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

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DILI Types

- **Intrinsic-** predictable, dose dependent injury (ie, acetaminophen/ APAP)
- **Idiosyncratic-** less common, only affects susceptible individuals, less consistent dose relationship, varied presentation
- **Chronic-** ongoing ↑LFTs or symptoms of liver disease 6-9 mo after DILI onset

Characterization

- Latency- Time from medication/ herbal/ supplement start to onset of DILI
- Pattern of Injury (R-Value)
- Mortality Risk (Hy's Law)
  - ~10% risk mortality if all 3 below
    1. ALT or AST >3x ULN
    2. T bili >2x ULN without initial cholestasis (↑ALP)
    3. No other reason found (ie viral hepatitis A, B, C, or preexisting/ acute liver disease)

R-Value

$$\text{R-Value} = \frac{(ALT/ALT_{ULN})}{(ALP/ALP_{ULN})}$$

- R >5 ⇒ Hepatocellular
- R 2-5 ⇒ Mixed
- R <2 ⇒ Cholestatic

Hepatocellular or Mixed DILI

- Exclude acute viral hepatitis (A, B, and C) and AIH with standard serologies & HCV RNA
- Recent travel to endemic area, atypical DILI, no obvious culprit ⇒ ✓ HEV IgM
- Atypical lymphocytosis & lymphadenopathy ⇒ ✓ CMV, EBV, & HSV
- Consider Wilson's and Budd-Chiari if appropriate

Cholestatic DILI

- Exclude biliary pathology & infiltrative process ⇒ US, CT, or MRI
- PBC testing *only* in those w/o obvious biliary pathology on imaging
- ERCP *only* if MRI or EUS unable to exclude impacted CBD stones, PSC, or pancreaticobiliary malignancy

Acute HCV & HEV are masqueraders of DILI!

Chalasani NP, Maddur H, Russo MW, Wong RJ, Reddy KR; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury. Am J Gastroenterol. 2021 May 1;116(5):878-898. doi: 10.14309/ajg.0000000000001259. PMID: 33929376.

Special Considerations

Herbal & Dietary Supplements (HDS)
- 20% hepatotoxicity cases in US!
- Anabolic steroids, green tea extract, multi-ingredient nutritional supplements

Immune-Checkpoint Inhibitors (ICI)
- Recognize HBV reactivation
- Tx: Withhold/ delay ICI + give immunosuppressants (steroids ⇒ MMF)

Chronic Liver Disease
- HBV or HCV ⇒ ↑risk injury w/ INH & ARVs
- ⊘ ↑risk statin hepatotoxicity in fatty liver
- Decompensated HCV cirrhosis ⇒ avoid protease inhibitors
- PSC w/ CTP B or C ⇒ ⊘ high doses OCA

Children
- AIH-like ⇒ r/o minocycline use

Causality Assessment

Diagnostic framework- not as a sole diagnostic tool
- Roussel Uclaf Causality Assessment Method (RUCAM)
- Maria and Victorino System (Clinical Diagnostic Scale, CDS)
- Digestive-Disease-Week Japan 2004 scale (DDW-J)

When Do I Get a Liver Biopsy?

- AIH still on differential
- Potential immunosuppressive tx
- ⇑ LFTs or worsening liver function
- Peak ALT ⊘ ↓ by >50% 30-60 d after onset hepatocellular DILI
- Peak ALP ⊘ ↓ by >50% 180 d after onset cholestatic DILI
- Continued use or re-exposure to agent contemplated
- Liver biochem abnormalities > 180d, esp if symptoms (ie, itching) or signs (eg, jaundice & hepatomegaly) ⇒ eval for chronic liver disease & chronic DILI

Rechallenge

- ⊘ ⇒ especially if LFTs > 5x ULN, Hy's law, or jaundice
- Exception= life threatening situation w/o suitable alternative

Prognosis

- 10% ⇒ ALF (of these, 40% require OLT & 42% mortality)
- <20% ⇒ chronic liver injury
- Cholestatic DILI 2x likely to develop chronic liver injury
- Hepatocellular injury more likely fatal or result in OLT (though rare)
- Prognostic modeling w/ MELD, Charlson comorbidity index, & albumin predicts 6 mo mortality http://gihep.com/calculators/hepatology/dili-cam/

Treatment

- 🛑 suspected agent
- ✓ NAC in adults w/ early stage ALF
- ⊘ NAC for children with severe DILI leading to ALF
- ? steroids for AIH-like features

Abnormal Liver Enzymes

Thorough history & physical w/ complete review of medications, herbals, & dietary supplements

Calculate R-value
R- value= (ALT/ ALT_{ULN}) ÷ (ALP/ ALP_{ULN})

- +: Short (3- 30 days)
- ++: Moderate (30- 90 days)
- +++: Long (>90 days)
- C: Cholestatic
- H: Hepatocellular
- M: Mixed
- V: Variable

R-value > 5 (Hepatocellular)

2 < R-value < 5 (Mixed)

R-value ≤ 2 (Cholestatic)

1st line tests: Acute viral hepatitis, HCV RNA, autoimmune hepatitis serologies, imaging studies (e.g., abdominal ultrasound)
2nd line tests on case-by-case basis: Ceruloplasmin, serologies for less common viruses (HEV, CMV, EBV), liver biopsy

1st line test: imaging studies (e.g., abdominal ultrasound)
2nd line tests on case-by-case basis: Cholangiography (ERCP or MRCP), serologies for PBC, liver biopsy

Assessment of data, causality assessment, and diagnosis

1. Assessment of data
   a. Completeness- Non-DILI etiologies reasonably excluded
   b. Literature review by use of *LiverTox* and PubMed
2. Clinical judgement for final DILI diagnosis
3. Expert consultation if doubt persists

Drug	Latency	Common Pattern
Amoxicillin/ Clavulanate	+ to ++	C > H
Isoniazid	++ to +++	H (like acute viral hep)
Trimethoprim/ sulfamethoxazole	+ to ++	C > H (immune- allergic features)
Fluoroquinolones	+	V
Macrolides	+	H > C
Nitrofurantoin- Acute (Rare)	+	H (like AIH)
Nitrofurantoin- Chronic	++ to +++	H
Minocycline	++ to +++	H (like AIH)
Phenytoin	+ to ++	V with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Carbamazepine	++	V with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Lamotrigine	++	H with immune-allergic features (anticonvulsant hypersensitivity syndrome)
Valproate	++ to +++	H
NSAIDS	++ to +++	H
Interferon β, anti-TNF	++ to +++	H
Interferon α	++	H (AIH-like)
Azathioprine	++ to +++	V, can present like VOD and NRH
Immune-Checkpoint Inhibitors (Ipilimumab, nivolumab, pembrolizumab, cemiplimab, atezolizumab, avelumab, durvalumab)	<12 wks	M ⇒ H
Methotrexate	+++	Fatty liver, fibrosis
Allopurinol	+ to ++	H or M, granulomas on bx
Amiodarone	++ to +++	V, macrovesicular steatosis & steatohepatitis on bx
Androgen-containing steroids	++ to +++	C; peliosis hepatitis, NRH, HCC
Inhaled anesthetics	+	H
Sulfasalazine	+ to ++	V (immune-allergic features)
PPI	+	H