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

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Idiosyncratic drug-induced liver injury (DILI) is a rare adverse drug reaction and it can lead to jaundice, liver failure, or even death. Antimicrobials and herbal and dietary supplements are among the most common therapeutic classes to cause DILI in the Western world. DILI is a diagnosis of exclusion and thus careful history taking and thorough work-up for competing etiologies are essential for its timely diagnosis. In this ACG Clinical Guideline, the authors present an evidence-based approach to diagnosis and management of DILI with special emphasis on DILI due to herbal and dietary supplements and DILI occurring in individuals with underlying liver disease.

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PREAMBLE

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 May 2013); (ii) the American College of Physicians' *Manual for Assessing Health Practices and Designing Practice Guidelines*; (iii) guideline policies of the American College of Gastroenterology; and (iv) the experience of the authors and independent reviewers with regard to idiosyncratic DILI.

These recommendations, intended for use by physicians and other health-care providers, suggest preferred approaches to the diagnosis and management of DILI. 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 classification used by the Grading of Recommendation Assessment, Development, and Evaluation (GRADE) workgroup with minor modifications (**Table 1**). The strength of recommendations in the GRADE system is classified as strong or conditional. The quality of evidence supporting strong or weak recommendations is designated by one of the following levels: high, moderate, low, or very low quality (1). This is a practice guideline for clinicians rather than a review article, and we refer interested readers to several comprehensive reviews published recently (2–6).

INTRODUCTION

Drug-induced liver injury (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, sulfonamides) (7,8). Many herbal and dietary supplements (HDS) can cause DILI, and thus they must be considered as a cause for DILI. For the purposes of this guideline, the term DILI will refer to idiosyncratic liver injury from HDS, as well as prescription drugs or 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

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Table 1. Grading of Recommendations, Assessment, Development and Evaluation (GRADE) (1)

Strength of recommendation	Criteria
Strong	Factors influencing the strength of the recommendation included the quality of the evidence, presumed patient-important outcomes, and cost
Conditional	Variability in preferences and values, or more uncertainty. Recommendation is made with less certainty, 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 very likely to impact confidence on the estimate of clinical effect
Very low	The estimate of the effect is very uncertain

data have begun to blur the distinction between these two categories somewhat, they remain useful conceptual paradigms. APAP, although 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 (9–11). 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) (5,12), and outcome (resolution versus 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 2**.

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 (2). Nongenetic risk factors can be host-related environmental factors, or they can be compound-specific in nature (**Table 3**).

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 manner. For example, drugs that act on the central nervous system and antimicrobials are the more common causes of DILI in children. Infants and children appear susceptible to liver injury caused by valproate and are at an increased risk of Reye's syndrome caused by aspirin. Although propylthiouracil may cause DILI in all age groups, children are more susceptible to severe and fatal hepatotoxicity due to propylthiouracil (13,14). With increasing age, there is an increasing risk of liver injury because of many medications such as isoniazid, amoxicillin–clavulanate, and nitrofurantoin (15).

There is no evidence to suggest that women are at a higher risk for "all-cause DILI" (i.e., DILI caused by any type of agent), but they appear to be at a 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 with female preponderance. Hepatotoxicity due to nevirapine is also more common in women, especially those with higher CD4+ cell count (5).

DILI is a rare cause of acute liver injury in pregnant women, which could well be due to generally infrequent use of prescription medications. There is no evidence to suggest that pregnancy by itself increases the susceptibility to DILI to any agents other than tetracycline. High-dose intravenous tetracycline has been classically described to cause DILI in pregnant women, but intravenous tetracycline is seldom used now in the developed world (2,4,5). Common causes of DILI in pregnant women are antihypertensive agents such as methyldopa and hydralazine, antimicrobials including antiretroviral agents, and propylthiouracil.

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 anti-tuberculosis medicines may be increased in individuals with diabetes. A preliminary report from the United States Drug-Induced Liver Injury Network (DILIN) showed that underlying diabetes mellitus was independently associated with the severity of DILI (odds ratio = 2.69; 95% CI = 1.14–6.45) (16).

Although alcohol consumption is included as one of the elements for assessing causality in the Roussel Uclaf Causality Assessment Method (RUCAM) causality instrument (17,18), 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 owing to 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 duloxetine hepatotoxicity.

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 due to antituberculosis agents and anticonvulsants such as valproate.

Summary statements

- 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.

Table 2. 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, coagulopathy) 6 months after DILI onset
Latency	Time from medication (or HDS*) start to onset of DILI
Wash-out, resolution, or de-challenge	Time from DILI onset to return of enzymes and/or bilirubin to pre-DILI baseline levels
Rechallenge	Re-administration 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 a 1 in 10 mortality risk of DILI if the following three criteria are met: 1. Serum ALT or AST >3×ULN 2. Serum total bilirubin elevated to >2×ULN, 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 preexisting or acute liver disease
Temple's corollary	An imbalance in the frequency of ALT >3×ULN 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
R-value	ALT/ULN ÷ AP/ULN. Used to defined hepatotoxicity injury patterns: hepatocellular ($R>5$), mixed ($R=2–5$), and cholestatic ($R<2$)
RUCAM	RUCAM. Diagnostic algorithm that uses a scoring system based on clinical data, pre-existing hepatotoxicity literature on the suspected agent and rechallenge

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

- Certain variables such as age, gender, and alcohol consumption may increase the risk for DILI in a drug-specific manner.

