Acute Liver Failure

TRACY DAUM DNP, AG-ACNP

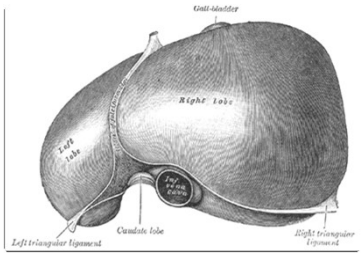
Disclosures

- Tracy Daum DNP, AG-ACNP has no financial relationships with commercial interests to disclose

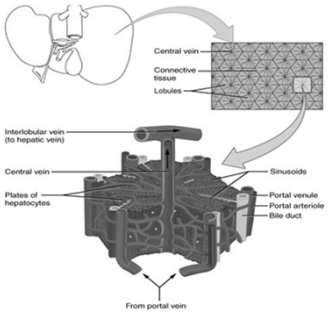
Objectives

- Discuss the etiology of acute liver failure.
- Explain the associated organ failure.
- Define treatment strategies for acute liver failure.

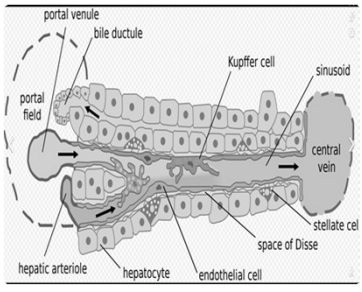
Anatomy of the Liver

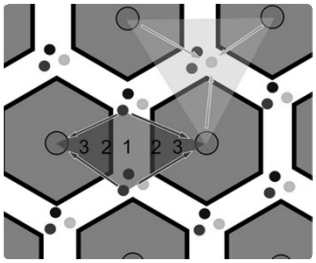


Anatomy of the Liver



Anatomy of the Liver





Hepatic Lobule: Zones

ALF: Pathophysiology

- Widespread hepatocellular necrosis beginning in the centrizonal distribution and progressing towards portal tracts.
- Parenchymal inflammation is variable and proportional to duration of disease

Acute Liver Failure (ALF)

- Originally defined in 1970 as fulminant liver failure as:
  - "a potentially reversible condition, the consequence of severe liver injury, with an onset of encephalopathy within 8 weeks of the appearance of the first symptoms and in the absence of pre-existing liver disease".

ALF

- In 1993, the syndrome was re-defined to take into the account of etiology, frequency of complications and prognosis.

ALF: Definition

- An acute abnormality of liver blood tests
  - Without an underlying chronic liver disease.
- Development of coagulopathy

ALF: Diagnosis

- Acute liver insult
- Encephalopathy

Acute Liver Failure (ALF) Definition

- Can be diagnosed in patients with undiagnosed Wilson's disease, vertically acquired hepatitis B virus or autoimmune hepatitis, in whom underlying cirrhosis may be present given that it was recognized <26 weeks.
- On the other hand, patients with acute severe alcoholic hepatitis, even if recognized for <26 weeks, are considered to have acute-on-chronic liver failure since most have a long history of heavy drinking.

Acute Liver Injury (ALI)

- Coagulopathy, abnormal liver function
  - In the absence of hepatic encephalopathy

Differentiating ALI vs. ALF

- ALF initiates with severe ALI.
  - 2-3x elevation of transaminases
- Absence of chronic liver disease

Differentiating ALI vs ALF

- Future considerations:
  - Biomarkers for prediction of the progression from ALI to ALF
  - Development and dissemination of better testing for subtle hepatic encephalopathy in patients with subacute presentations.
  - Review of INR/prothrombin cut-off for definition of ALF in the context of both hyperacute, acute and subacute liver failure

AASLD Guidelines: ALF

- AASLD practice guidelines are developed by a multidisciplinary panel of experts who rate the quality (level) of the evidence and the strength of each recommendation using the Grading of Recommendations Assessment, Development, and Evaluation system (GRADE).

Guidelines for General Management of ALF

- Patients with ALF should be hospitalized and monitored frequently, preferably in an ICU. (***III***)
- Contact with a transplant center and plans to transfer appropriate patients with ALF should be initiated early in the evaluation process. (***III***)
- The precise etiology of ALF should be sought to guide further management decisions. (***III***)

ALF Subclassifications

- Hyperacute (<7 days)
- Acute (7 to 21 days)
- Subacute (>21 days and <26 weeks)

Hyperacute ALF: Definition

- Considering jaundice as the first symptom, hyperacute liver failure describes patients developing hepatic encephalopathy within 7 days of noting jaundice.

