Definitions of Liver Injury and Failure and Evaluation of Abnormal Liver Tests

ACG, CCM Guidelines and Baveno Consensus: Updated 2023

DEFINITIONS:

Acute liver injury

- Elevation of liver enzymes including ALT, AST and alkaline phosphatase.

Acute liver failure (ALF)

- Defined by the presence of acute liver injury, hepatic synthetic dysfunction (elevated INR >1.5), and encephalopathy within 26 weeks of the first symptoms of liver disease in a patient without evidence of chronic liver disease.

Fulminant liver failure

- Encephalopathy that rapidly develops within 8 weeks of jaundice in patients with ALF.

Compensated advanced chronic liver disease (cACLD)

- Defined by the absence of present or past complications of cirrhosis
- The use of elastography has enabled the early identification of patients with untreated/active chronic liver disease at risk of having clinically significant portal hypertensin (CSPH) and consequently, at risk of decompensation and liver-related death.
- cACLD can be divided into 2 stages
    - With CSPH defined as an HVPG ≥10 mmHg
        - Are at increased risk of decompensation and increased mortality risk
    - Absence of CSPH

Acutely decompensated cirrhosis

The events that define decompensation are:

- Overt ascites (or pleural effusion with increased serum ascites albumin gradient (>1.1 g/dl)
- Overt hepatic encephalopathy (West Haven grade ≥ II)
- Variceal bleeding
- Insufficient data are available regarding whether a minimal amount of ascites only detected in imaging procedures, minimal hepatic encephalopathy, and occult bleeding from portal hypertensive gastroenteropathy can be considered as decompensation

Acute on chronic liver failure (ACLF)

- Clinical syndrome characterized by acutely decompensated cirrhosis resulting in one or more extrahepatic organ failures.
    - ACLF is caused by an excessive systemic inflammatory response triggered by precipitants that are clinically apparent (e.g., proven infection with sepsis, severe alcohol-related hepatitis) or not.
    - The presence of organ failure distinguishes ACLF from acute decompensation of cirrhosis (acute development of ascites, variceal bleeding, and hepatic encephalopathy).

Accelerated intravascular coagulation and fibrinolysis (AICF):

- Refers to a clinically relevant state of hyperfibrinolysis resulting from cirrhosis. Although there are no precise diagnostic criteria for AICF, it should be considered in patients with advanced cirrhosis with:
    - Intractable bleeding which fails to respond to usual therapy
    - Following procedures or trauma (e.g., oozing from line sites) or spontaneous bleeding or persistent gastrointestinal bleeding due to portal gastropathy.
    - D-dimer levels are profoundly elevated.
    - Fibrinogen levels are unusually low compared to most patients with cirrhosis.

- AICF and DIC share several similarities, however, unlike in DIC, patients with AICF typically have:
  - Reasonably stable platelet counts.
  - Elevated levels of factor VIII (values which would be reduced in DIC).

ACUTE LIVER INJURY

Markers of liver injury.

- ALT, AST, alkaline phosphatase, and bilirubin are markers of liver injury, not liver function, and should be referred to as liver tests.

Markers of liver function.

- PT/INR.
  - It is a far more sensitive measure of liver function than albumin because prothrombin time may be prolonged in patients with severe liver disease of <24 h duration.
  - Nevertheless, it is not specific.
- Albumin
  - It is exclusively synthesized by the liver with a circulating half-life of 3 weeks.
    - So, a reduction in albumin usually indicates liver disease of more than 3 weeks duration.
    - In addition, any significant illness can decrease albumin levels due to cytokine effects and volume redistribution.
    - Therefore, albumin is not a useful marker for the diagnosis of acute liver dysfunction.

Classification of ALI

- *Hepatocellular injury* defined as disproportionate elevation of ALT and AST levels as compared with the alkaline phosphatase level.
- *Cholestatic injury* defined as disproportionate elevation in alkaline phosphatase level as compared with ALT and AST levels with or without elevated bilirubin.
- *Mixed pattern of injury* defined as elevation of both alkaline phosphatase and ALT/AST levels.

HEPTATOCELLULAR INJURY

Severity

- Borderline AST and/or ALT elevation <2X ULN
- Mild AST and/or ALT elevation 2–5X ULN
- Moderate AST and/or ALT elevation 5–15X ULN
- Severe AST and/or ALT elevation >15X ULN
- Massive AST and/or ALT >10,000 IU/l
  - Generally only seen with:
    - Shock liver/ischemic hepatopathy.
    - Drug-induced/toxic hepatitis.
    - Non-liver-related conditions
      - Rhabdomyolysis and heat stroke.

Causes of elevated AST and ALT

The ratio of AST to ALT may be useful in determining the etiology of abnormal liver tests.

- ALT is present primarily in the liver and thus is a more specific marker of hepatic injury than AST.