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 (17–19). Although they can help organize the clinician's history and testing by providing a diagnostic framework, they lack clarity and proven accuracy. Recently, suggested minimum data required for the diagnosis of DILI were published (20) (**Table 4**).

Table 3. Variables that may predispose individuals to idiosyncratic DILI

Host factors	Environmental factors	Drug-related factors
Age	Smoking	Daily dose
Gender	Alcohol consumption	Metabolic profile
Pregnancy	Infection and inflammatory episodes	Class effect and cross-sensitization
Malnutrition		Drug interactions and polypharmacy
Obesity		
Diabetes mellitus		
Co-morbidities including underlying liver disease		
Indications for therapy		

DILI, drug-induced liver injury.

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 the 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, statins; **Table 5**). History taking is greatly enhanced by knowledge of the most common and most rarely implicated DILI agents. Overall, antibiotics and antiepileptics are most commonly reported accounting for >60% of DILI overall, whereas antihypertensive and diabetic medications are less common (2,4–6,16). There are increasing reports of DILI due to HDS, and thus close questioning regarding HDS consumption is crucial (2,3,21). **Table 5** lists the most notorious and 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 5**).

Harnessing knowledge of rare or newly reported cases of DILI is more daunting. The Food and Drug Administration (FDA) approved an average of 90 drugs per year from 2007 to 2011 (22). Published case reports of DILI are spread across general medical, subspecialty, toxicology, pharmacology, and gastroenterology journals, and they are of varying quality (20). Recently, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Library of Medicine launched *LiverTox* (http://www.livertox.nih.gov/), a free and helpful online DILI resource consisting of detailed information on more than 600 agents, and it is updated periodically (23).

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/upper limit of normal (ULN) divided by serum alkaline phosphatase/ULN. By common convention,

Table 4. Recommended minimal elements of a diagnostic evaluation in the work-up of suspected DILI

Element	Comments
Gender	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, 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 done
History of other drug reactions	Certain cross-reactivities may exist (e.g., anti-epileptics)
History of other liver disorders	Chronic viral hepatitis, NAFLD, hemochromatosis, alcoholic liver disease, PSC, PBC, 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, rash)
Physical findings	Fever, rash, hepatomegaly, hepatic tenderness, 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 months
Laboratory results	Day of first abnormal liver biochemistry; liver biochemistries, eosinophil counts at presentation
Viral hepatitis serologies	Anti-HAV IgM, HBsAg, anti-HBc IgM, anti-HCV, HCV RNA
Auto-immune hepatitis serologies	ANA, anti-smooth muscle antibody, IgG level
Imaging	US±Doppler, CT, or MRI±MRCP
Histology, if available	Timing of biopsy in relation to enzyme elevation and onset
Washout (de-challenge) data	Follow-up liver biochemistries
Clinical outcome	Resolution, transplant, death, and timing of each

ANA, anti-nuclear antibody; CT, computerized tomography; DILI, drug-induced liver injury; HAV, hepatitis A virus; HBc, hepatitis B core antigen; HBs, hepatitis B surface antigen; HCV, hepatitis C virus; HDS, herbal or dietary supplement; HEV, hepatitis E virus; NAFLD, nonalcoholic fatty liver disease; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis; Ig, immunoglobulin; MRI, magnetic resonance imaging; MRCP, magnetic resonance cholangiopancreatography; US, ultrasound.
Modified from Agarwal VK *et al.* (4).

$R \geq 5$ 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, autoimmune hepatitis, ischemic liver injury, acute Budd–Chiari syndrome, and Wilson's disease.

Acute hepatitis C and acute hepatitis E infections are known masqueraders of DILI. The diagnosis of acute hepatitis C can be challenging because anti-hepatitis C virus (HCV) antibodies may be negative initially. In the initial report of the DILIN Prospective Study, acute hepatitis C infection masqueraded as DILI in 1.3% of cases, leading to the recommendation that acute hepatitis C infection should be excluded in patients with suspected DILI by HCV RNA testing (16). Another published report from the DILIN showed that 3% of individuals with suspected DILI tested positive for anti-hepatitis E virus 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 (24). Although the diagnosis of acute hepatitis E can be made most readily by testing for IgM anti-hepatitis E virus antibodies, the reliability of currently available tests is not high (25). The use of this test 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 biochemistries, although patients with such acute infections often have characteristic accompanying systemic manifestations such as lymphadenopathy, rash, and atypical lymphocytes.

Autoimmune hepatitis should be considered in the differential diagnosis of all cases of DILI, and, in fact, it is well known that

Table 5. Most common or well-described DILI agents and the patterns of their liver injury

