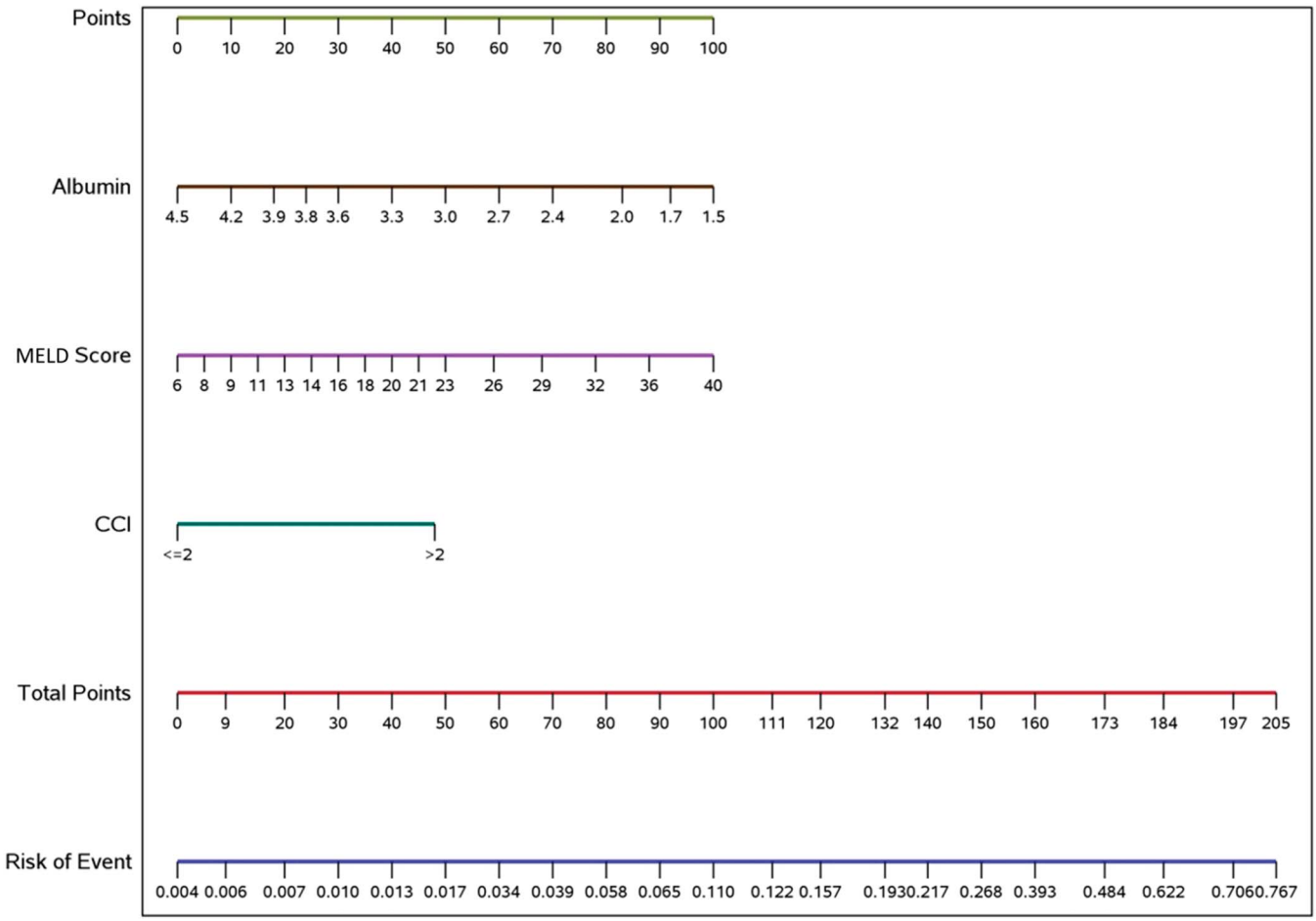

Figure 2. Drug-induced liver injury 6-month mortality prediction nomogram. This validated prediction incorporates Charlson comorbidity index, model for end-stage liver disease (MELD), and serum albumin in predicting 6-month mortality in patients with suspected acute drug-induced liver injury. Points are assigned for Charlson comorbidity index, MELD, and serum albumin scales using the linear points scale at the top of the figure. The risk of 6-month mortality correlating with the total points is on the 2 linear scales at the bottom of the figure. Reproduced with permission from Elsevier (Ghabril et al. [75]).

