

# Acute hepatitis and Acute Hepatic failure

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- A true case:
  - DILI

# Background

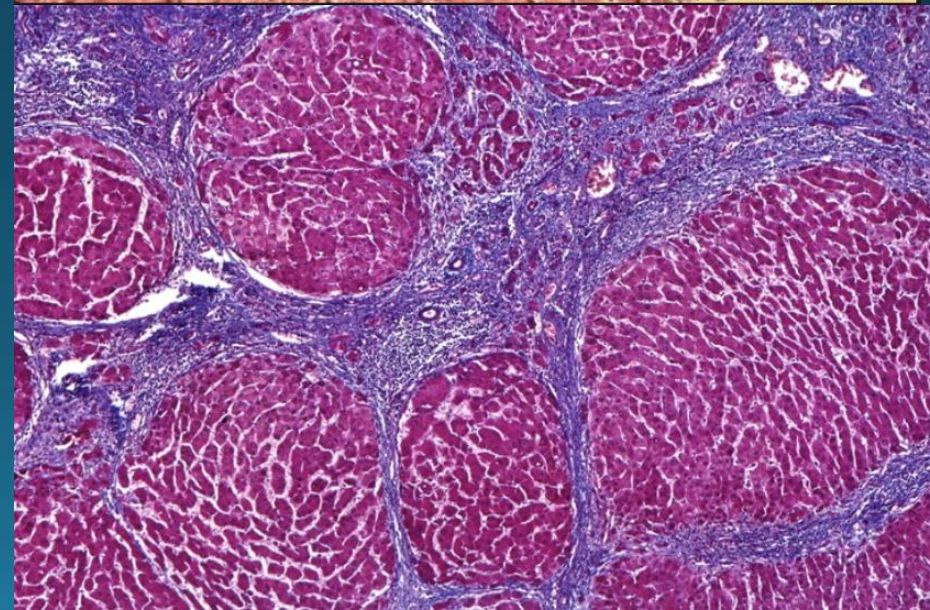
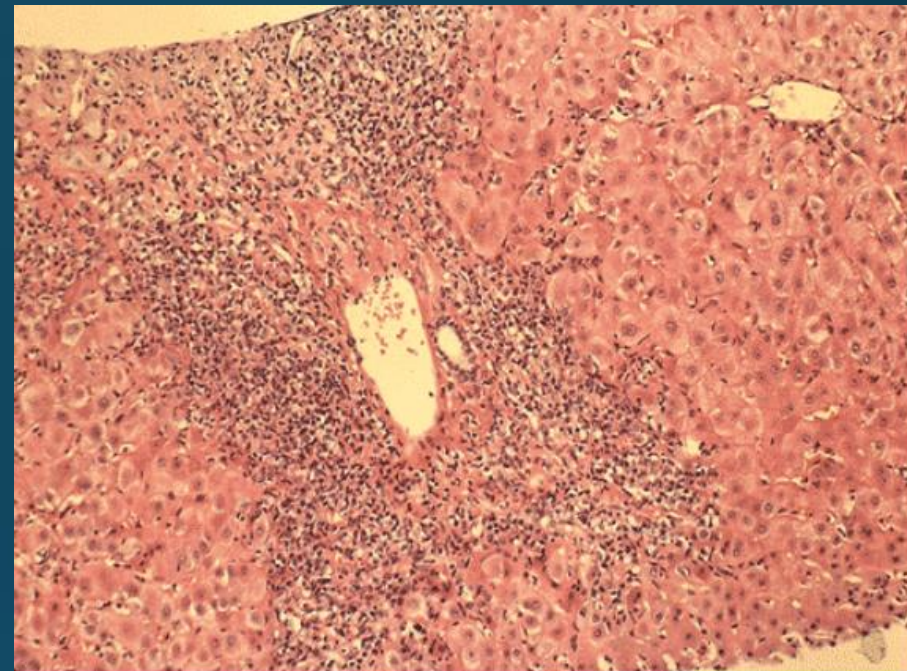
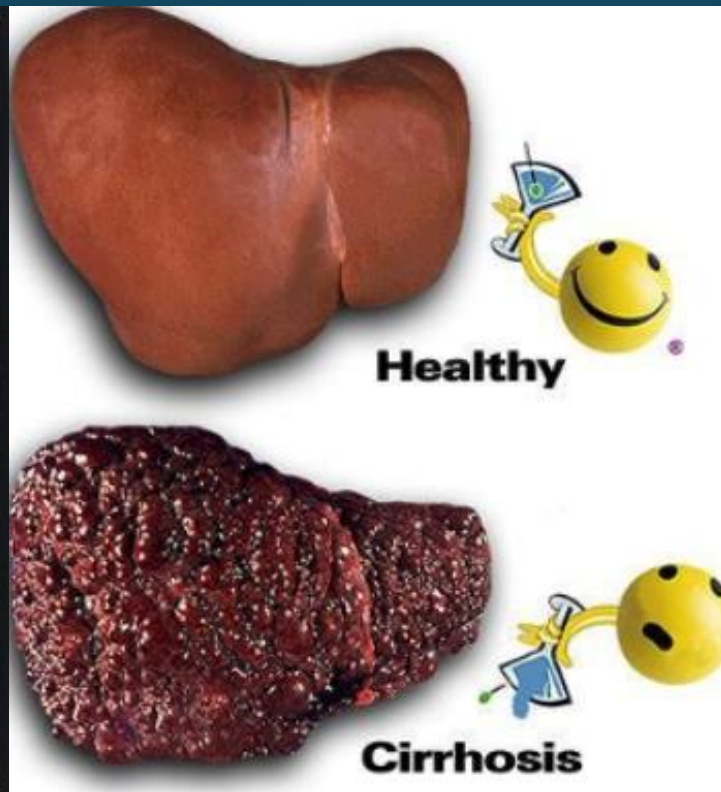
- Is a clinical syndrome that results from the sudden loss of hepatic parenchymal and metabolic functions results in altered mentation and coagulopathy in individuals without known pre-existing liver disease.
- ALF is a rare condition.

