



- What is acute liver failure:

- **It is a rapid damage of liver function –with a very high mortality rate- which will result in:**

- ✓ Coagulopathy: the liver has the central role in the synthesis of almost all coagulation factors and some inhibitors of coagulation and fibrinolysis. Hepatocellular necrosis leads to impaired synthesis of many coagulation factors and their inhibitors. The former produces a prolongation in prothrombin time which is widely used to monitor severity of hepatic injury.
- ✓ Encephalopathy: due to build-up of toxic substances such as ammonia.

- What are the causes which lead to acute liver failure?

- **Drug-related hepatotoxicity:**

- ✓ Paracetamol (acetaminophen) overdose: chronic alcohol use may greatly increase the susceptibility to hepatotoxicity from paracetamol because of depleted glutathione stores.
- ✓ Idiosyncratic drug reactions (referring to unpredictable bizarre reaction of hypersensitivity to a substance without connection to the pharmacology of the drug).
- ✓ Other drugs which might cause hepatotoxicity include the following: fluoroquinolones (moxifloxacin), antibiotics, antidepressants, antiepileptics, anesthetic agents (halothane), lipid-lowering medications, NSAIDs, immunosuppressive agents (methotrexate and cyclophosphamide) and salicylates (Reye syndrome).
- ✓ Toxins: Amanita phalloides mushroom toxin.

- **Viral hepatitis (الكبد الوبائي):**

- ✓ Most common: hepatitis A and B.
- ✓ Hepatitis D might also lead to acute liver failure as there is a co-infection with hepatitis B.
- ✓ Hepatitis E (especially in pregnant females).

- **Autoimmune hepatitis**: it is a chronic autoimmune disease of the liver that occurs when the body's immune system attacks liver cells causing the liver to be inflamed. Anomalous presentation of HLA class-II on the surface of liver cells, possibly due to genetic predisposition or acute liver infection, causes a cell-mediated immune response against the body's own liver, resulting in autoimmune hepatitis.

- **Atypical viral causes:**

- ✓ Cytomegalovirus (CMV).
- ✓ Herpes simplex virus (HSV).

- **Metabolic causes:**

- ✓ Alpha 1-antitrypsin deficiency: it is a genetic disorder that causes defective production of alpha1-antitrypsin (A1AT) leading to decreased (A1AT) activity in the blood and lungs, and deposition of excessive abnormal (A1AT) protein in liver cells.
- ✓ Hereditary fructose intolerance (HFI): it is an inborn error of fructose metabolism caused by a deficiency of the enzyme aldolase B.
- ✓ Galactosemia: a rare genetic –autosomal recessive- metabolic disorder that affects an individual's ability to metabolize the sugar galactose properly. It has three types depending on which enzyme is defected:
  - ❖ *Type-I*: galactose-1-phosphate uridyl transferase is defected → leading to classic galactosemia.
  - ❖ *Type-II*: galactokinase is defected.
  - ❖ *Type-III*: UDP galactose epimerase is defected.
- ✓ LCAT deficiency: Lecithin Cholesterol Acyltransferase Deficiency is a disorder of lipoprotein metabolism.



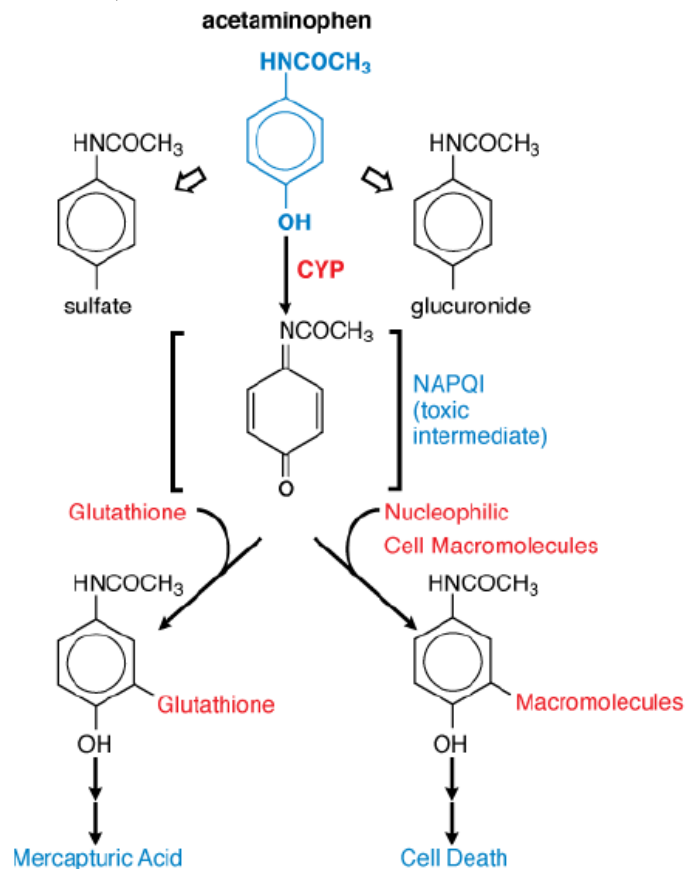
- ✓ **Reye syndrome:** it is an extremely rare rapidly progressive encephalopathy which usually begins shortly after recovery from an active viral illness. It is a potentially fatal syndrome causing damage especially to the brain and liver. It is associated with aspirin consumption by children with viral illness.
- ✓ **Tyrosinemia:** an error of metabolism, usually inborn, in which the body cannot effectively break down the amino acid tyrosine. There are three types of this disease.
- ✓ **Wilson's disease:** it is an autosomal recessive genetic disorder in which copper accumulates in tissues (one of them is the liver).