Antibiotics	Latency[a]	Typical pattern of injury/identifying features
Amoxicillin/clavulanate	Short to moderate	Cholestatic injury, but can be hepatocellular; DILI 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, eosinophilia)
Fluoroquinolones	Short	Variable: hepatocellular, cholestatic, or mixed in relatively similar proportions
Macrolides	Short	Hepatocellular, but can be cholestatic
Nitrofurantoin		
Acute form (rare)	Short	Hepatocellular
Chronic form	Moderate to long (months–years)	Typically hepatocellular; often resembles idiopathic autoimmune hepatitis
Minocycline	Moderate to long	Hepatocellular and often resembles autoimmune hepatitis
Anti-epileptics		
Phenytoin	Short to moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (e.g., fever, rash, eosinophilia) (anti-convulsant hypersensitivity syndrome)
Carbamazepine	Moderate	Hepatocellular, mixed, or cholestatic often with immune-allergic features (anti-convulsant hypersensitivity syndrome)
Lamotrigine	Moderate	Hepatocellular often with immune-allergic features (anti-convulsant hypersensitivity syndrome)
Valproate		
Hyperammonemia	Moderate to long	Elevated blood ammonia, encephalopathy
Hepatocellular	Moderate to long	Hepatocellular
Reye-like syndrome	Moderate	Hepatocellular, acidosis; microvesicular steatosis on biopsy
Analgesics		
Non-steroidal anti-inflammatory agents	Moderate to long	Hepatocellular injury
Immune modulators		
Interferon-β	Moderate to long	Hepatocellular
Interferon-α	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, nodular regenerative hyperplasia)
Herbals and dietary supplements		
Green tea extract (catechin)	Short to moderate	Hepatocellular
Anabolic steroids	Moderate to long	Cholestatic; likely contained as adulterants in performance-enhancing products
Pyrrolizidne alkaloids	Moderate to long	Sinusoidal obstruction syndrome/veno-occlusive disease; contained in some teas
Flavocoxib	Short to moderate	Mixed hepatocellular and cholestatic
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
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

DILI, drug-induced liver injury; TNF, tumor necrosis factor.
[a]Short=3–30 days; moderate=30–90 days; long >90 days.

some medications have high propensity to cause autoimmune-like DILI (e.g., minocycline, nitrofurantoin). Serum autoantibodies (antinuclear antibody and anti-smooth muscle antibody) and immunoglobulin Ig G 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 (26).

Although rare, one should screen for Wilson's disease with a serum ceruloplasmin level particularly in patients younger than 40 years. 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-h urine collection for copper, slit-lamp eye examination for Kayser–Fleischer rings, serum copper levels, and genetic testing of the *ABC B7* gene are indicated as outlined in diagnostic guidelines for diagnosing Wilson's disease (27). Budd–Chiari syndrome may sometimes mimic DILI, and thus it should be considered, especially if tender hepatomegaly and/or ascites are evident.

Competing etiologies in individuals with suspected cholestatic DILI are pancreatico-biliary 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, computerized 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 (anti-mitochondrial antibody for primary biliary cirrhosis), or imaging (infiltrating disorders 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 with certainty.

Diagnostic evaluation: liver biopsy. Liver biopsy is not mandatory in the evaluation of DILI. Of the DILIN registry's first 300 cases, <50% had a liver biopsy (14). The DILIN cases have more severe injury owing 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 recent report from the DILIN Prospective Study provides extensive characterization of biopsies from a large cohort of patients with well-defined DILI (28). Other descriptions are also available (2,4,29). 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" DILI injury.

There are instances where biopsy can be strongly recommended such as to help discern between autoimmune hepatitis and DILI. Current diagnostic algorithms for autoimmune hepatitis (AIH) include histology (24). AIH is typically responsive to immunosuppressive therapy, but commitment to therapy is often long term and has risks and side effects (30,31). 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 appear to trigger the development of autoimmune hepatitis. 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.

In general, persistence of biochemical abnormalities lowers the threshold for liver biopsy. The majority of DILI cases show steady decline in liver biochemistries after the presumed culprit agent is stopped. This observation is often referred to as "washout" or "de-challenge" and is a major factor in DILI diagnostic scoring algorithms (17–19). Persistence of elevations weakens the case for DILI, thereby strengthening the possibility of other diagnoses such as primary sclerosing cholangitis, autoimmune hepatitis, primary biliary cirrhosis, cancer, or granulomatous hepatitis. Typically, cholestatic DILI takes longer to resolve than the hepatocellular DILI. The decision on how long to wait on a biopsy must be made on a case-by-case basis. Some experts consider lack of the 50% decline in the peak alanine aminotransferase value 30 days after stopping the suspected agent as reducing the likelihood of a DILI diagnosis (17,18). Others consider the cutoff time for a significant decrease in alanine aminotransferase at 60 days (19). For cholestatic injury, lack of significant drop in alkaline phosphatase or bilirubin (>50% drop in peak-ULN or drop to less than twice ULN) at 180 days is considered significant. There are no prospective studies examining the 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 biopsy is certainly justified, if there is continued rise in liver biochemistries particularly when any signs of liver failure develop. Conversely, if 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, 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 biopsy for patients receiving chronic methotrexate have been published (32,33). The clinical need for other medications (e.g., isoniazid, 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 (34). 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 (28,35).