law," which states that, if drug-induced hepatocellular injury causes jaundice in a patient, then for every 10 jaundiced patients, 1 will develop ALF (23). In a study of 1,198 individuals with ALF enrolled in the US ALF Study Group, 11% of ALF were adjudicated to be due to DILI and their transplant-free survival at 3 weeks was only 27% (72). The mortality in the absence of transplantation was primarily due to systemic infection and/or cerebral edema. In the United States, the most common drugs other than APAP that are associated with ALF resulting in liver transplantation include anti-TB drugs, antiepileptics, and antibiotics (21). In patients with DILI who developed ALF, the King's College criteria or the US ALF Study Group criteria for non-APAP ALF can be applied for assessing the prognosis and for timing liver transplant evaluation, but these models are not specific for DILI (73,74).

A model for end-stage liver disease (MELD) score cutoff of 19 and a modified Hy's law (nr Hy's law, defined as bilirubin ≥2.5 mg/dL, and [(ALT/ULN) ÷ (Alk P/ULN)] >5) have good test performance for predicting liver-related death within 26 weeks of onset with c-statistics of 0.83 and 0.73, respectively (30). Ghabril et al. (75) recently developed and validated a model that incorporates albumin, MELD score, and the Charlson comorbidity index for accurately predicting 6-month mortality in patients with suspected DILI. This model had a c-statistic of 0.89 (95% CI 0.86–0.94) for predicting 6-month mortality in a discovery cohort consisting of 306 patients with suspected DILI and a c-statistic of 0.91 (95% CI 0.83–0.99) in a validation cohort consisting of 254 patients. A DILI mortality calculator was developed by the authors that can be applied in the clinic or at the bedside (Figure 2) (76).

Key concepts

1. The outcomes of idiosyncratic DILI are relatively favorable, with only ~10% reaching the threshold of ALF (coagulopathy and encephalopathy) and fewer than 20% developing chronic liver injury.
2. DILI that results in ALF carries a poor prognosis with 40% requiring liver transplantation and 42% dying of the episode. Advanced coma grade and high MELD scores are associated with poor outcomes.
3. Prognostic scores have been developed that incorporate readily available clinical and laboratory data that have good test performance of identifying individuals at risk of death from DILI.

Recommendation

4. We suggest using a prognostic model consisting of MELD, Charlson comorbidity index, and serum albumin in clinical practice for predicting 6-month mortality in individuals presenting with suspected DILI. A web-based DILI mortality calculator is available at http://gihep.com/calculators/hepatology/dili-cam/ (conditional recommendation, low quality of evidence).

RECHALLENGE

In general, readministration of a suspected hepatotoxic drug in a patient with ongoing or previous DILI is best avoided. In some instances, rechallenge occurs because of failure to recognize the previous toxic reaction. In other instances where the causal relationship is uncertain or the history unknown, and/or when the drug is considered very important, rechallenge has been undertaken. The fear of rechallenge held by clinicians is based on understanding the anamnestic response. Reintroducing a medication in this context may be associated with a more rapid return of injury than was initially experienced, and a more severe and possibly fatal reaction may result, even when the first instance was relatively mild. Although this may not apply to all drugs, an immune basis for the toxic reaction underlies many such injuries and provides support for the concept that repeated exposure results in worse outcomes. Although rechallenge may occur and may even be performed intentionally recognizing the risks, it is generally discouraged in all but the most life-threatening situations where a suitable alternative is unavailable (77,78). The package inserts for newer anticancer agents (e.g., idelalisib, regorafenib, ribociclib, and pazopanib) are increasingly recommending resumption of treatment, with dose modification. Clinicians who have recognized a toxic reaction should be careful to educate the patient with the name of the suspect drug and the reminder (medical alert bracelets and cards encouraged) that re-exposure may have even more deleterious effects.