Hyperacute ALF: Laboratory Findings

- Severe coagulopathy
- Markedly increased serum transaminases
- Initially only moderate, if any, increase in bilirubin

Acute ALF: Definition

- Development of hepatic encephalopathy between 8 and 28 days of noting jaundice

Subacute ALF: Definition

- Milder increase in serum transaminases
- Deep jaundice
- Mild to moderate coagulopathy

Subacute ALF: Definition

- Development of hepatic encephalopathy within 5-12 weeks of jaundice.

Chronic Liver Disease (CLD): Definition

- Disease duration of greater than 28 weeks before onset of encephalopathy.

ALF Subcategories/Prognosis

- Subcategories are associated with underlying causes
  - Prognosis is determined by etiology of ALF

ALF Subcategories/Prognosis

- Hyperacute liver failure tend to have a better prognosis than those with subacute liver failure. The better prognosis is related to the fact that these patients often have acetaminophen toxicity or ischemic hepatopathy, diagnoses associated with a better prognosis than many of the disorders that may result in subacute liver failure, such as Wilson disease.

Acute Liver Failure vs. Chronic Liver Failure

- Time varies among reports.
  - Commonly used cutoff: >26 weeks.

Prerequisites for defining ALF

- Absence of previous severe fibrotic or cirrhotic CLD.
- Acute presentations of autoimmune hepatitis and Budd-Chiari syndrome.
- Wilson disease

Etiology

- Acetaminophen
- Idiosyncratic drug reactions
- Viral hepatitis
- Alcoholic hepatitis
- Autoimmune hepatitis
- Wilson disease
- Budd-Chiari syndrome
- Veno-occlusive disease
- Acute fatty liver of pregnancy
- HELLP syndrome
- Malignant infiltration
- Partial hepatectomy
- Toxin exposure
- Sepsis

Clinical Manifestations

- Fatigue/malaise
- Lethargy
- Anorexia
- Nausea and/or vomiting
- Right upper quadrant pain
- Pruritus
- Jaundice
- Abdominal distention from ascites

ALF: Physical Examination Findings

- Neurological findings
- Jaundice
- Vesicular skin lesions
- Fever
- Right upper quadrant tenderness
- Hepatomegaly
- Ascites
- Signs of intravascular volume depletion

Overview of Liver Function Testing

- Total bilirubin
- Alanine transaminase
- Aspartate transaminase (AST)
- AST/ALT ratio
- Alkaline phosphatase (ALP)
- Gamma-glutamyltransferase (GGT)
- Albumin

Laboratory Testing Overview

- Albumin
- Ceruloplasmin
- Alpha-fetoprotein (AFP)
- Coagulation test
- Serum glucose
- Lactate dehydrogenase
- Cholesterol

Laboratory findings

- Prolonged prothrombin time, resulting in INR >/= 1.5
- Elevated aminotransferase level
- Elevated bilirubin level
- Low platelet count
- Hemolytic anemia
- Elevated serum creatinine and blood urea nitrogen
- Elevated amylase and lipase
- Hypoglycemia
- Hypophosphatemia
- Hypomagnesemia
- Hypokalemia
- Acidosis or alkalosis
- Elevated ammonia level
- Elevated LDH level

Laboratory testing associated with specific diagnoses

- Acetaminophen
- Ischemic hepatic injury
- Hepatitis B virus
- Wilson disease
- Acute fatty liver of pregnancy/HELLP syndrome
- Herpes simplex virus
- Reye syndrome, valproate toxicity or tetracycline toxicity

Acetaminophen

- Aminotransferase levels >3500 international units/L
- Low bilirubin
- High INR

Acetaminophen Metabolism

- At therapeutic doses, 90% of acetaminophen is metabolized in the liver to sulfate and glucuronide conjugates that are then excreted in the urine.
- One-half of the remaining acetaminophen is excreted unchanged in the urine and one-half is metabolized via hepatic cytochrome P450 mixed function oxidase pathway to N-acetyl-p-benzoquinoneimine (NAPQI), which is hepatotoxic.

Acetaminophen Metabolism

- With normal doses, NAPQI is rapidly conjugated to hepatic glutathione, forming nontoxic cysteine and mercaptate compounds that are excreted in the urine.

Acetaminophen Metabolism

- With toxic doses, the sulfate and glucuronide pathways become saturated, resulting in an increased fraction of acetaminophen being metabolized by cytochrome P450 enzymes.
- Once glutathione stores are depleted,
  - NAPQI accumulates and hepatic injury begins.