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

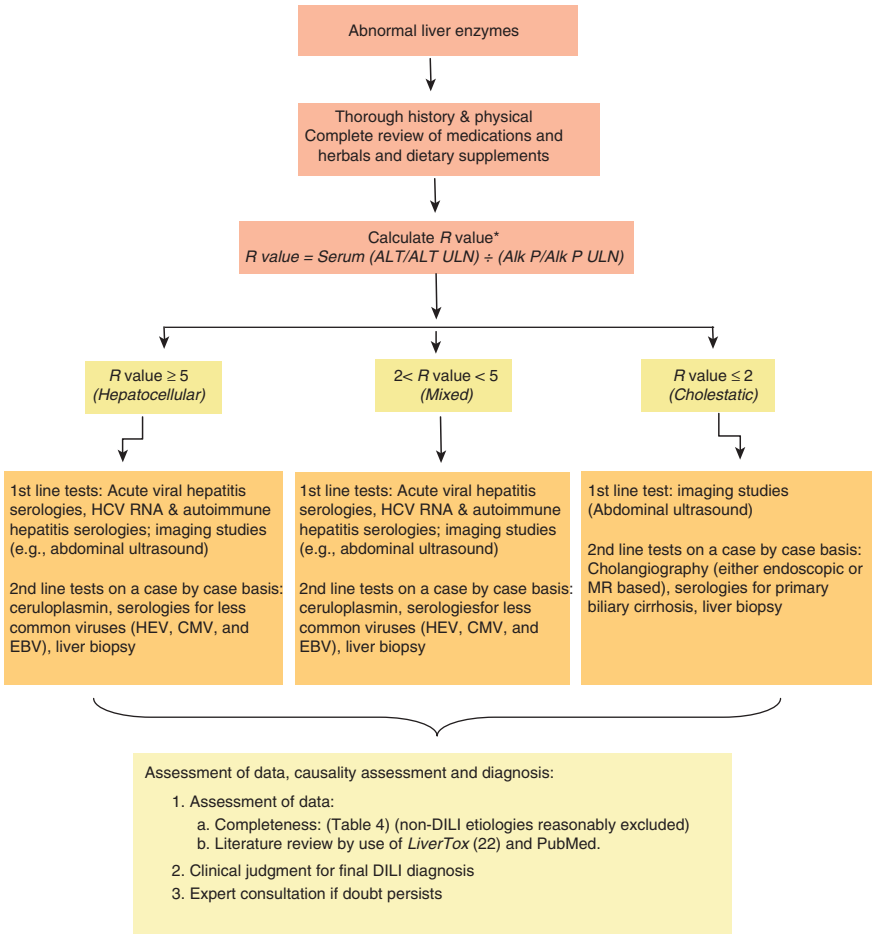

Figure 1. An algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI). The *R*-value cutoff numbers of 2 and 5 serve only as a guideline. Which tests and their order must be based on the overall clinical picture including risk factors for competing diagnosis (e.g., recent travel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

Summary statements

- Accurate clinical history related to medication exposure and the onset of liver test abnormalities should be obtained when DILI is suspected.
- DILI is a diagnosis of exclusion, and thus appropriate competing etiologies should be excluded in a systematic manner.
- On the basis of 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.
- Liver biopsy can help confirm 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 autoimmune hepatitis should be excluded with standard serologies and HCV RNA testing (Strong recommendation, very low level evidence).
   (b) Routine anti-hepatitis E virus IgM testing cannot be recommended owing to unclear performance characteristics of the currently available commercial tests. However, it should be considered in the setting of heightened clinical suspicion (e.g., recent travel in an endemic area) (Conditional recommendation, very low level of evidence).
   (c) Testing for acute cytomegalovirus, acute Epstein–Barr virus, or acute herpes simplex virus infection should 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 level of evidence).
   (d) Wilson's disease and Budd-Chiari syndrome should be considered when clinically appropriate (Strong recommendation, low level of evidence).

(2) In individuals with suspected cholestatic DILI:
   (a) Abdominal imaging (ultrasound or computerized tomography scan) should be performed in all instances to exclude biliary tract pathology and infiltrative processes (Strong recommendation, low level of evidence).
   (b) Serological testing for primary biliary cirrhosis should be limited to those with no evidence of obvious biliary tract pathology on abdominal imaging (Strong recommendation, low level of evidence).
   (c) Endoscopic retrograde cholangiography should be limited to instances where routine imaging is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis, or pancreatico-biliary malignancy (Strong recommendation, very low level of evidence).
(3) When to consider a liver biopsy?
   (a) A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated (Strong recommendation, low level of evidence).
   (b) A liver biopsy may be considered in the following situations:
      (i) If there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent (Strong recommendation, very low level of evidence),
      (ii) If the peak alanine aminotransferase level has not decreased by >50% at 30–60 days after the onset in cases of hepatocellular DILI, or if the peak alkaline phosphatase has not fallen by >50% at 180 days in cases of cholestatic DILI despite stopping the suspected offending agent (Conditional recommendation, very low level of evidence),
      (iii) In cases of DILI where continued use or re-exposure to the implicated agent is expected (Strong recommendation, very low level of evidence),
      (iv) If liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases (CLDs) and chronic DILI (Conditional recommendation, very low level of evidence).

Causality assessment. The RUCAM (17,18) and Maria and Victorino system (19) are two instruments to facilitate the causality attribution for suspected DILI. Although both of these instruments perform reasonably well in comparison with the "gold standard" of expert consensus opinion, the RUCAM seems to be used more widely by some clinicians, the pharmaceutical industry, and the regulatory agencies (**Table 6**). It was intended for use at the bedside or in clinic (17). It yields a summed score from −9 to +10, higher scores indicating higher likelihood of DILI. Scores are often 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 versus 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 6**). 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) (36). Furthermore, a recent study showed that the concordance between RUCAM and the DILIN causality scoring system, which is based on expert consensus opinion, is modest ($r = 0.42$, $P < 0.05$) (37). 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 upon which the clinician can organize history taking and tests. It reminds the clinician of the important areas of a DILI history (**Table 6**) and requires precision in recording exposure times and latency (17,18,37).