- **Malignancies:**

- ✓ Primary liver tumor.
- ✓ Secondary liver tumor (metastasis).

- **Paracetamol/acetaminophen metabolism (see the image):**

- Acetaminophen is primarily metabolized by conjugation in the liver to non-toxic, water-soluble compounds that are eliminated in the urine.
- In acute overdose of this drug (10 grams), metabolism by conjugation becomes saturated and excess acetaminophen is oxidatively metabolized by the CYP enzymes to the hepatotoxic reactive metabolite NAPQI. Notice that NAPQI is metabolized in the presence of glutathione to mercapturic acid.
- The ingested amount of acetaminophen at which toxicity may occur may be less in the setting of:
  - ✓ Chronic ethanol use.
  - ✓ Compromised nutritional states.
  - ✓ Fasting.
  - ✓ Viral illness with dehydration.
  - ✓ Co-ingestions of inducers of the activity of CYP oxidative enzymes.



- **Treatment of acetaminophen toxicity: NAC (N-acetylcysteine)**

- ✓ It is a precursor of glutathione which aims to increase the concentration of glutathione.
- ✓ It is also considered to be anti-inflammatory and antioxidant.
- ✓ Positive inotropic effect: an agent that increases the strength of muscular contractions (especially heart muscle).
- ✓ It increases local nitric oxide (NO) concentrations. Therefore, enhancing local oxygen delivery to peripheral tissues.

- **Signs and symptoms of acute liver failure:**

- **Encephalopathy:** due to accumulation of ammonia which is toxic to the brain. Therefore, resulting in altered mental function.
- **Cerebral edema (astrocyte edema):** due to increased intracranial pressure which is also associated with papilledema. Another cause may be due to accumulation of glutamine in astrocytes resulting in their swelling



- Jaundice (not always present!).
- Ascites (accumulation of fluid in the abdomen due to hepatic vein thrombosis that results in increased hydrostatic pressure → shifting fluid outside the vessels to the interstitial space).
- Right upper quadrant tenderness (the site where the liver is located).
- Hepatitis or Budd-Chiari syndrome (a condition caused by occlusion of hepatic veins that drain the liver. It presents with classic triad of abdominal pain, ascites and liver enlargement. The formation of a blood clot within the hepatic veins can lead to Budd-Chiari syndrome).
- Hematemesis (vomiting blood) or melena (blood in stool).
- Hypotension and tachycardia: due to reduced systemic vascular resistance.

- **Consequences of acute liver failure:**

- Electrolyte imbalance: represented by decreased sodium and calcium levels.
- Severe metabolic acid-base disturbances.
- Hypoglycemia.
- May give rise to renal failure (exposure of glomeruli to toxins which are supposed to be metabolized by the liver).
- Increase in blood ammonia (because of failure to convert it to urea in the liver).
- Hypoalbuminemia (resulting in edema/ascites due to decreased colloid osmotic pressure in the blood).
- Failure in the synthesis of clotting factors which results in hemorrhage.

- **Laboratory investigations of acute liver failure:**

CBC	Thrombocytopenia (reduced platelets)
Coagulation studies	PT/INR
Liver enzymes	↑ AST, ALT, ALP, GGT
Serum bilirubin	↑
Serum ammonia	↑↑↑
Serum glucose	↓
Serum lactate	↑ (often)
ABG (Arterial Blood Gas)	Hypoxemia
Serum creatinine	↑ (might be)
Serum free copper and ceruloplasmin	↓ with Wilson's disease
Serum phosphate	↓ (might be)
Acetaminophen level	-
Blood culture (if infection is suspected)	-
Viral serology	<ul style="list-style-type: none"> <li>• Hepatitis A: IgM</li> <li>• Hepatitis B: HBsAg and anticore IgM</li> <li>• Hepatitis D: IgM (if HBsAg is positive)</li> <li>• Cytomegalovirus.</li> <li>• Herpes simplex virus.</li> </ul>
Autoimmune markers	ANA and immunoglobulins
EEG	-
Intracranial pressure monitoring	-
Liver biopsy	-
Hepatic ultrasonography	-
Abdominal CT/ cranial CT scanning	-

- **Management of acute liver failure:**

- **Intensive care support:**
  - ✓ Protection of the airway.
  - ✓ Specific therapy (example: antidotes).
  - ✓ Patient's fluid management and hemodynamics.
  - ✓ Monitor their metabolic parameters.
  - ✓ Assess for infection.
  - ✓ Maintain nutrition.
  - ✓ Recognize GI bleeding.



- **Medications:**
  - ✓ Antidotes (e.g. activated charcoal, NAC).
  - ✓ Osmotic diuretics (e.g. mannitol).
- **Surgery:**
  - ✓ Liver transplantation (definitive treatment).
  - ✓ Non-biologic extracorporeal liver support systems: hemodialysis, hemofiltration, charcoal hemoperfusion, plasmapheresis and exchange transfusions.