Acetaminophen Toxicity: Management Guidelines

- For patients with known or suspected acetaminophen overdose within 4 hours of presentation, give activated charcoal just prior to starting N-acetylcysteine (NAC) dosing. (***I***)
- Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impending or evolving liver injury. (***II-1***)
- NAC may be used in cases of acute liver failure in which acetaminophen ingestion is possible or when knowledge of circumstances surrounding admission is inadequate but aminotransferases suggest acetaminophen poisoning. (***III***)

Ischemic Hepatic Injury

- High aminotransferase levels (25 to 250 times the upper limit of normal)
- Elevated serum LDH levels

Ischemic Liver Disease: Management Guidelines

- In ALF patients with evidence of ischemic injury, cardiovascular support is the treatment of choice. (***III***)
- Hepatic vein thrombosis with acute hepatic failure is an indication for liver transplantation, provided underlying malignancy is excluded. (***II-3***)

Hepatitis B Virus

- Aminotransferase levels of to 1000 to 2000 international units/L are common
- Alanine aminotransferase (ALT) level that is higher than the asparate aminotransferase (AST) level

Hepatitis: Management Guidelines

- Viral hepatitis A- (and E-) related acute liver failure must be treated with supportive care as no virus-specific treatment has proven to be effective. (***III***)
- Nucleos(t)ide analogues should be considered for hepatitis B-associated acute liver failure and for prevention of post-transplant recurrence. (***III***)
- Patients with known or suspected herpes virus or varicella zoster as the cause of acute liver failure should be treated with acyclovir (5-10 mg/kg IV every 8 hours) and may be considered for transplantation. (***III***)

Autoimmune Hepatitis: Management Guidelines

- Liver biopsy is recommended when autoimmune hepatitis is suspected as the cause of acute liver failure, and autoantibodies are negative. (***III***)
- Patients with coagulopathy and mild hepatic encephalopathy due to autoimmune hepatitis may be considered for corticosteroid treatment (prednisone, 40-60 mg/day). (***III***)
- Patients with autoimmune hepatitis should be considered for transplantation even while corticosteroids are being administered. (***III***)

Wilson Disease

- Coombs-negative hemolytic anemia
- Aminotransferase levels <2000 international units/L
- AST to ALT ratio of >2
- Normal or markedly subnormal alkaline phosphatase (<40 international units/L)
- Alkaline phosphatase to total bilirubin (mg/dL) ratio <4
- Rapidly progressive renal failure
- Low uric acid levels

Wilson Disease: Management Guidelines

- To exclude Wilson disease one should obtain ceruloplasmin, serum and urinary copper levels, slit lamp examination for Kayser-Fleischer rings, hepatic copper levels when liver biopsy is feasible, and total bilirubin/alkaline phosphatase ratio. (***III***)
- Patients in whom Wilson disease is the likely cause of acute liver failure must be promptly considered for liver transplantation. (***III***)

Acute fatty liver of pregnancy/HELLP syndrome

- Aminotransferase levels <1000 international units/L
- Elevated bilirubin
- Low platelet count (Hemolysis, elevated liver enzymes and low platelets)

Pregnancy: Guidelines

- For acute fatty liver of pregnancy or the HELLP syndrome, expeditious delivery of the infant is recommended. Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery. (***III***)

Herpes Simplex Virus

- Markedly elevated transaminases
- Leukopenia
- Low bilirubin

Reye Syndrome, Valproate toxicity or tetracycline toxicity

- Minor to moderate elevations in aminotransferase and bilirubin levels

Toxicity Guidelines

- In ALF patients with known or suspected mushroom poisoning, consider administration of penicillin G and N-acetylcysteine. (***III***)
- Patients with acute liver failure secondary to mushroom poisoning should be listed for transplantation, as this procedure is often the only lifesaving option. (***III***)
- Obtain details (including onset of ingestion, amount and timing of last dose) concerning all prescription and non-prescription drugs, herbs and dietary supplements taken over the past year. (***III***)
- Determine ingredients of non-prescription medications whenever possible. (***III***)
- In the setting of acute liver failure due to possible drug hepatotoxicity, discontinue all but essential medications. (***III***)
- N-acetylcysteine may be beneficial for acute liver failure due to drug-induced liver injury. (***I***)

ALF Diagnosis

- Elevated aminotransferases: often with abnormal bilirubin and alkaline phosphatase levels
- Hepatic encephalopathy
- Prolonged prothrombin time (INR> 1.5)

Etiology of ALF

- Etiology can be established in 60-80% of patients.
- Underlying etiology of ALF influences the management and provides prognostic information.