Recommendation

5. We strongly recommend against re-exposure to a drug thought likely to have caused hepatotoxicity, especially if the initial liver injury was associated with significant aminotransferase elevation (e.g., >5xULN, Hy's law, or jaundice). An exception to this recommendation is in cases of life-threatening situations where there is no suitable alternative (strong recommendation, low quality of evidence).

TREATMENT

The hallmark of treatment of DILI is withdrawal of the offending medication. It is said (and it seems inherently reasonable) that early withdrawal prevents progression to ALF, but there is little firm evidence to support this. In some instances, a drug taken only for 2–3 days may lead to a fatal outcome. Currently, there is no approved antidote for ALF due to idiosyncratic DILI. Most clinicians use antihistamines such as diphenhydramine and hydroxyzine for symptomatic pruritus. In addition, as many as 30% of patients enrolled in DILIN prospective study were given ursodeoxycholic acid, but the efficacy of this agent in acute and chronic DILI is not established (79).

It is not uncommon for patients with severe DILI to receive corticosteroid therapy, but there have been no randomized controlled trials to evaluate their efficacy and safety. A limited number of retrospective studies suggested that steroid therapy may be associated with improvement (80–82), but in other studies, corticosteroid therapy was either not associated with improvement and/or associated with increased adverse events (83,84). *N*-acetylcysteine (NAC), the proven antidote for APAP overdoses (intrinsic DILI), was subjected to a randomized placebo-controlled trial for non-APAP ALF that included DILI as 1 subgroup (85). The primary outcome (improvement in overall survival) was not achieved, but significant improvement was observed within early coma grade patients (I–II): transplant-free survival was 52% with NAC vs 30% with placebo (86). All ALF trials in the modern era are confounded by the availability of transplantation that rescues ~40% of those with non-APAP ALF, so that their true natural histories will never be known (87). Overall survival is improved because of the use of liver grafting (as it should be). For those with a DILI etiology within the NAC trial (N = 42), transplant-free survival was 58% for those who received NAC vs 27% for those who did not receive NAC. However, outcomes with the use of IV NAC in children with non-APAP ALF demonstrated a lower rate of survival at 1 year (88). A recent South African study evaluated the role of intravenous NAC in 102 hospitalized patients with liver injury because of anti-TB agents (89). The primary endpoint (time to ALT <100 U/L) and overall mortality were not different between 2 treatment arms. Interestingly, time to discharge from hospital was significantly shorter in the NAC arm (median 9 vs 18 days). The authors concluded that intravenous NAC should be considered in the management of patients with DILI because of anti-TB agents who are hospitalized.

Recommendations

6. We recommend promptly stopping suspected agent(s) in individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction (strong recommendation, low quality of evidence).
7. Although no definitive therapies are available either for idiosyncratic DILI with or without ALF, we suggest consideration of NAC treatment in adults with early stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients (conditional recommendation, low quality of evidence).
8. We suggest against using NAC for children with severe DILI leading to ALF (conditional recommendation, low quality of evidence).
9. There are no well-conducted studies to either recommend or refute corticosteroid therapy in patients with DILI. However, they may be considered in a subset of patients with DILI exhibiting AIH-like features (conditional recommendation, low quality of evidence).

FOLLOW-UP

Patients with any acute hepatic illness should be followed to its resolution whenever possible. In the case of DILI, recent data suggest that chronicity (evaluated liver tests at 6 months after DILI onset) occurs in approximately 17% of those experiencing DILI, with a significantly higher frequency among individuals with cholestatic liver injury (15). In another study which assessed for chronicity at 1 year after DILI onset, the frequency of chronic DILI was 8% and predictors were older age, dyslipidemia, severe DILI, and hepatotoxicity associated with the use of statins and anti-infectives (90). Chronic DILI may resemble AIH and might respond to corticosteroids, provided serological markers, and biopsy findings are

suggestive of this diagnosis. Late development to cirrhosis and its complications have been observed but are quite rare after acute DILI.

HDS-INDUCED LIVER INJURY

Epidemiology

Liver injury due to HDS is increasingly common and can lead to significant morbidity and mortality worldwide (41,91,92). HDS are the second most common class of agents to cause DILI in the United States (79). No population-based statistics in the United States are available to facilitate an understanding of the true prevalence and incidence of HDS-hepatotoxicity. However, in the DILIN prospective study, there has been an increasing representation of HDS-hepatotoxicity among all enrolled cases from 2004 to 2014, and supplements used for body building and weight loss are the most common types of HDS implicated in disease (18,79).