# Background

- Acute liver failure often affects young persons
- The most prominent causes include
  1. Viral hepatitis
  2. DILI
  3. Autoimmune liver disease
  4. many cases ( 15%) have no discernible cause.
- Because of its rarity, ALF has been difficult to study in depth and very few controlled therapy trials have been performed.



# Cirrhosis vs ALF



# Criteria for Diagnosis

- in a patient without preexisting cirrhosis & with an illness of <26 weeks' duration with the following three criteria:
  - Massive cellular necrosis
  - Any degree of mental alteration (encephalopathy)
  - Coagulation abnormality, INR  $\geq 1.5$
- *Can develop*
  1. *Infectious complications*
  2. *Multi-organ failure*
  3. *Cerebral edema (Most serious complications of acute liver failure)*

# Classification

- Terms used signifying length of illness, such as “hyperacute” (<7 days), “acute” (7-21 days) and “subacute” (>21 days and <26 weeks), are popular but not particularly helpful since they do not have prognostic significance distinct from the cause of the illness.

# Causes

- Viral Hepatitis
- DILI
- Toxins/herbs
- Vascular injury
- AIH
- Wilson's disease
- HELLP/Acute fatty liver
- Malignant infiltration



# Initial evaluation

- Conduct complete relevant history and physical exam.
- History:
  - Review of possible exposures to viral infection and drugs or other toxins.
  - If severe encephalopathy is present, the history may be provided entirely by the family or may be unavailable.
  - Further history....
- Px:
  - RUQ tenderness is variably present.
  - An enlarged liver may be seen early in viral hepatitis but is particularly noteworthy for malignant infiltration, or acute Budd-Chiari syndrome.

# Management

- Admit patient to ICU if evidence elevated INR or altered MS

# Management: Investigations

- CBC, Lyte, urea , Cr, Glucose
- All liver enzymes, INR, Albumin, Bilirubin
- ABG
- Pregnancy test in females.
- **Plasma ammonia:** A detailed analysis of serum ammonia in patients with ALF identified a concentration of 75 IM as an important threshold below which patients rarely develop intracranial hypertension (ICH). Conversely, arterial ammonia levels of >100 IM on admission represent an independent risk factor for the development of high-grade hepatic encephalopathy, and a level of >200 IM predicts ICH.