        - AST is present in the liver and other organs including cardiac muscle, skeletal muscle, kidney, and brain.
        - AST increase without elevation in ALT is suggestive of cardiac or muscle disease.
        - ALT levels are typically greater than AST levels in most primary liver conditions including chronic viral hepatitis and NAFLD.
    - An AST:ALT ratio of at least 2:1 suggests alcohol liver disease.
        - 90% of patients with alcoholic liver disease have AST>ALT, and >70% have an AST/ALT ratio>2.
        - AST>ALT can also be seen in patients with cirrhosis of any etiology, although the AST:ALT ratio is typically not >2:1.

- *Hepatic (generally AST>ALT)*
    - Alcoholic liver disease
    - Cirrhosis (of any etiology)
    - Ischemic hepatitis, congestive hepatopathy
    - Acute Budd-Chiari syndrome
    - Hepatic artery damage/thrombosis/occlusion
    - TPN
- *Hepatic (generally ALT>AST)*
    - NAFLD - NASH
    - Viral hepatitis
    - Drug-induced liver injury and toxic hepatitis (amanita exposure)
    - Hemochromatosis, Wilson's disease, Alpha-1-antitrypsin deficiency, Celiac disease
    - Acute bile duct obstruction
    - Liver trauma, post-liver surgery
    - Veno-occlusive disease/sinusoidal obstruction syndrome
    - Diffuse infiltration of the liver with cancer
    - HELLP syndrome
    - Acute fatty liver of pregnancy
    - Sepsis
    - Hemophagocytic lymphohistiocytosis
- ***Non-hepatic***
    - Skeletal muscle damage/rhabdomyolysis
    - Cardiac muscle damage
    - Thyroid disease
    - Macro-AST
    - Strenuous exercise
    - Heat stroke
    - Hemolysis
    - Adrenal insufficiency

Evaluation

- Mild ALT and/or AST elevation
    - Abdominal ultrasound, CBC/platelet count, Alk Phos, bilirubin, PT/INR and viral serology with PCR confirmation if HCV Ab is positive.
- Moderate or severe ALT and/or AST elevation
    - As above and iron panel, ceruloplasmin, ANA, SMA, gamma-globulin.

- Severe or massive elevation of ALT
    - As above and assess for toxic ingestions, ischemia, and rhabdomyolysis.
- Patients with moderate, severe, and massive elevations of ALT and/or AST require immediate evaluation.
- Fulminant hepatic failure or acute liver failure requires immediate evaluation and referral to liver specialist with consideration of referral to a liver transplant center regardless of ALT level.

CHOLESTATIC INJURY

They can be categorized as either:

- Extrahepatic cholestasis: anatomic obstructions to bile flow.
- Intra-hepatic cholestasis: functional impairments of bile formation by the hepatocytes.

Evaluation

- If the alkaline phosphatase is elevated in the presence of other elevated liver enzymes
    - Confirmation of hepatic origin is not required.
- If the alkaline phosphatase is elevated with normal total bilirubin and aminotransferases, confirm with serum GGT.
    - If GGT normal, evaluate for non-hepatobiliary etiologies.
    - If GGT abnormal: abdominal ultrasound, check AMA, and SMA
- Abdominal ultrasound
    - If ductal dilatation request ERCP, MRCP
    - If no ductal dilatation
        - Positive AMA: evaluate for primary biliary cholangitis formerly named primary biliary cirrhosis
        - Positive SMA, evaluate for autoimmune hepatitis
- Unexplained alkaline phosphatase elevation:
    - MR cholangiography/MRCP or ERCP in conjunction with IgG4 for evaluation of primary sclerosing cholangitis and IgG4-related disease
    - Consider liver biopsy

HYPERBILIRUBINEMIA

Classified as conjugated or direct and unconjugated or indirect

- Elevated unconjugated bilirubin implies:
    - Over-production of bilirubin - hemolysis.
    - Decreased hepatic uptake.
    - Decreased hepatic conjugation.
- Elevated conjugated bilirubin implies:
    - Hepatocellular disease, or
    - Cholestasis.

Evaluation

If predominantly unconjugated evaluate for:

- Hemolysis
    - Peripheral smear, reticulocyte count, LDH and haptoglobin)
    - Potential source for SIRS like sepsis or ischemia
        - Induce increased production of bilirubin, impaired hepatic bilirubin uptake and Impaired bilirubin conjugation.

- Gilbert's syndrome
    - Most common cause of isolated mildly elevated unconjugated bilirubin
    - Total bilirubin levels almost never exceed 6 mg/dl and are usually <3 mg/dl.
    - Diagnosis of exclusion.
        - Exclude hemolysis and medications that cause hyperbilirubinemia, and
        - Confirm normal serum aminotransferases and alkaline phosphatase levels.
    - If these criteria are met then a presumptive diagnosis of Gilbert's syndrome can be made and additional evaluation is not routinely necessary.

If predominantly conjugated evaluate for:

- Hepatocellular disease or cholestasis, so evaluation is directed accordingly.