Summary statements

- RUCAM should not be used as the sole diagnostic tool in isolation owing to its suboptimal retest reliability and lack of robust validation, but it is useful in providing a diagnostic framework upon which to guide an evaluation in patients with suspected DILI.
- Consensus expert opinion following 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.
- If uncertainty persists following through 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

Most reactions to prescription drugs or HDS are considered idiosyncratic, that is, they are unpredictable, vary greatly in severity, and occur at varying time intervals after exposure (anywhere from a few days to 1 year) (2,4,5). Classically in idiosyncratic DILI, toxicity is considered to be unrelated to dose, route, or duration of drug administration (although a review of drugs withdrawn from the market in the United States recently found that most were prescribed at daily doses exceeding 50 mg per day) (9,38). Liver-related deaths due to acute liver failure (ALF) following DILI occur in only a fraction of cases and usually occur within 6 months. The ten-percent rule was initially promulgated by Dr Hyman Zimmerman in 1978 (5), and more recently codified as "Hy's Law" (12), which states that if hepatocellular injury causes jaundice in a patient during a phase 3 trial then for every 10 jaundiced patients 1 will develop ALF. Among the first 300 patients enrolled in DILIN, the National Institutes of Health-supported DILIN, 33% were hospitalized, 15% were considered severe, and 6% died or underwent transplantation (16). Thus, only a small fraction of the overall group experienced ALF. Where hepatocellular injury was present, there were 9% fatalities or transplants. Thus, the spectrum of types and severity of liver injury due to DILI overall is broad. Expectation for recovery from the average

Table 6. RUCAM causality assessment method

Criteria	RUCAM					
Enzyme pattern	Hepatocellular			Cholestatic or mixed		
Exposure	Initial exposure	Subsequent exposure	Patients	Initial exposure	Subsequent exposure	Patients
Timing from						
Drug start	5–90 d	1–15 d	+2	5–90 d	1–90d	+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 AP (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 info.		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 (years)	≥50		+1	≥50		+1
	<50		0	<50		0
Other drugs	None or no info.		0	None or no info.		0
	Drug with suggestive timing		−1	Drug with suggestive timing		−1
	Known hepatotoxin w/suggestive timing		−2	Known hepatotoxin w/suggestive timing		−2
	Drug with other evidence for a role (e.g., + rechallenge)		−3	Drug with other evidence for a role (e.g., + rechallenge)		−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
	Non-drug cause highly probable		−3	Non-drug cause 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 done or not interpretable		0	Not done or not interpretable		0

ALT, alanine aminotransferase; AP, alkaline phosphatase; AST, aspartate aminotransferase; d, day; RUCAM, Roussel Uclaf Causality Assessment Method; ULN, upper limit of normal.

[a]Group I: HAV, HBV, HCV (acute), biliary obstruction, alcoholism, recent hypotension (shock liver).

[b]Group II: CMV, EBV, herpes virus infection.

instance of DILI is the rule as, even among jaundiced patients, 90% recover. In addition, those with cholestatic injury generally fare better than those experiencing a hepatocellular injury.

In most instances, the common hepatocellular DILI phenotype leading to ALF evolves more slowly than that due to APAP. If ALF (coagulopathy and any degree of encephalopathy) develops (39), spontaneous recovery is relatively limited, although the slower evolution of disease (median 2 weeks from onset of jaundice to onset of coma) may allow listing for transplantation and for a suitable donor liver to be identified more frequently than in cases evolving to death or transplant in <1 week. Transplant-free survival for ALF due to DILI was 23%, with 40% undergoing liver transplantation, giving an overall survival of only 58% (39 and unpublished data). By comparison, for ALF due to APAP, short-term results for 916 individuals admitted with ALF included 63% transplant-free survival, 9% undergoing liver transplantation, giving a 70% overall short-term survival (unpublished data). Despite its apparent greater initial severity, APAP ALF may have more rapid hepatocyte regeneration and greater likelihood of resolution of the hepatic damage due to the self-limited duration of injury.

Clinical recognition of ALF due to DILI is little different from that of ALF due to APAP overdose, except for the slower speed of disease evolution. Patients with ALF due to DILI are more likely to develop ascites, infection, and renal insufficiency as preterminal complications. Causes of death in the absence of transplantation are mainly due to systemic infection and/or cerebral edema (40,41).

Few prognostic scores have focused on overall DILI because of its relative rarity and its overall favorable prognosis, with improvement assumed to follow once the offending drug is recognized and withdrawn.

Liver transplantation provides a rescue for patients when signs of spontaneous recovery are not evident. For each patient, a careful assessment of need and appropriateness precedes listing. A prognostic score for ALF due to DILI (or for that matter any form of ALF) has long been considered a vital but elusive goal. In the UNOS database for an 11-year period, 7% received a graft for idiosyncratic DILI, and the relative rarity of bad outcomes once again limits understanding of the condition (10).