# Management: Investigations

- **Viral Hepatitis A-E**
  - Anti-HAV IgM
  - HBsAg, anti-HBc IgM
  - Anti-HCV, HCV RNA
  - Anti-HEV IgM
  - HSV IgM
  - VZV
  - CMV
- Acetaminophen level or any other suspected drug
- Urine toxin & Toxicology screen
- Autoimmune Hepatitis: ANA, ASMA, Immunoglobulin levels
- Serum ceruloplasmin ( very low ALP suggest WD.....Hemolysis )
- **US with doppler: Imaging:** could suggest "cirrhosis," but this is often an overcall by radiology, because a regenerating massively necrotic liver will give the same nodular profile as cirrhosis.
- Pregnant test if female
- Liver biopsy, most often done via the transjugular route because of coagulopathy, is indicated when certain conditions such as autoimmune hepatitis need to be ruled out.

# Management: Treatment

- Supportive
- Treat the cause
- **Consult liver transplant service** : Liver transplantation remains the only definitive treatment for patients who fail to demonstrate recovery.

# Liver support systems

- Despite great early interest in liver support systems, the field has had little forward movement. Both artificial (i.e., sorbent-based) and bio-artificial (i.e., cell-based) systems have been tested. There has been no good evidence that any artificial support system reliably reduces mortality in the setting of ALF.
- Currently available liver support systems are not recommended outside of clinical trials; their future in the management of acute liver failure remains unclear.



# Prognosis

- To date, it often remains difficult to predict which ALF patients will ultimately require transplantation.
- The model for end-stage liver disease (MELD) score, have not improved our accuracy. not found to be superior to that of the INR or the King's College Hospital criteria.
- Etiology of ALF provides one of the best indicators of prognosis:
  - ❑ **Acetaminophen toxicity or ischemic hepatopathy**, both of which have good initial recovery rates.
  - ❑ **Etiology with poor prognosis:**
    - Idiosyncratic drug injury
    - Mushroom poisoning
    - Budd-Chiari syndrome
    - Autoimmune hepatitis
    - Wilson disease
    - Indeterminate cause

# Acetaminophen hepatotoxicity

- It is suggested by historic evidence for excessive ingestion either as an
  - ✓ intended suicidal overdose or
  - ✓ the inadvertent use of supratherapeutic quantities of pain medications.
- It is a dose-related toxin;
  - ✓ most ingestions leading to ALF exceed 10 gm/day.
  - ✓ However, severe liver injury can occur rarely when doses as low as 3-4 gm/day are taken.
- Very high aminotransferase levels are typically seen;
  - ✓ serum levels exceeding 3,500 IU/L are highly correlated with acetaminophen poisoning and
  - ✓ should prompt consideration of this etiology even when historic evidence is lacking.
- Acetaminophen is the leading cause of ALF (at least in the United States and Europe) and there is an available antidote, acetaminophen levels should be drawn in all patients presenting with ALF.

# Acetaminophen Hepatotoxicity Management

- Activated charcoal:

- useful for gastrointestinal decontamination.
- While it is most effective if given within one hour of ingestion, it may be of benefit as long as 3 to 4 hours after ingestion.

# Acetaminophen Hepatotoxicity Management

- N-acetylcysteine (NAC): Begin NAC promptly in all patients where the quantity of acetaminophen ingested, serum drug level or rising aminotransferases indicate impending or evolving liver injury.
  - ✓ NAC should be given as early as possible, but may still be of value 48 hours or more after ingestion.
  - ✓ *If administered within 12 hours & possibly ein 16 hours of acetaminophen ingestion, Chances of severe liver injury are virtually abolished*
  - ✓ Controversy exists over when to stop use of NAC, whether a standard 72-hour period is optimal or continuation until liver chemistry values have improved.
  - ✓ May be given orally or IV
  - ✓ Has few side effects occasionally (nausea and vomiting, rare urticaria or bronchospasm).
  - ✓ Allergic reactions are infrequent and are successfully treated with discontinuation, antihistamines and epinephrine if bronchospasm is present.
- 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.
- Low or absent levels of the parent compound, acetaminophen, do not rule out hepatotoxicity since the time of ingestion may be relatively remote or unknown, especially when overdose may have been unintentional or occurred over several days.