HDS regulation

It is important for clinicians and consumers to understand that HDS are not subject to the same rigorous drug development oversight process as are pharmaceuticals. In particular, HDS do not undergo preclinical and clinical toxicology safety testing nor clinical trials for safety or efficacy.

Governed by the Dietary Supplement Health Education and Safety Act of 1994, HDS can be marketed without previous approval by the FDA (93). Under this Act, dietary supplements are defined as substances intended to supplement the diet, but not to constitute a complete meal. Supplements consist of dietary ingredients which are further defined as vitamins, minerals, botanicals, amino acids, enzymes, organ or glandular tissues, and metabolites. Also covered by current dietary supplement regulation are medical foods (94). Although considered dietary supplements, medical foods are administered under the supervision of a physician, as are conventional drugs. Unlike drugs, however, medical foods are not subject to the same rigorous safety and efficacy testing. In a case series from the DILIN, the medical food flavocoxid caused a mixed hepatocellular/cholestatic pattern, with some patients experiencing severe injury (95).

The Dietary Supplement Health Education and Safety Act of 1994 (93) and the subsequent Final Rule for Dietary Supplement Current Good Manufacturing Practices of 2007 (96) place the responsibility to generate truthful labels and to market safe products on the manufacturer. The FDA's responsibility is to monitor reports of adverse events attributable to HDS after marketing through its Center for Food Safety and Applied Nutrition and to deem a product unsafe when a suspicion of toxicity is raised. Reporting of adverse events by consumers and health care providers is voluntary, through the MEDWATCH system (97). Supplement manufacturers are required to report adverse events associated with their products. However, the voluntary nature of reporting probably leads to underreporting (98). Once a product has been deemed unsafe by the FDA, a warning to consumers will be published and the warning will be sent to physicians especially if the drug is restricted in use or requires withdrawal from the market.

Causality assessment

As discussed elsewhere in this guideline, the process of causality assessment is a structured approach to assessing the clinical circumstances and data surrounding a case. Whatever process is used, the goal of causality assessment is to generate a score that reflects the likelihood that a drug or HDS accounts for the injury the case of HDS-hepatotoxicity, important limitations to the causality assessment process must be considered. First, none of the causality assessment processes in use was created specifically for HDS-hepatotoxicity. As such, the nuances associated with HDS confound any causality assessment approach. Dietary supplements are susceptible to a variety of factors, including the location or conditions of growth of the herbal constituents, as well as their methods and standards of manufacture. These factors can lead to significant variability in the ingredients or their concentrations over time and from batch to batch (99–102). In addition, products may contain ingredients not identified on the label, as either contaminants or adulterants. These unlabeled ingredients often take the form of powerful prescription pharmaceuticals in keeping with a product-intended effect, such as to enhance sexual performance (103). Other unlabeled ingredients, more accurately regarded as contaminants, include microbials or heavy metals (104–107). Finally, even when a connection can be drawn between an injury event and a product, it is not uncommon for products to contain a myriad of ingredients. Although some components can be considered more likely to be injurious based on published experience, a categorical statement impugning any 1 ingredient cannot be made as the effects of other ingredients cannot be excluded.

The second important consideration in causality assessment of HDS-hepatotoxicity cases concerns the selection of the assessment approach. The more commonly used approaches include the RUCAM and expert opinion process. Common to both, but more significant in the RUCAM, is the impact of label warnings and published reports of hepatotoxicity pertinent to an implicated agent. In the RUCAM, the presence of a labeled warning of hepatotoxicity increases the score. However, since warnings typically do not exist on HDS labels, the highest score could rarely be awarded.

Arguably, the expert opinion process is the approach best adapted for HDS-hepatotoxicity. Expert opinion allows assessors to consider all available clinical information, including a qualitative assessment of the published literature and personal experience with any given product.

