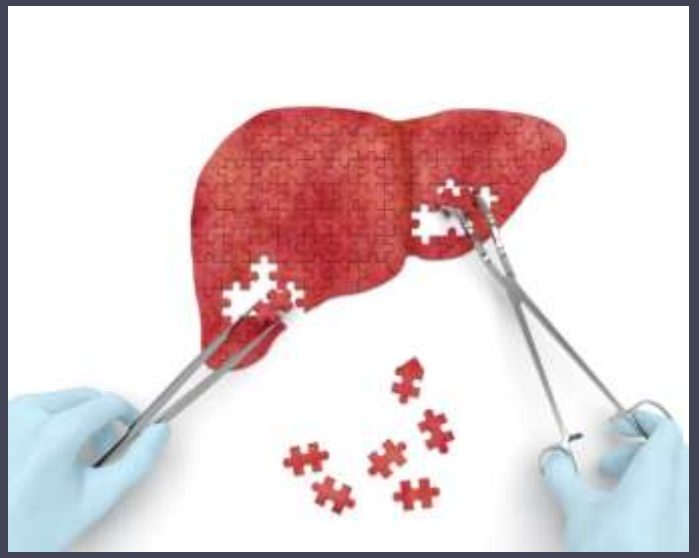

Acute liver failure

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Introduction

Acute liver failure (ALF) is a rare but a life-threatening condition. ALF causes severe injury and massive necrosis of hepatocytes resulting in severe liver dysfunction that can lead to multi-organ failure and death.

It can occur in patients without preexisting liver disease and cause rapid deterioration of liver function within days. Patients with ALF are almost always managed in an intensive care unit and in some cases need a liver transplantation to prevent death.

Definition

ALF is defined as the occurrence of coagulopathy (INR greater than 1.5) and altered mental status (encephalopathy) in an individual without pre-existing cirrhosis and with a duration of less than 26 weeks of liver disease.

Incidence

- Rare, but with high mortality without transplantation (30 – 80%)
- Estimate: 1 – 6 cases/million inhabitants/year
- More common in women (especially post-paracetamol intoxication)
- In Europe and the USA, is the No. 1 cause of poisoning

Classification

O'Grady and colleagues classify ALF into 3 categories based on the interval between the development of jaundice and the onset of encephalopathy.

1. Hyperacute liver failure: the onset of encephalopathy less than 7 days after the development of jaundice.
2. Acute liver failure: the onset of encephalopathy 8 to 28 days after the development of jaundice.
3. Sub-acute liver failure: the onset of encephalopathy more than 5 weeks but less than 12 weeks after the development of jaundice.

This classification may help to inform the etiology of the liver failure.

For example, hyperacute liver failure is usually from acetaminophen toxicity or viral infections, while subacute liver failure is usually caused by an idiosyncratic drug-induced liver injury, autoimmune hepatitis or Wilson's disease.

However, the classification does not have a prognostic significance that is distinct from the etiology of the illness itself.

Etiology

Drug-induced Liver injury

- Acetaminophen (Paracetamol)
- Antibiotics: amoxicillin-clavulanate, ciprofloxacin, nitrofurantoin, minocycline, dapsone, doxycycline, trimethoprim-sulfamethoxazole, efavirenz, didanosine, abacavir
- Anti-epileptics: valproic acid, phenytoin, carbamazepine
- Anti-tuberculosis drugs: isoniazid, rifampin-isoniazid, pyrizinamide
- Miscellaneous: propylthiouracil, amitryptiline, statins, amiodarone, methotrexate, methyldopa
- NSAID: Diclofenac, ibuprofen, indomethacin, naproxen
- Herbs: ma huang, kava kava, herbalife

Etiology

- Acetaminophen

Hepatotoxicity is the most common cause of ALF in the U.S. and Western Europe.

It results from excessive ingestion of acetaminophen either from suicidal ideations or inadvertent use of supratherapeutic doses for pain control.