# Mushroom Poisoning

- Mushroom Poisoning (usually Amanita phalloides) may cause ALF.
- Initial history should always include inquiry concerning recent mushroom ingestion.
- There is **no available blood test to confirm the presence of these toxins**, but this diagnosis should be suspected in patients with a history of **severe gastrointestinal symptoms** (nausea, vomiting, diarrhea, abdominal cramping), which occur within hours to a day of ingestion.
- If these effects are present, it may be early enough to treat patients with gastric lavage and **activated charcoal via nasogastric tube**.
- Traditionally, very low rates of survival have been reported without transplantation.

# Drug Induced Liver Injury (DILI)

- Determination of a particular medication as the cause of ALF is a **diagnosis of exclusion**. Other causes of ALF should still be ruled out even if a drug is suspected.
- Many prescription and over-the-counter medications have been associated with acute liver injury and liver failure.
- **Most examples of idiosyncratic drug hepatotoxicity occur within the first 6 months after drug initiation**. A potentially hepatotoxic medication that has been used continually for more than 1 to 2 years is unlikely to cause de novo liver damage.
- Certain herbal preparations, weight loss agents and other nutritional supplements have been found to cause liver injury, **Classes of drugs commonly implicated include**
  1. **Antibiotics,**
  2. **NSAIDs and**
  3. **Anticonvulsants**
- Rx: **Stop suspected Meds & supportive treatment**



# Viral Hepatitis

- History?
- Acute hepatitis A ---99% self-limited, rarely cause fulminant hepatic failure –
- Acute Hepatitis B :
  - Age: Infant vs adult
  - Reactivation of chronic or inactive hepatitis B may occur in the setting of chemotherapy or immunosuppression , Nucleos(t)ide analogues should be considered for hepatitis B-associated acute liver failure and for prevention of post-transplant recurrence.
- Acute hepatitis D may occasionally be diagnosed in a hepatitis B positive individual.
- Although controversial, hepatitis C alone does not appear to cause ALF.
- Acute Hepatitis E
  - is a significant cause of liver failure in countries where it is endemic,
  - Tends to be more severe in pregnant women.
  - This virus should be considered in anyone with recent travel to an endemic area such as Russia, Pakistan, Mexico, or India.
- Herpes virus infection rarely causes ALF.
  - **Immunosuppressed patients or pregnant women** (usually in the third trimester) are at increased risk, but occurrences of herpes virus ALF have been reported in healthy individuals.
  - Liver biopsy is helpful in making the diagnosis.
  - Treatment: Acyclovir

# Wilson's Disease

- is an uncommon cause of ALF
- Early identification is critical because the fulminant presentation of Wilson disease is considered to be uniformly fatal without transplantation.
- Usually in young patients. :
- Finding support the diagnosis:
  - Coombs negative hemolytic anemia
  - Low ALP
- To exclude Wilson disease one should obtain:
  1. Serum ceruloplasmin
  2. 24hr urinary copper levels,
  3. slit lamp examination for Kayser-Fleischer rings,
  4. Liver Biopsy: to assess hepatic copper levels if feasible

# Autoimmune Hepatitis

- Work up for Diagnosis:
  - Auto-immune markers & IgG
  - Liver biopsy is recommended when autoimmune hepatitis is suspected as the cause of ALF, and autoantibodies are negative.
- Treatment: Steroids, Azathioprine

# Acute Fatty Liver of Pregnancy/HELLP Syndrome

- Expeditious delivery of the infant is recommended.
- Recovery is typically rapid after delivery, and supportive care is the only other treatment required.
- Transplantation may need to be considered if hepatic failure does not resolve quickly following delivery.
- Generally confined to the last trimester.
- Features of pre-eclampsia such as hypertension and proteinuria are common.

# Acute Ischemic Injury

- A syndrome often referred to as “shock liver” may occur after cardiac arrest, any period of significant hypovolemia/hypotension, or in the setting of severe congestive heart failure.
- Long-term outcome depends on the underlying cardiac process.
- Rx: supportive

# Budd-Chiari Syndrome

- The Budd-Chiari syndrome (acute hepatic vein thrombosis) can also present as ALF.
- Abdominal pain, ascites and striking hepatomegaly are often present.
- **Diagnosis: should be confirmed with hepatic imaging studies** (computed tomography, Doppler ultrasonography, venography, magnetic resonance venography).
- Overall, the prognosis in this condition is poor if hepatic failure is present, and transplantation may be required as opposed to venous decompression .



