Drug-Induced Liver Injury
ACG Clinical Guidelines

Characterization

- Diagnosis of exclusion based on detailed history, laboratory testing, hepatobiliary imaging, and liver biopsy
- Typically occurs within six months of new medication, some compounds have longer latency period

Types

- Intrinsic: Predictable, dose dependent injury
- Idiosyncratic - less common, affects susceptible individuals, less consistent dose relationship, with varied presentation
- Chronic: Ongoing increased LFTs or symptoms of liver disease 6-9 months after DILI onset

R-Value

- Characterizes pattern of injury: **R < 2: Cholestatic** **2-5: Mixed** **>5: Hepatocellular**

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

Cholestatic

- Rule out biliary pathology and infiltrative processes with imaging (US, CT, or MRI)
- PBC testing only in those without obvious biliary path on imaging
- ERCP only if MRI or EUS CANNOT rule out choledocholithiasis, PSC, pancreaticobiliary malignancy

Hepatocellular or Mixed

- Check for acute HAV, HBV, HCV, and AIH
- If recent travel to endemic area, atypical DILI, or no obvious culprit, check HEV IgM
- If atypical lymphocytosis & lymphadenopathy, check CMV, EBV, and HSV
- Consider Wilson's and Budd-Chiari if appropriate

Special Considerations

Herbal & Dietary Supplements

- 20% of hepatotoxicity cases in USA!

Immune-Checkpoint Inhibitors

- Recognize HBV reactivation
- Tx: Stop or delay ICI and give immunosuppressants (steroids → MMF)

Children

- Think minocycline DILI in children w/ AIH-like presentation

Chronic Liver Disease

- HBV & HCV have increased risk injury w/ INH & ARVs
- NO increased risk of statin hepatotoxicity with fatty liver
- Avoid protease inhibitors in decompensated HCV cirrhosis
- Avoid high doses obeticholic acid in Child Pugh's B or C PSC

When to Biopsy?

- AIH still on the differential
- Potential immunosuppressive therapy
- LFTs or liver function worsening
- Peak ALT does not ↓ by 50% within 30-60 days of hepatocellular DILI
- Peak ALP does not ↓ by 50% within 180 days of cholestatic DILI
- Culprit agent might need to be used
- Abnormal LFTs +/- bilirubin > 180 days of DILI, especially if signs & symptoms of chronic liver disease

Treatment

- Stop suspected agent
- Use NAC in adults with early stage acute liver failure (ALI + hepatic encephalopathy)
- Do not use NAC in children with ALF from DILI

Prognosis

Hy's law: Helps determine mortality risk, 10% mortality if all 3 of following: ALT or AST >3x ULN, T bili >2x ULN without initial cholestasis, no other reason found

- 10% progress to acute liver failure (40% of whom require OLT, 42% mortality rate)
- < 20% develop chronic liver injury
- Cholestatic DILI 2x likely develop chronic liver injury
- Hepatocellular Injury more likely fatal or result in OLT
- Predict 6 month mortality with MELD, Charlson comorbidity index, & albumin

Rechallenge?

- Do NOT rechallenge if LFTs >5x ULN, Hy's law applies, or jaundice present
- Exception if life threatening situation without alternative

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Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. Am J Gastroenterol. 2014 Jul;109(7):950-66; quiz 967. doi: 10.1038/ajg.2014.131. Epub 2014 Jun 17. PMID: 24935270.