Key concepts

1. HDS account for an increasing proportion of DILI events in the United States, with body building and weight loss supplements being the most commonly implicated.
2. The current regulation for HDS differs substantially from conventional prescription medications. Most importantly, there is no requirement for premarketing safety analyses of HDS.
3. Patients and providers must be aware that regulation is not rigorous enough to assure complete safety of marketed products. Patients should be made aware of this fact and of the potential for HDS to cause liver injury.
4. Current causality assessment approaches are not well suited for HDS-hepatotoxicity, given the possibility of product variability and contamination; however, expert opinion is probably the best suited for HDS-hepatotoxicity because all information is taken into consideration in assigning a likelihood of injury.
5. Voluntary reporting of suspected HDS-hepatotoxicity cases through the FDA MEDWATCH system is essential.

CLINICAL PRESENTATION AND DIAGNOSIS

The diagnosis of HDS-hepatotoxicity is made with the same clinical approach as for conventional drugs, where an accurate

diagnosis hinges on the exclusion of nondrug causes for injury. However, clinicians must query patients about their use of HDS, realizing that many will not be forthcoming with this history (68). An important consideration in making the diagnosis of HDS-hepatotoxicity is the possibility that latency may be quite prolonged in some instances. HDS-induced liver injury currently accounts for 20% of cases of hepatotoxicity in the United States, with major implicated ingredients including anabolic steroids, green tea extract, and multi-ingredient nutritional supplements. Anabolic steroids typically cause prolonged cholestatic injury, whereas green tea extract induced injury that is acute and hepatocellular (106,108–113).

An important feature of DILI which permits clinicians to render a more confident diagnostic impression is the recognition of liver injury patterns that are typical for certain drugs or drug classes. Many of these associations result from detailed observations of carefully documented cases. In the case of HDS-hepatotoxicity, there are only a few agents in which common and repeating patterns of injury have been observed. Apart from cholestasis from bodybuilding products, shown in some instances to contain anabolic steroids, pyrrolizidine alkaloids typically have been associated with the sinusoidal obstruction syndrome (114–119). Furthermore, flavocoxid, a medical food, and OxyELITE Pro, a nutritional supplement, have been associated with severe liver injury (95,120). With the notable exception of HDS marketed for bodybuilding, most HDS cause a hepatocellular-type liver injury ($R > 5$). For example, in a recent article from the DILIN, in 40 patients with green tea–induced liver injury, the pattern of liver injury was hepatocellular in 95% of patients and was associated with HLA-B*35:01 (121). In those with a cholestatic injury, the degree of bile duct loss was predictive of a poor outcome (122).

MANAGEMENT

The best management approach to HDS-hepatotoxicity is for the clinician to have a high level of suspicion that HDS are implicated in injury. The suspected agent(s) must be stopped, and the patient observed closely because herbal products may cause an unpredictable course of injury. The management of ALF and severe cholestatic injury because of HDS is similar to how patients with ALF and severe cholestasis because of prescription agents are managed.

Recommendations

10. We recommend encouraging patients to report use of HDS to their health care providers and be reminded that supplements are not subjected to the same rigorous testing for safety and efficacy as are prescription medications (strong recommendation, low quality of evidence).
11. We recommend applying the same diagnostic approach for DILI to suspected HDS-hepatotoxicity. That is, other forms of liver injury must be excluded through a careful history and appropriate laboratory testing and hepatobiliary imaging. Excluding other causes, the diagnosis of HDS-hepatotoxicity can be made with confidence in the setting of recent use of HDS (strong recommendation, low quality of evidence).
12. We recommend stopping all HDS in patients with suspected HDS-hepatotoxicity and continued monitoring for resolution of their liver injury (strong recommendation, low quality of evidence).
13. We recommend consideration of liver transplantation evaluation in patients who develop ALF and severe cholestatic injury from HDS-DILI (strong recommendation, low quality of evidence).