# Malignant Infiltration

- 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 .
- Malignant infiltration of the liver may cause ALF.
- Diagnosis should be made by biopsy.
- Acute severe hepatic infiltration occurs with breast cancer, small cell lung cancers, lymphoma, melanoma, and myeloma.

# Indeterminate Etiology

- When the etiology of ALF cannot be determined after routine evaluation, biopsy using a trans-jugular approach may be helpful in diagnosing
  - Malignant infiltration,
  - Autoimmune hepatitis,
  - Certain viral infections and
  - Wilson disease.
- Lack of a clear diagnosis suggests that the history may have been **inadequate regarding toxin or drug exposures.**

# ICU Management

- Monitor for
  - *Hypoglycemia*
  - *Encephalopathy & Cerebral edema*
  - *Coagulopathy +/- DIC → daily INR/PTT, Give vit K*
  - *Infection — daily pan-culture & low threshold to for ABx*
  - *MOF: renal failure, hemodynamic collapse.*

# CNS

- Encephalopathy
- Cerebral edema & ICH
- Seizures increase ICP, and must be promptly controlled with
  - Phenytoin
  - Short-acting benzodiazepines should be administered in phenytoin-refractory cases.
  - Prophylactic phenytoin is not recommended

# Hepatic Encephalopathy

- Frequent neurological assessments should be performed.
- Transfer to an ICU should occur promptly if the level of consciousness declines.
- Head imaging with computerized tomography (CT) may be used to exclude other causes of decline in mental status such as intracranial hemorrhage.
- Sedation is to be avoided, if possible; unmanageable agitation may be treated with short-acting benzodiazepines in small doses.
- Lactulose may be used either orally or rectally.
- As patients progress to severe encephalopathy, intubation and mechanical ventilation are mandatory.
- The occurrence of cerebral edema and ICH in ALF is related to the severity of hepatic encephalopathy. Cerebral edema is seldom observed in patients with grade I-II encephalopathy, but increases to 25% to 35% with progression to grade III, and 65% to 75% or more in patients reaching grade IV coma.

# ICH

- **Intracranial pressure monitoring** is recommended in ALF patients with high grade hepatic encephalopathy, in patients awaiting and undergoing liver transplantation.
- In the absence of ICP monitoring, **frequent (hourly) neurological evaluation is recommended** to identify early evidence of intracranial hypertension (III).
- The pathogenic mechanisms leading to the development of cerebral edema and intracranial hyper-tension in ALF are not entirely understood.

# Infection

- All ALF patients are at risk for bacterial or fungal infection, which may preclude liver transplantation or complicate the post-operative course.
- 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)
- 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

# Coagulopathy

- The synthesis of coagulation factors is universally decreased, while consumption of clotting factors and platelets also may occur
- In the absence of bleeding, it is not advisable to correct the INR with plasma, since clinically significant blood loss is rare and correction obscures trends in the INR, an important marker of prognosis.
- 
- Vitamin K (5-10 mg subcutaneously) should be administered routinely, since vitamin K deficiency has been reported in patients with ALF.



# Thrombocytopenia

- Replacement therapy for thrombocytopenia and/or prolonged prothrombin time is recommended only in the setting of
  1. hemorrhage or
  2. prior to invasive procedures or
  3. PLT < 10,000.
- Experience in patients without ALF suggests that platelet counts of 10,000/mm<sup>3</sup> are generally well tolerated. When invasive procedures must be performed in patients with ALF, platelet counts of 50-70,000/mm<sup>3</sup> have been considered adequate.
- Patients who develop significant bleeding with platelet levels below approximately 50,000/mm<sup>3</sup> should generally be transfused with platelets provided no contraindication (such as thrombotic thrombocytopenic purpura or heparin-induced thrombocytopenia).

# Portal hypertension

- Although portal hypertension occurs in acute liver injury due to architectural collapse of the liver, bleeding from esophageal varices almost never occurs.

# Hemodynamic (hypotension)

- Hemodynamic derangements occur frequently in patients with ALF and contribute
  1. Peripheral tissue oxygenation and
  2. Multi-organ system failure.
- The fundamental hemodynamic abnormality in ALF, similar to cirrhosis or sepsis, is low systemic vascular resistance.

- Renal failure
- Respiratory failure

- $Q_s$