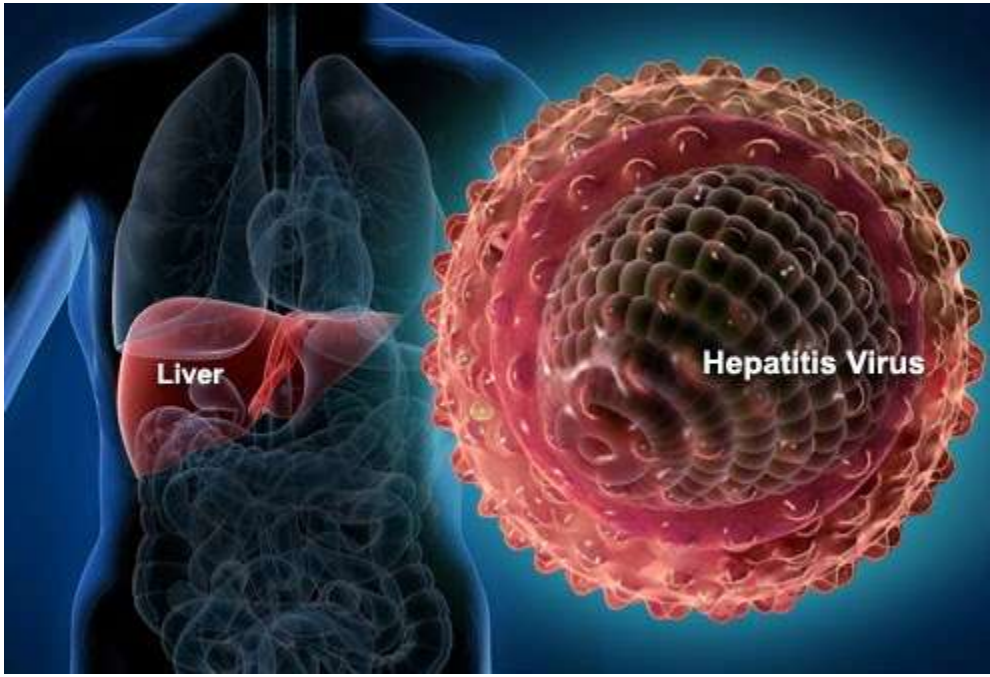
Hepatic toxicity from acetaminophen is due to increased production of the toxic metabolite N-acetyl-p-benzoquinoneimine.

Acetaminophen toxicity is dose related with typically at least 10 gram/day required to cause ALF; however, patients with history of chronic alcohol abuse and who are on concomitant cytochrome P450 enzyme inducing drugs are at increased risk of developing acetaminophen toxicity at substantially lower acetaminophen doses.

Etiology

- **Viral hepatitis**

Hepatitis A, B, C and E
Citomegalovirus,
Epstein – Barr Virus,
Herpes virus,
Varicella zoster virus



Etiology

- **Pregnancy specific liver diseases**

Acute fatty liver of pregnancy
HELLP syndrome
Preeclampsia-associated liver diseases

Etiology

Toxin related hepatotoxicity

- amanita phalloides
- mushroom toxin
- cyanobacteria toxin
- organic solvents
- yellow phosphorus

