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ACG Guidelines for the diagnosis and management of DILI

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CME

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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Grading of Recommendations, Assessment, Development and Evaluation (GRADE)

<u>Strength of Recommendation</u>	<u>Criteria</u>
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
<u>Quality of Evidence</u>	<u>Criteria</u>
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



Recommendations

1. In individuals with suspected hepatocellular or mixed DILI:

- *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)*
- *Anti-HEV IgM testing cannot be recommended due 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)*
- *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)*
- *Wilson's disease and Budd-Chiari syndrome should be considered when clinically appropriate. (Strong recommendation, low level of evidence)*



Recommendations

2. *In individuals with suspected cholestatic DILI:*

- *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)*
- *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)*
- *Endoscopic retrograde cholangiography should be limited to instances where routine imaging is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis or pancreatobiliary malignancy. (Strong recommendation, very low level of evidence)*



Recommendations

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:

- *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)*
- *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)*
- *in cases of DILI where continued use or re-exposure to the implicated agent is expected. (Strong recommendation, very low level of evidence)*
- *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)*



Recommendations

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 (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)*
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)*



Recommendations

8. *Patients should be encouraged to report use of HDS to their healthcare 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)*



Recommendations

12. *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. Additionally, 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)*