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

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Abstract

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.

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 (2,3,4,5,6).

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

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 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 (9,10,11). 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.

| 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.	

GENETIC AND NONGENETIC RISK FACTORS

Summary Statements
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, gender, and alcohol consumption may increase the risk for DILI in a drug-specific manner.

DIAGNOSIS AND CAUSALITY ASSESSMENT IN DILI
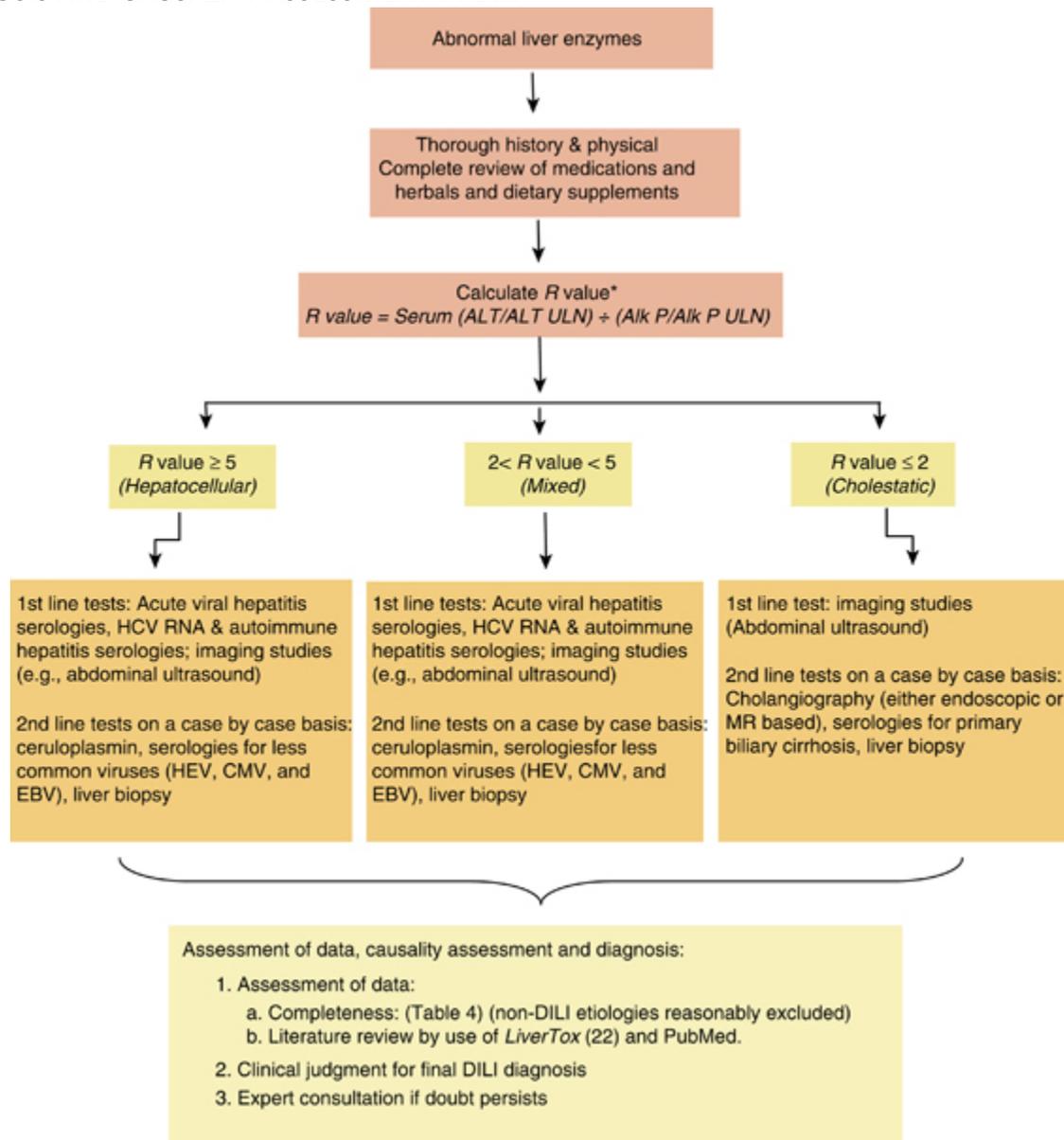
Figure 1. An algorithm to evaluate suspected idiosyncratic drug-induced liver injury (DILI). The *R*-value cutoff numbers of 2 and 5 serve only as a guideline. Which tests and their order must be based on the overall clinical picture including risk factors for competing diagnosis (e.g., recent travel 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
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 manner.
3. 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.
4. 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 off ending agent (Strong recommendation, very low level of evidence),

ii. If the peak alanine aminotransferase level has not decreased by > 50 % at 30 – 60 days aft er 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 off ending 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
Summary Statements
1. 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.
2. 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.
3. 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

Summary Statements
1. In general, outcomes of idiosyncratic DILI are good, with only ~10% reaching the threshold of ALF (coagulopathy and encephalopathy).
2. 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.
3. Prognostic scores to predict outcome for DILI reaching the threshold of ALF are poor or rudimentary.

RECHALLENGE

Recommendation
1. 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 signifi cant 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

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

Summary Statements
1. Chronic DILI occurs in about 15–20% of cases of acute DILI.
2. Patients experiencing DILI because of prescription medications or dietary supplements or herbal products should be followed up clinically and biochemically to complete resolution.
3. 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

Causality assessment
Summary Statements
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, as 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.

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

Summary Statements
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 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).