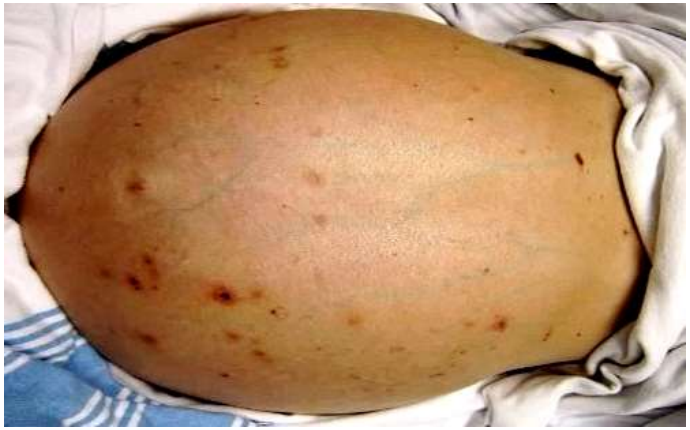
Etiology

Metabolic causes

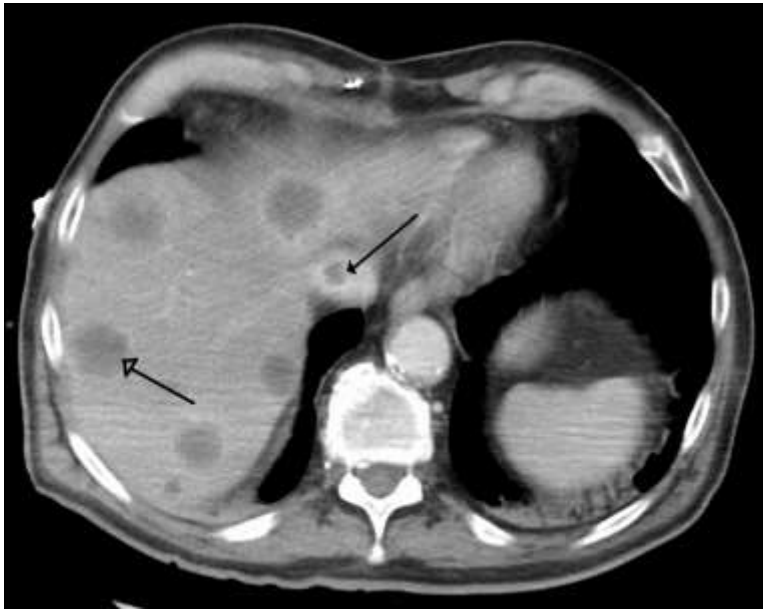
- Alpha 1-antitrypsin deficiency
- Fructose intolerance
- Galactosemia
- Reye syndrome (fatty liver and encephalopathy)
- Wilson disease (copper accumulation)

Etiology

Vascular causes



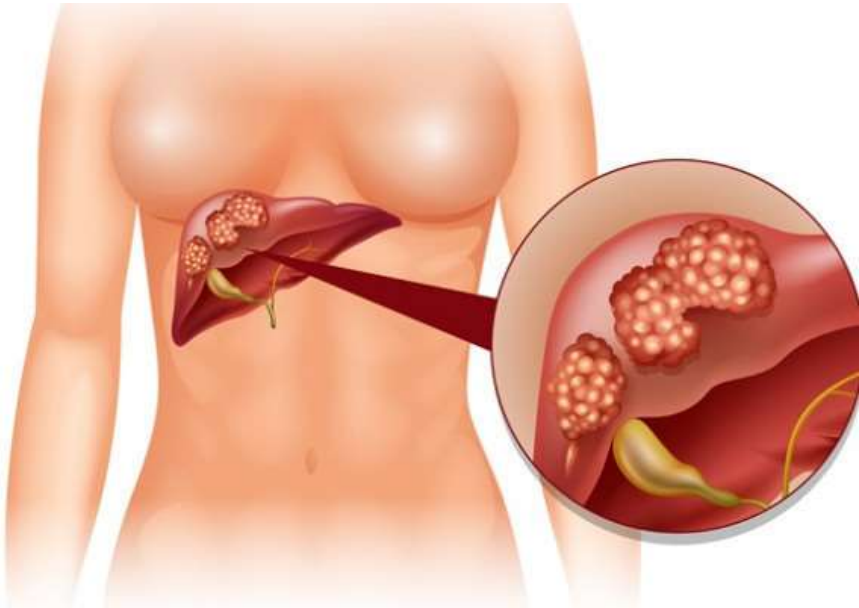
- Ischemic hepatitis/shock liver - liver injury caused by insufficient blood flow
- Budd Chairi syndrome occlusion of hepatic veins that drains liver
- portal vein thrombosis blockage or narrowing of the portal vein



Etiology

Malignancies

- Primary liver tumour (hepatocellular carcinoma)
- Secondary tumour includes hepatic metastasis or breast and lung cancer



Pathophysiology

Massive hepatocyte necrosis

- Sudden loss of > 50 – 70% of functional liver mass

- Rapid loss of essential liver functions:
  - ✓ Detoxification (↑ ammonia, toxins)
  - ✓ Synthesis (↓ clotting factors, albumin, glucose)
  - ✓ Metabolic regulation