ALF Etiology

If the initial evaluation fails to identify an etiology, a liver biopsy may be required.

ALF: Consideration for NAC administration

- Evidence supports N-acetylcysteine (NAC) to improve outcomes
- NAC has been used in non-acetaminophen induced ALF.

ALF: Medications

- Abacavir
- Acetaminophen
- Alcohol
- Allopurinol
- Amiodarone
- Amoxicillin
- Aspirin
- Carbamazepine
- Carbon tetrachloride
- Ciprofloxacin
- Cocaine
- Comfrey
- Dapson
- Didanosine
- Dideoxyinosine
- Disulfiram

ALF: Medications

- Doxycycline
- Efavirenz
- Gemtuzumab
- Gold
- Greater celandine
- Halothane
- He Shou Wu
- Herbalife
- Hydroxycut
- Isoflurzne
- Isoniazid
- Irtaconazole
- Kava
- Ketoconazole
- Labetalol
- LipoKinetix
- Ma Huang
- MDMA (Ectasy)

ALF: Medications

- Methamphetamine
- Monamine oxidase inhibitors
- Methyldopa
- Nicotinic acid
- Nitrofurantoin
- Nonsteroidal anti-inflammatory drugs
- Phenprocoumon
- Phenytoin
- Poison mushrooms
- Propylthiouracil
- Pyrazinmide
- Rifampin
- Senecio
- Statins
- Sulfonamides
- Terbinafine
- Tetracycline

ALF: Medications

- Tolcapone
- Tricyclic antidepressants
- Valproic acid

ALF: Prognostication

- King's College Criteria
- Clichy Criteria
- MELD,MELD-Na
- Child's Pugh Score
- Gc Globulin
- Lactate
- Alpha Fetoprotein
- Factor V, Factor VIII, V ratio
- Phosphate levels

ALF: Assessment and Management

- Early discussion with a tertiary liver center
- Rule out the presence of cirrhosis and/or alcoholic-induced liver injury
- Etiology

ALF: History, Physical and Interview (HPI)

- Comprehensive clinical assessment and history taking of patients and their relatives
  - Questions regarding etiology
  - Comorbid conditions
  - Interval between jaundice and the first signs of hepatic encephalopathy

ALF: HPI

- Use of medications, herbal medications and food supplementations <6 months
- Substance abuse
- History of suicide attempt/depression
- Gastrointestinal complaints after mushroom ingestion

ALF: HPI

- Pregnancy
- Travelling in viral hepatitis endemic areas
- Immunosuppressed?

ALF: HPI

- Conditions that may impact decision in respect to emergent Liver Transplantation:
  - History of CLD
  - Active and dependent alcohol or substance misuse
  - History of cancer in recent past
  - Severe co-morbid conditions

ALF: Laboratory testing

- PT, INR or factor V and full coagulation screen including fibrinogen
- Liver blood tests including LDH and conjugated and unconjugated bilirubin and creatinine kinase
- Renal function assessment
- Arterial blood gas and lactate
- Ammonia
- Toxicology screen and paracetamol serum level
- Serological screen for viral infections
- Autoimmune markers

ALF: Diagnostic considerations

- Cultures
- Chest x-ray, EKG
- Imaging
- Liver Biopsy

Liver Biopsy

- Transjugular approach is preferred in the setting of ALF.
- Portal pressure measurements
- Histologic evaluation

Liver Biopsy: Guidelines

- In patients with acute liver failure who have a previous cancer history or massive hepatomegaly, consider underlying malignancy and obtain imaging and liver biopsy to confirm or exclude the diagnosis. (***III***)
- If the etiological diagnosis remains elusive after extensive initial evaluation, liver biopsy may be appropriate to attempt to identify a specific etiology that might influence treatment strategy. (***III***)

CNS Management: Guidelines

- In early stages of encephalopathy, lactulose may be used either orally or rectally to effect a bowel purge, but should not be administered to the point of diarrhea, and may interfere with the surgical field by increasing bowel distention during liver transplantation. (***III***)
- Patients who progress to high-grade hepatic encephalopathy (grade III or IV) should undergo endotracheal intubation. (***III***)
- Seizure activity should be treated with phenytoin and benzodiazepines with short half-lives. Prophylactic phenytoin is not recommended. (***III***)
- Intracranial pressure monitoring is recommended in ALF patients with high grade hepatic encephalopathy, in centers with expertise in ICP monitoring, in patients awaiting and undergoing liver transplantation. (***III***)