When outcomes for a group of DILI patients were reviewed, the Model for End-Stage Liver Disease (MELD) score and coma grade upon admission were the strongest predictors of liver transplantation (39). Because most ALF patients would have received a listing as Status 1, the highest priority, it is not clear whether MELD is relevant here, as it is not used in the Status 1 patients. To date, other prognostic scoring systems have not proven to be useful for the overall condition of ALF. Although Kings College Hospital criteria are used by some centers, the use of these criteria yields reasonable specificity but low sensitivity, frequently below 50%, indicating that if criteria are met the patient will die or require transplantation, but if criteria are not met a large percentage still die or require orthotopic liver transplantation (11). Other more global scores that reflect intensive care unit survival have proven to be of little additional value. A study comparing Sequential Organ Failure Assessment, MELD, Acute Physiologic and Chronic Health Assessment II, and King's College Hospital criteria found that Sequential Organ Failure Assessment performed best, but this was limited to APAP patients (42) and may not be as applicable to other etiologies such as idiosyncratic DILI. Studies combining apoptotic markers such as M-30 or M-65 antigens plus clinical markers seem more robust but are not readily available to clinicians (43,44).

Summary statements

- In general, outcomes of idiosyncratic DILI are good, with only ~10% reaching the threshold of ALF (coagulopathy and encephalopathy).
- DILI that does evolve to 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 bad outcomes.
- Prognostic scores to predict outcome for DILI reaching the threshold of ALF are poor or rudimentary.

Rechallenge

Re-administration of a suspected hepatotoxic drug is best avoided. In some instances, rechallenge occurs because of failure to recognize the prior toxic reaction. Alternatively, in some instances where the causal relationship is uncertain or the prior 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 initially experienced, and a more severe and possibly fatal reaction, 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 done intentionally recognizing the risks, it is generally discouraged in all but the most life-threatening situations where a suitable alternative is unavailable (45,46). Clinicians who have recognized a toxic reaction should be careful to educate the patient with the name of the suspect drug and the reminder (Medic Alert bracelets and cards encouraged) that re-exposure may have even more deleterious effects.

Recommendation

- Re-exposure to a drug that is thought likely to have caused hepatotoxicity is strongly discouraged, especially if the initial liver injury was associated with significant aminotransferase elevation (for example, >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 level of evidence).

Treatment

The hallmark of treatment of DILI is withdrawal of the offending medication. It is said (and it seems 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 the DILIN prospective study were given ursodeoxycholic acid, but the efficacy of this agent in acute and chronic DILI is not established (16).

Corticosteroid therapy has been proposed as treatment for DILI in the ALF setting, but little evidence advanced to support it, and, unlike alcoholic hepatitis or AIH, no controlled trials of steroid therapy for DILI have been performed. *N*-Acetylcysteine, the proven antidote for APAP overdoses (intrinsic DILI), was subjected to a randomized placebo-controlled trial for non-APAP ALF that included DILI as one subgroup (47). 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 N-acetyl cysteine (NAC) vs. 30% with placebo (44). All ALF trials in the modern era are compromised by transplantation that "rescues" ~40% of those with non-APAP ALF so that their true natural histories will never be known (48). Overall survival is improved owing to the use of liver grafting (as it should be). For those with etiology as DILI 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 (49). To date, FDA has not approved NAC for the indication of non-APAP ALF.

Recommendations

1. In individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction, the suspected agent(s) should be promptly stopped (Strong recommendation, low level of evidence).
2. No definitive therapies are available either for idiosyncratic DILI with or without ALF: however, NAC may be considered in adults with early-stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients (Conditional recommendation, low level of evidence).
3. NAC is not recommended for children with severe DILI leading to ALF (Strong recommendation, low level of evidence).

Follow-up

Patients with any acute hepatic illness should be followed up to its resolution where possible. In the case of DILI, recent data suggest that chronicity occurs in approximately 13.6% of those experiencing DILI, with little difference between hepatocellular and mixed or cholestatic liver injury (16). Subjects who presented with cholestatic DILI were more likely to develop chronic DILI compared with those with acute hepatocellular liver injury (50). Chronic DILI may resemble autoimmune hepatitis and might respond to corticosteroids, provided that 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.

Summary statements

- Chronic DILI occurs in about 15–20% of cases of acute DILI.
- Patients experiencing DILI because of prescription medications or dietary supplements or herbal products should be followed up clinically and biochemically to complete resolution.
- DILI patients with severe acute cholestatic liver injury appear to be at an increased risk of developing chronic liver injury and require careful long-term follow-up.

HDS INDUCED LIVER INJURY

Epidemiology

HDS hepatotoxicity has received increasing attention over the past few years, in part owing to the recognition in the United States that among DILI cases HDS are the second most common cause (16). 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 2012. In addition, supplements used for body building and weight loss are the most common types of HDS implicated in disease (21).

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 prior approval by the FDA (51). Under the 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 (52). 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 recent case series, the medical food flavocoxid caused a mixed hepatocellular/cholestatic pattern, with some patients experiencing severe injury (53).

The Dietary Supplement Health Education and Safety Act of 1994 (51) and the subsequent "Final Rule for Dietary Supplement Current Good Manufacturing Practices" of 2007 (54) 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 (https://www.accessdata.fda.gov/scripts/medwatch/). Supplement manufacturers are required to report adverse events associated with their products. However, the voluntary nature of reporting probably leads to underreporting (55). 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 event.