Critical pathophysiological issue

Hepatic encephalopathy

- ↑ Ammonia → astrocytic dysfunction → cerebral edema
- Neurotransmitter imbalance: GABA ↑, glutamate ↓

Severe coagulopathy

- ↓ factors V, VII, X, fibrinogen
- INR ≥ 1.5 = *diagnostic criterion*

Circulatory instability

- Systemic vasodilation, hypotension
- Sepsis – like: systemic inflammatory syndrome

Critical pathophysiological issue

Metabolic disorders

- Hypoglycemia
- Metabolic acidosis with increased anion gap
- Hyperlactatemia

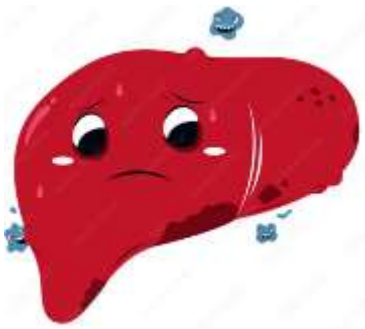
Cerebral edema and intracranial hypertension

- Major risk in hyperacute forms (paracetamol)

Hepatorenal syndrome

- Renal vasoconstriction → oligoanuria
- Poor response to fluids

Clinical manifestation



General symptoms (onset)

- Sudden onset of jaundice
- Nausea, vomiting, intense asthenia
- Abdominal pain (right hypochondrium), hepatomegaly

Hepatic encephalopathy

- Progressive alteration of mental status: confusion → drowsiness → hepatic coma
- Asterixis
- ↑ Plasma ammonia
- Major risk of cerebral edema and intracranial hypertension

Coagulation disorders

- INR ≥ (without anticoagulant treatment)
- Thrombocytopenia
- Echimoses, spontaneous bleeding (gingival, GI, intracranial)

Diagnosis

Diagnostic criteria

1. Coagulopathy INR ≥ 1.5
2. Hepatic encephalopathy
3. Absence of known chronic liver disease
4. Onset of symptoms: < 26 weeks from jaundice

Diagnosis

Liver function:

- AST/ALT very high
- Total bilirubin ↑
- Alkaline phosphatase, albumin ↓

Coagulation:

- INR, TTP ↑
- Fibrinogen ↓
- D – dimers ↑

Metabolism

- Glicemie ↓
- Amoniac ↑
- Lactat ↑
- Electroliți: hiponatremie, hipokaliemie

Insuficiență renală

- Uree/creatinină ↑
- Ionograma urinară

Diagnosis

Etiological investigations

- Viral serologies: HBV, HCV, VHS, CMV, EBV
- Toxicology: paracetamol, drugs, fungi
- Autoimmunity: ANA, ASMA, IgG
- Ceruloplasmin, Simple copper (Wilson's disease)
- Hepatic ultrasound/Doppler (thrombosis, Budd-Chiari)

Imaging and neurology

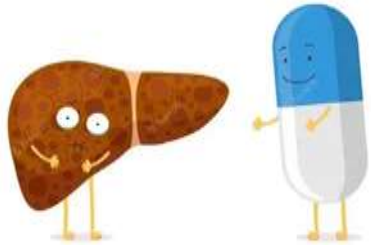
- CT/MRI brain: cerebral edema
- EEG: metabolic encephalopathy
- CT/abdominal ultrasound: liver size, vascular flow

Management

Therapy of ALF consist of

- general supportive measures,
- specific therapies for some of the etiologies,
- liver transplantation
- other methods of temporary liver support

Etiologic treatment



Etiology	Treatment
Acetaminophen overdose	Oral doses of N-acetylcysteine: attack dose of 140 mg/kg followed by 70 mg/kg every 4 hours, up to 15-20 doses I/v doses of NAC: attack dose of 150 mg/kg followed by an infusion at a rate of 12.5 mg/kg/hour for 4 hours, then the infusion rate is reduced to 6.25 mg /kg /hour .
Poisonous mushrooms	Penicillin G 1 g/kg /day and NAC (similar to acetaminophen overdose)
Autoimmune hepatitis	Metilprednisolon 60 mg/day
Hepatitis with herpes simplex virus	Aciclovir 30 mg/kg/day
Hepatitis B virus	Lamivudine 100-150 mg/day oral
Pregnant fatty liver / HELP	The birth of the child

Specific treatment

- *Cardiovascular system*

Manifestations: increased portal pressure, decreased venous return, peripheral vasodilation, hypotension, compensatory increase in cardiac output.