LIVER INJURY DUE TO IMMUNE-CHECKPOINT INHIBITORS

Gastroenterologists and oncologists are encountering an increasing number of patients with advanced malignancies with hepatotoxicity due to ICIs (123,124). The ICIs are proving to be effective therapies for a growing number of advanced cancers. Their mechanisms of action include the blockade of cytotoxic T-lymphocyte antigen-4, programmed cell death receptor-1, and programmed cell death receptor-ligand 1. To date, there have been 7 ICIs approved by the US FDA. They include ipilimumab (cytotoxic T-lymphocyte antigen-4 inhibitor), nivolumab, pembrolizumab, and cemiplimab which are programmed cell death receptor-1 inhibitors and atezolizumab, avelumab, and durvalumab which are programmed cell death receptor-ligand 1 inhibitors (125). Immune-related adverse events are seen in up to 90% of individuals receiving ICIs and are thought to be due to their off-target effects. Liver enzyme elevations have been reported in up to 30% of patients (9,123,126). It is important to recognize that hepatitis B reactivation may occur in those with either chronic infection or past exposure to hepatitis B infection and the clinical picture may mimic DILI (127–129) and as such patients should be serologically evaluated for it. The onset of DILI typically occurs at 4–12 weeks or after 1–3 doses of ICIs. The DILI at presentation is often asymptomatic and is generally mixed pattern liver injury, although the liver injury often evolves primarily to a hepatocellular pattern subsequently (123). Low titers of antinuclear antibodies can be present in up to 50% but anti-smooth muscle antibodies are infrequent (123). Jaundice and liver failure are distinctly uncommon (130,131). Histologically, DILI due to ICIs does not resemble that of AIH. A recent large retrospective study from the MD Anderson Cancer Center in Texas described 2% frequency of moderate or severe hepatotoxicity (defined according to the Common Terminology Criteria for Adverse Events criteria) in more than 5,000 individuals with advanced malignancies who received various ICIs (130). In this study, characteristics of liver injury, response to steroid therapy, and outcomes were not different between patients with and without underlying liver disease. Although there was higher prevalence of DILI in individuals who received combination of ICIs as compared to ICI monotherapy (9.2% vs 1.2%, $P < 0.001$), the severity of liver injury was not different between ICI monotherapy and combination therapy.

Before initiating ICI or other chemotherapeutic agents, serological tests for viral hepatitis B and C should be performed and those with positive serology should receive appropriate antiviral hepatitis B or C therapy or hepatitis B prophylaxis either previous or concomitantly as dictated by the clinical picture (132).

Mainstay for treating moderate to severe ICI hepatotoxicity is to consider withholding or delaying ICI administration and initiating immunosuppressive therapy. Corticosteroids are the primary immunosuppressants used with alternate agents such as mycophenolate mofetil being added or reserved for severe hepatotoxicity unresponsive or with adverse events to systemic corticosteroids. In those with HBV reactivation, appropriate therapy should be directed at the HBV infection. A detailed discussion of treatment algorithms for ICI DILI are beyond the scope of this practice guideline. Interested readers are referred to excellent reviews and consensus statements on the management of ICI hepatotoxicity (6,123,133,134).

DILI in patients with CLD

In the United States, 4.5 million adults or 1.8% of adults are diagnosed with CLD (135). The most common CLD are nonalcoholic fatty liver disease (NAFLD) (20%), alcoholic liver disease (5%), chronic HCV (1%–5%), and chronic HBV (0.5%–1%) (136). The rising incidence of CLD in the general population coupled with the increasing use of medications to treat various acute and chronic diseases will likely lead to more instances where clinicians are faced with a diagnosis of possible DILI in a CLD patient (137). Indeed, the DILIN Prospective Study demonstrated that 10% of enrolled patients had preexisting CLD (15). However, DILI accounts for <1% of consecutive inpatients or outpatients presenting with clinically apparent acute liver injury (138,139). The presence of certain clinical features such as the exposure to a known hepatotoxic agent, latency to DILI onset, biochemical, clinical, and histological features at presentation and after dechallenge as well as previous published reports can help raise the index of suspicion of DILI in CLD. However, the lack of an objective and confirmatory laboratory test makes it difficult to confidently establish a diagnosis of DILI in CLD. Therefore, DILI is largely a diagnosis of exclusion that requires one to consider more common causes of acute liver injury such as viral hepatitis, pancreaticobiliary disease, alcohol, and ischemia depending on the clinical setting (35,140). To further complicate matters, some forms of CLD can present with an icteric flare (e.g., alcoholic hepatitis, AIH, and chronic HBV) that may be mistaken as DILI. Fortunately, most patients with NAFLD and HCV do not experience icteric flares in disease activity, although liver biochemical indices may wax and wane from 2- to 5-fold (141,142). Interested readers are referred to an excellent review by Lewis and Stine which offers a practical guide for prescribing medications in patients with cirrhosis (143).