CNS Management: Guidelines

- In the absence of ICP monitoring, frequent (hourly) neurological evaluation is recommended to identify early evidence of intracranial hypertension. (***III***)
- In the event of intracranial hypertension, a mannitol bolus (0.5-1.0 gm/kg body weight) is recommended as first-line therapy; however, the prophylactic administration of mannitol is not recommended. (***II-2***)
- In ALF patients at highest risk for cerebral edema (serum ammonia > 150 IM, grade 3/4 hepatic encephalopathy, acute renal failure, requiring vasopressors to maintain MAP), the prophylactic induction of hypernatremia with hypertonic saline to a sodium level of 145-155 mEq/L is recommended. (***I***)
- Short-acting barbiturates and the induction of hypothermia to a core body temperature of 34- 35C° may be considered for intracranial hypertension refractory to osmotic agents as a bridge to liver transplantation. (***II-3***)

CNS Management: Guidelines

- Corticosteroids should not be used to control elevated ICP in patients with ALF. (***I***)
- Periodic surveillance cultures are recommended to detect bacterial and fungal pathogens as early as possible. Antibiotic treatment should be initiated promptly according to surveillance culture results at the earliest sign of active infection or deterioration (progression to high grade hepatic encephalopathy or elements of the SIRS). (***III***)
- Prophylactic antibiotics and antifungals have not been shown to improve overall outcomes in ALF and therefore cannot be advocated in all patients, particularly those with mild hepatic encephalopathy. (***III***)
- Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of hemorrhage or prior to invasive procedures. (***III***)
- Patients with ALF in the ICU should receive prophylaxis with H2 blocking agents or proton pump inhibitors (or sucralfate as a second-line agent) for acid-related gastrointestinal bleeding associated with stress. (***I***)

Hemodynamics: Guidelines

- Fluid resuscitation and maintenance of adequate intravascular volume are recommended on presentation in patients with ALF. The initial treatment of hypotension should be with intravenous normal saline. (***III***)
- If dialysis support is needed for acute renal failure, it is recommended that a continuous mode rather than an intermittent mode be used. (***I***)
- Pulmonary artery catheterization is rarely necessary in patients with ALF and is associated with significant morbidity. Instead, appropriate volume status should be ensured with a volume challenge.. (***III***)

Hemodynamics: Guidelines

- Systemic vasopressor support with agents such as norepinephrine should be administered in volume-refractory hypotension or to ensure adequate CPP. Vasopressin or terlipressin can be added to norepinephrine in norepinephrine-refractory cases, but should be used cautiously in severely encephalopathic patients with intracranial hypertension. (***II-1***)
- Goals of circulatory support in patients with ALF are a MAP ≥75 mmHg and CPP 60-80 mmHg. (***II-1***)

Metabolic: Guidelines

- Metabolic homeostasis must be carefully maintained in ALF patients. Overall nutritional status as well as glucose, phosphate, potassium and magnesium levels should be monitored frequently, with expeditious correction of derangements. (***III***)

Transplantation and Prognosis: Guidelines

- Currently available prognostic scoring systems do not adequately predict outcome and determine candidacy for liver transplantation. Reliance entirely upon these guidelines is thus not recommended. (***III***)
- Urgent hepatic transplantation is indicated in acute liver failure where prognostic indicators suggest a high likelihood of death. (***II-3***)
- Living donor or auxiliary liver transplantation may be considered in the setting of limited organ supply, but its use remains controversial. (***II-3***)
- Currently available liver support systems are not recommended outside of clinical trials; their future in the management of acute liver failure remains unclear. (***II-1***)

Liver Transplantation: AASLD Guidelines

- Acute Liver Failure Complications of Cirrhosis
- Liver-Based Metabolic Conditions with Systemic Manifestations
- Systemic Complications of Chronic Liver Disease

LT Evaluation Process

- Financial evaluation
- Hepatology evaluation
- Surgical evaluation
- Laboratory evaluation
- Cardiac testing
- Hepatic imaging
- General health assessment
- Dental assessment
- Anesthesia evaluation
- Psychiatric evaluation
- Social work
- Nutritional evaluation
- Infectious Disease evaluation

Contraindications to Liver Transplantation

- MELD score <15
- Severe cardiac or pulmonary disease
- AIDS
- Ongoing alcohol or illicit drug use
- Hepatocellular carcinoma with metastatic disease
- Uncontrolled sepsis
- Anatomic anomaly that precludes transplantation
- Intrahepatic cholangiocarcinoma
- Extrahepatic malignancy
- Fulminant hepatic failure
- Hemangiosarcoma
- Persistent noncompliance
- Lack of social support

Liver Support Devices

Thank You.