Treatment:

- Aggressive fluid resuscitation with the fluid volume often exceeding 3 litres (crystalloids, colloids).
- If the infusion treatment does not restore BP and tissue infusion, vasopressor therapy is started, the goal is a MBP of over 75 mmHg and a cerebral infusion pressure of 60-80 mmHg.
- Choice agents Dopamine or Noradrenaline.

Specific treament

- *Respiratory system*

Manifestations: a severe complication is acute respiratory distress.

Treatment:

- Patients with grade III of encephalopathy will be intubated.
- When performing mechanical ventilation, large current volumes and high inspiratory pressure are avoided. Will be used Current Volumes 5-6 ml/kg, plateau pressure below 30 cm water.
- Pulmonary recruitment will be performed by applying a minimal PEEP that ensures a good oxygenation.

Specific treament

- *Nervous system*

Manifestations: cerebral edema and intracranial hypertension.

The mechanisms of cerebral edema are not fully elucidated, the hypotheses being:

- ✓ increased levels of ammonium and serum glutamine, which leads to translocation of water,
- ✓ loss of self-regulation of cerebral blood flow,
- ✓ action of proinflammatory mediators, release of toxins from the liver,
- ✓ hyposodemia.

Specific treament

- *Nervous system*

Cerebral edema occurs depending on the degree of hepatic encephalopathy.

Cerebral edema occurs in patients with grade III (25-35%) and grade IV (65-75%) of the encephalopathy.

Grading of encephalopathy

Grade	Clinical signs
I	Subtle changes in level of consciousness, reduced concentration span and ability to perform simple sums.
II	Obviously drowsy but remaining awake, disoriented, slow or slurred speech, 'liver flap'(asterixis).
III	Somnolent but responds to stimulation, very confused, occasionally aggressive or violent, hypertonic, hyperreflexic, ankle clonus
IV	Comatose. Physical signs as in grade 3, or evolving into decerebrate posturing. Signs of intracranial hypertension should be sought

Specific treament

- *Nervous system*

Lactulose – theoretically, it could decrease intracerebral pressure by lowering the serum ammonia concentration, but recent studies have not shown a significant improvement in neurological status or increased survival. It also causes abdominal distension, which could cause technical difficulties during liver transplantation.

Specific treament

- *Nervous system*

Mannitol. It is administered for the treatment of episodes of intracranial hypertension in bolus 0.5-1 g/kg, which can be repeated if necessary, following that the serum osmolarity does not exceed 320 mosm/l. Mannitol will not be used prophylactically and in the long term.

Hyperventilation with the decrease of $PaCO_2$ to 25-30 mm Hg induces vasospasm with decreased cerebral flow and intracerebral pressure, but the effect is short-therm. Randomized trials have not shown a reduction in the incidence of cerebral edema or increased survival in the use of prolonged hyperventilation. Cerebral vasospasm, on the other hand, can induce cerebral hypoxia.

Specific treament

- *Nervous system*

Barbiturates can be used to treat refractory intracerebral hypertension.

Posture positioning the head in the midline, with the angle of the body 20° from horizontal will aid cerebral venous outflow.

Corticosteroids used extensively for the prophylaxis and treatment of intracerebral hypertension induced by brain tumors or infections, but have been shown to be ineffective in the treatment of cerebral edema or to increase survival of patients with acute hepatic failure.

Specific treament

- *Sepsis*

Acute liver failure patients with multi-organ dysfunction are at high risk of infective complications, especially overwhelming Gram-negative and fungal sepsis. Pathogens may emerge from a patient's own microbiological flora or may be acquired from the hospital environment.

Common sites of infection include the lower respiratory tract, the urinary tract and invasive vascular access devices.