Although one may hypothesize that CLD patients may be more susceptible to DILI through reduced drug clearance, aberrant metabolism, altered excretion, or impaired adaptive responses, there are currently limited data to support the increased susceptibility of CLD patients to DILI. A few studies raised the possibility that suspected NAFLD may increase the risk of all-cause DILI (144–147) as well as specific compounds such as methotrexate, tamoxifen, and ICIs (148–154). Despite the hesitation against using statins in individuals with underlying liver diseases such as NAFLD, there is a large body of literature to show that individuals with underlying liver disease are not at an increased risk of DILI (148,150,153,155). In fact, over an 8-year period, the US DILIN reported only 22 cases of DILI attributed to statins among 1,188 total DILI cases and underlying liver disease was not a risk factor for DILI (155). Furthermore, evolving data suggest that individuals with NAFLD or hepatitis C may actually benefit from statins (156–159). Antiretroviral hepatotoxicity seems to be more common in human immunodeficiency virus patients with HCV or HBV coinfection (160). However, the greater use of tenofovir containing regimens and less frequent use of other agents associated with acute hepatic injury (i.e., dideoxynucleotides, abacavir, and nevirapine) may be leading to a decline in the incidence of severe acute DILI due to human immunodeficiency virus–related medications (161). Nonetheless, it remains difficult to reliably distinguish a DILI episode from that of immune reconstitution in an HIV-HBV–coinfected individual who presents with acute hepatitis (161). Patients with chronic HBV, HCV, and human immunodeficiency virus may also be at increased risk of isoniazid hepatotoxicity, but again, it can be difficult to distinguish a spontaneous disease flare or disease-related fluctuations in liver tests from a bonafide DILI episode (162,163). Obtaining liver histology may be of benefit in diagnosing DILI in liver transplant recipients, but additional data are needed to confirm these observations (164).

Caution should be exercised when prescribing medications to patients who are potentially at increased risk of complications from DILI, such as patients with Child-Pugh class B and C cirrhosis. Protease inhibitors used to treat hepatitis C have been associated with exacerbating hepatic decompensation in Child-Pugh B and C cirrhosis and non–protease-containing regimens should be used (165). A warning about hepatoxicity and an advise for dose reduction exist for obeticholic acid in Child-Pugh class B and C cirrhosis due to PBC, and dose-related liver toxicity has been reported with obeticholic acid in patients with cirrhosis due to PBC, and dose modification is required in patients with PBC Child B or C cirrhosis (166).

Outcomes of DILI in patients with CLD

It is reasonable to suspect that CLD patients would be more likely to develop severe or would be slower to resolve DILI due to impaired liver regeneration as has been noted with acute hepatitis A and B infection in patients with chronic HCV (167). In support of this notion, patients with chronic HBV who develop isoniazid hepatotoxicity have more severe hepatocellular injury compared with uninfected patients, and liver injury due to highly active antiretroviral agents (HAART) seems to be more severe in patients with viral hepatitis (161,162). The DILIN Prospective Study observed that DILI occurring in individuals with underlying CLD was associated with much higher mortality rate, as compared to individuals without underlying liver disease (16% vs 5.2%, $P < 0.001$) (15). Among individuals with DILI, heavy alcohol consumption was associated with higher peak aminotransferases compared with no alcohol consumption, but liver-related deaths or liver transplantation was not significantly different between the 2 groups (33). Patients with cirrhosis hospitalized for DILI were reported to have an in-hospital mortality of 15.8% (168).

Key concepts

1. There are no definitive data to show that underlying CLD is a major risk factor for all-cause DILI, but it may increase the risk of DILI due to selected medications. Patients with chronic HBV and HCV may be more prone to develop liver injury due to specific agents such as isoniazid and antiretrovirals and may experience more severe outcomes.
2. Individuals with underlying fatty liver disease are not at increased risk of hepatotoxicity from statins. Indications for statins should be reevaluated in patients with decompensated cirrhosis because their risk to cause rhabdomyolysis may be heightened in such patients.
3. Patients with decompensated cirrhosis who have chronic hepatitis C should avoid protease inhibitors. Obeticholic acid has been associated with hepatic decompensation in patients with PBC and Child-Pugh class B and C cirrhosis who received a higher than recommended dose.