In 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 variability depending upon the location or conditions of growth, as well as their methods of manufacture. These factors can lead to variability in the ingredients or their concentrations over time and from batch to batch (56–59). In addition, products may contain ingredients that are not identified on the label, as contaminants or adulterants. These unlabeled ingredients often take the form of powerful prescription pharmaceuticals in keeping with a product's intended effect, such as to enhance sexual performance (60). Other unlabeled ingredients, more accurately regarded as contaminants, include microbials or heavy metals (61–64). Finally, even when a connection can be drawn between an injury event and a product, it is not uncommon for products to contain myriad ingredients. Although some ingredients can be considered more likely to be injurious based on published experience, a categorical statement impugning any one ingredient cannot be made as 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; as 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.

Summary statements

- 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.
- The current regulation for HDS differs substantially from conventional prescription medications. Most importantly, there is no requirement for premarketing safety analyses of HDS.
- 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.
- 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, as all information is taken into consideration in assigning a likelihood of injury.
- Voluntary reporting of suspected HDS hepatotoxicity cases through the FDA MEDWATCH system is essential.

Clinical presentation and diagnosis

Diagnosis of HDS hepatotoxicity is made with the same clinical approach as for conventional drugs, where an accurate diagnosis hinges upon 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 (65). An important consideration in making the diagnosis of HDS hepatotoxicity (as for DILI) is the possibility that latency may be quite prolonged.

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. Among these are body-building products, shown in some instances to contain anabolic steroids. These products have been associated with an initial cholestatic hepatitis followed by prolonged jaundice (66–68). Pyrrolizidine alkaloids typically have been associated with sinusoidal obstruction syndrome (69–74). More recently, flavocoxid, a medical food, has been associated with severe liver injury (53). Such careful observations exemplify a necessary approach to better define clinical patterns of injury common to certain products; these observations will facilitate diagnosis. With the notable exception of HDS marketed for body-building, most HDS cause hepatocellular-type liver injury ($R > 5$).

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 should be observed closely, as herbal products may cause an unpredictable course of injury.

Recommendations

1. Patients should be encouraged to report the 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 level of evidence).
2. The same diagnostic approach for DILI is applicable 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 level of evidence).
3. Patients with suspected HDS hepatotoxicity should stop all HDS hepatotoxicity and be monitored for resolution of their liver injury (Strong recommendation, low level of evidence).

DILI in patients with CLD

The most common causes of CLD in the general US population are nonalcoholic fatty liver disease (NAFLD; 20%), alcoholic liver disease (5%), chronic HCV (1–5%), and chronic HBV (0.5–1%) (75). 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 (76). In support of this, the DILIN Prospective Study has demonstrated that at least 6% of enrolled patients had pre-existing CLD (16). However, DILI accounts for $<1\%$ of consecutive inpatients or outpatients presenting with clinically apparent acute liver injury (77,78). 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 following de-challenge, as well as prior published reports, can help raise the index of suspicion of DILI. However, the lack of an objective and confirmatory laboratory test makes it difficult to confidently establish a diagnosis of DILI. Therefore, DILI is largely a diagnosis of exclusion that requires one to consider more common causes of acute liver injury such as viral hepatitis, pancreatico-biliary disease, alcohol, and ischemia depending on the clinical setting (20,79). To further complicate matters, some forms of CLD can present with an icteric flare (e.g., alcoholic hepatitis, autoimmune hepatitis, 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 two- to fivefold (80,81). Interested readers are alerted to an excellent recent review by Lewis and Stine, which offers a practical guide for prescribing medications in patients with cirrhosis (82).

Although one may hypothesize that CLD patients may be more susceptible to DILI via reduced drug clearance, aberrant metabolism, altered excretion, or impaired adaptive responses, there is currently limited data to support the increased susceptibility of CLD patients to DILI. Overall, patients with obesity and NAFLD do not appear to be at an increased risk of developing DILI, with the possible exception of methotrexate- and tamoxifen-induced chronic liver injury (83–88). Despite the widespread 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 for DILI (83–85). Furthermore, evolving data suggest that individuals with NAFLD or hepatitis C may actually benefit from statins (89,90). Antiretroviral hepatotoxicity appears to be more common in HIV patients with HCV or HBV co-infection (91). However, the greater use of tenofovir-containing regimens and less frequent use of other agents associated with acute hepatic injury (i.e., dideoxynucleotides, abacavir, nevirapine) may be leading to a decline in the incidence of severe acute DILI due to HIV-related medications (92). Nonetheless, it remains difficult to reliably distinguish a DILI episode from that of immune reconstitution in an HIV-HBV co-infected individual who presents with acute hepatitis (92). Patients with chronic HBV, HCV, and HIV may also be at an increased risk of isoniazid hepatotoxicity, but it can again be difficult to distinguish a spontaneous disease flare from a bona-fide DILI episode (93,94) Obtaining liver histology may be of benefit in diagnosing DILI in liver transplant recipients, but additional data are needed to confirm these observations (95). Nonetheless, it remains difficult to reliably distinguish a DILI episode from that of immune reconstitution in an HIV-HBV co-infected individual who presents with acute hepatitis (95). Patients with chronic HBV, HCV, and HIV may also be at increased risk of isoniazid hepatotoxicity, but it can again be difficult to distinguish a spontaneous disease flare from a bona-fide DILI episode (96,97). Obtaining liver histology may be of benefit in diagnosing DILI in liver transplant recipients, but additional data are needed to confirm these observations (98).