Specific treament

- *Coagulopathy*

It is one of the defining features of liver decompensation. Hepatic synthesis of coagulation factors fails and many patients also develop significant thrombocytopenia.

Bleeding may occur when invasive devices are inserted or spontaneous.

Sometimes, despite severe disturbance of the measured coagulation parameters, a state of hypercoagulation and thrombotic complications may develop (finger ischemia, portal vein thrombosis or deep vein thrombosis of the lower limbs).

A patient coagulation profile may be a marker for the severity of liver failure.

Specific treament

- *Coagulopathy*

Fresh frozen plasma will be administered only to patients with coagulopathy with documented coagulation factor deficiency, INR or partially activated thromboplastin time, in the presence of acute haemorrhage or before invasive procedures to achieve an INR value of 1.5.

Platelet it is indicated only when the platelet level is below 10,000/mm3, for invasive procedures or surgeries a higher platelet level is needed (above 50,000 / mm3).

Specific treament

- *Coagulopathy*

Vitamin K routine administration is recommended to all patients with ALF (10 mg subcutaneously).

Cryoprecipitate is indicated in case of hypofibrinogenemia (fibrinogen concentration <1 g/l).

Antifibrinolytic agents will be administered to patients with bleeding by hyperfibrinolysis confirmed by laboratory tests (increased clot lysis time)

Recombinant factor VII (40 g/kg) is indicated when the means listed above fail (in cases where laboratory indices (prothrombin time/INR) have not been normalized by administration of fresh frozen plasma, cryoprecipitate or in the presence of signs of volume overload to prevent bleeding related to invasive procedures/diagnostics (liver biopsy, monitoring of intracranial pressure).

Specific treament

- *Renal failure*

Manifestations: occurs in over 50% of patients with ALF, the causes being nephrotoxins, sepsis, hypovolemia (decreased oral water intake, translocation of water, vasodilating effect of toxins, digestive bleeding).

Treatment:

- Maintaining hemodynamic indices in the normal values.
- Avoidance of drugs with nephrotoxic action.
- Prompt identification and treatment of infections.
- Continuous veno-venous hemodialysis.

Specific treament

- *Metabolic disorders and nutrtion*

Manifestations: hypoglycemia (depletion of hepatic glycogen stores and impaired gluconeogenesis), hypokalemia, hypophosphataemia, hypomagnesemia, alkalosis, acidosis.

Treatment:

- Identification of the cause and treatment of acid-base balance disorders.
- Correction of hypokalemia, hypophosphataemia, hypomagnesaemia.
- Continuous intravenous infusion of glucose.
- Enteral or parenteral nutrition as needed.

Specific treament

- *Prophylaxis for gastrointestinal bleeding*

Treatment:

Intravenous use of H2-histamine receptor blockers (ranitidine, famotidine) or proton pump inhibitors (pantoprazole) is recommended for the prevention of gastrointestinal bleeding.

Liver transplant

It remains the only effective therapy for patients with ALF who fail to recover.

Kings College criteria are used to select the patient who should be sent to a liver transplant center.

Kings college criteria

Acetaminophen	Nonacetaminophen
pH <7.3	PT >100 s (INR >6.5)
Or all three of: Grade 3–4 encephalopathy PT >100 s (INR >6.5) Cr >3.4 mg/dL	Or any three of: Age <10 or >40 y Etiology (non-A, non-B hepatitis, halothane, drug reaction, Wilson disease) Period of transition from jaundice to encephalopathy <7 d PT >50 s (INR >3.5) Total bilirubin >17.5 mg/dL

Liver transplant

In the USA, it is performed in approximately 10% of patients with paracetamol-induced ALF and 30-50% of other etiology.

The survival of patients after one year of the transplantation is 60-80%, the cause being the presence of polyoragnic insufficiency.

Prognosis

It depends on the etiology, the degree of hepatic encephalopathy and the occurrence of complications.

Mortality from acetaminophen poisoning is 30%, viral hepatitis A 50%, other etiologies 80-100%.

Patients with grade II, III and IV of the encephalopathy have a mortality of 30%, 45-50% and over 80% respectively.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