Recommendations

14. As the diagnosis of DILI in patients with CLD requires a high index of suspicion, we recommend exclusion of other more common causes of acute liver injury including a flare-up of the underlying liver disease (strong recommendation, low quality of evidence).
15. The decision to use potentially hepatotoxic drugs in CLD patients should be based on the risk vs benefit of the proposed therapy on a case-by-case basis (conditional recommendation, low quality of evidence).
16. There are no data to recommend a specific liver biochemistry monitoring plan when a potential hepatotoxic agent is prescribed in individuals with known CLD. Often, information contained in the package inserts is incomplete or unhelpful. Patients should be advised to promptly report any new onset symptoms such as scleral icterus, abdominal pain/discomfort, nausea/vomiting, itching, or dark urine. In addition, it is reasonable to monitor serum liver biochemistries at 4–6 weekly intervals, especially during the initial 6 months of treatment with a potentially hepatotoxic agent (conditional recommendation, very low quality of evidence).

DILI IN CHILDREN

DILI is often ascribed to adults, with advanced age being an associated risk factor. The misconception that DILI is rare in children is largely fueled by the fact that pharmacologic agents are less frequently prescribed in the pediatric population. Nonetheless, it is a phenomenon that does occur in children, albeit, very likely underreported (169–171). In general, DILI tends to be hepatocellular in children (170). More intriguing is that injury responses vary, i.e., APAP hepatotoxicity is associated with less severe injury in children as compared to adults and, conversely, antiepileptic agents lead to more severe injury in children (172,173).

The DILIN Prospective Study observed that antimicrobial and antiepileptic agents are the most common causes of DILI in children (170). The antimicrobials associated with DILI are different in children as compared to adults. In children, minocycline is the most common antimicrobial associated with DILI, whereas it is the amoxicillin-clavulanate in adults. DILI related to valproic acid and other antiepileptic drugs occurs at a far higher rate in children as compared to adults. In the instance of APAP hepatotoxicity, the lack of concomitant risk factors such as heavy alcohol consumption has been suggested as an explanation for attenuated injury response, although the presence of increased glutathione in children may also be explanatory (172,173).

Risk factors associated with pediatric DILI may include previous documented medication allergy in addition to presence of underlying medical conditions, although it is unclear whether the latter is a true risk factor because those with fewer comorbidities are less likely to be prescribed pharmacologic therapies (174). Ontogeny of drug metabolizing enzymes may be a risk factor for DILI in children due to specific agents. In case of valproate, its increased risk of hepatotoxicity in infants was attributed to lower expression of hepatic cytochrome P450 2C9 (175), although inborn errors of metabolism and mitochondrial function may play an important role as well (176,177).

In most instances, the clinical features of DILI resemble that those in adults with some exceptions (170,178). Pediatric DILI is associated with significant morbidity and mortality as in adults. In the DILIN Prospective Study, 63% of children with DILI were hospitalized and 24% had evidence for severe liver dysfunction, with liver transplantation required in 5% (170). The incidence of chronic DILI in their experience at 6 months was 17%. Long latency can be seen in pediatric DILI, especially with minocycline administered for facial acne. Minocycline DILI may present with features consistent with AIH including elevated autoantibodies and serum immunoglobulins. Many children with minocycline DILI may need corticosteroid therapy (170).

Key concepts

1. Children may rarely develop DILI. Antimicrobial agents such as minocycline administered for facial acne and antiepileptic agents are the most common culprits for DILI in children in the United States.
2. Pediatric DILI may be associated with significant morbidity and mortality including requiring liver transplantation and death.
3. Minocycline DILI may have long latency (e.g., >1 year) and can present with features resembling AIH. Adolescents with presenting autoimmune such as liver disease should be carefully questioned about their minocycline use for facial acne.

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CONFLICTS OF INTEREST

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