Outcomes of DILI in patients with CLD

It is reasonable to hypothesize that CLD patients would be more likely to develop severe or slower to resolve DILI owing to impaired liver regeneration, as has been noted with acute hepatitis A and B infection in patients with chronic HCV (99). In support of this, 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 appears to be more severe in patients with viral hepatitis (92,93). However, most studies have been plagued by the small number of patients enrolled and less than satisfactory causality assessment methods used. DILIN and other groups are prospectively studying the risk factors and outcomes in patients with viral hepatitis and NAFLD who present with DILI to provide more reliable information on this important topic (16).

Summary statement

1. There are no data to show that underlying CLD is a major risk factor for all-cause DILI, but it may increase the risk for

Summary and strength of recommendations
1. *In individuals with suspected hepatocellular or mixed DILI:*
(a) *Acute viral hepatitis (A, B, and C) and auto-immune hepatitis should be excluded with standard serologies and HCV RNA testing (Strong recommendation, very low level evidence).*
(b) *Anti-HEV IgM testing cannot be recommended because of unclear performance characteristics of the currently available commercial tests. However, it should be considered in the setting of heightened clinical suspicion (e.g., recent travel in an endemic area), (Conditional recommendation, very low level of evidence).*
(c) *Testing for acute CMV, acute EBV, or acute HSV infection should be undertaken if classical viral hepatitis has been excluded or clinical features such as atypical lymphocytosis, lymphadenopathy suggest such causes (Strong recommendation, very low level of evidence).*
(d) Wilson's disease and Budd-Chiari syndrome should be considered when clinically appropriate (Strong recommendation, low level of evidence).
2. *In individuals with suspected cholestatic DILI:*
(a) *Abdominal imaging (ultrasound or CT scan) should be performed in all instances to exclude biliary tract pathology and infiltrative processes (Strong recommendation, low level of evidence).*
(b) *Serological testing for primary biliary cirrhosis should be limited to those with no evidence of obvious biliary tract pathology on abdominal imaging (Strong recommendation, low level of evidence).*
(c) *Endoscopic retrograde cholangiography should be limited to instances where routine imaging is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis, or pancreatico-biliary malignancy (Strong recommendation, very low level of evidence).*
3. *When to consider a liver biopsy?*
(a) *A liver biopsy should be considered if autoimmune hepatitis remains a competing etiology and if immunosuppressive therapy is contemplated (Strong recommendation, low level of evidence).*
(b) *A liver biopsy may be considered:*
(i) *If there is unrelenting rise in liver biochemistries or signs of worsening liver function despite stopping the suspected offending agent (Strong recommendation, very low level of evidence).*
(ii) *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 level of evidence).*
(iii) *In cases of DILI where continued use or re-exposure to the implicated agent is expected (Strong recommendation, very low level of evidence).*
(iv) *If liver biochemistry abnormalities persist beyond 180 days to evaluate for the presence of chronic liver diseases and chronic DILI (Conditional recommendation, very low level of evidence).*
4. *Re-exposure to a drug thought likely to have caused hepatotoxicity is strongly discouraged, 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 level of evidence).*
5. *In individuals with suspected DILI, especially when liver biochemistries are rising rapidly or there is evidence of liver dysfunction, suspected agent(s) should be promptly stopped (Strong recommendation, low level of evidence).*
6. *No definitive therapies are available either for idiosyncratic DILI with or without ALF: however, NAC may be considered in adults with early-stage ALF, given its good safety profile and some evidence for efficacy in early coma stage patients (Conditional recommendation, low level of evidence).*
7. *NAC is not recommended for children with severe DILI leading to ALF (Strong recommendation, low level of evidence).*
8. *Patients should be encouraged 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 level of evidence).*
9. *The same diagnostic approach for DILI is applicable 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 level of evidence).*
10. *Patients with suspected HDS-hepatotoxicity should stop all HDS-hepatotoxicity and be monitored for resolution of their liver injury (Strong recommendation, low level of evidence).*
11. *The diagnosis of DILI in patients with CLD requires a high index of suspicion and exclusion of other more common causes of acute liver injury including a flare-up of the underlying liver disease (Strong recommendation, low level of evidence).*
12. *The use of potentially hepatotoxic drugs in CLD patients should be based upon the risk vs. benefit of the proposed therapy on a case-by-case basis (Strong recommendation, low level of evidence).*
13. *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 yellowing of their eyes, 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 level of evidence).*

ALF, acute liver failure; ALT, alanine aminotransferase; Alk P, alkaline phosphatase; CMV, cytomegalovirus; CT, computerized tomography; DILI, drug-induced liver injury; EBV, Epstein–Barr virus; HCV, hepatitis C virus; HDS, herbal and dietary supplement; HEV, hepatitis E virus; HSV, herpes simplex virus; ULN, upper limit of normal.

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 an increased risk for hepatotoxicity from statins.

Recommendations

1. The diagnosis of DILI in patients with CLD requires a high index of suspicion and exclusion of other more common causes of acute liver injury, including a flare-up of the underlying liver disease (Strong recommendation, low level of evidence).
2. The use of potentially hepatotoxic drugs in CLD patients should be based upon the risk versus benefit of the proposed therapy on a case-by-case basis (Strong recommendation, low level of evidence).
3. 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, pruritis, or choluria. In addition, it is reasonable to monitor serum liver biochemistries at 4–6 week intervals, especially during the initial 6 months of treatment with a potentially hepatotoxic agent (Conditional recommendation, very low level of evidence).

CONFLICT OF INTEREST

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