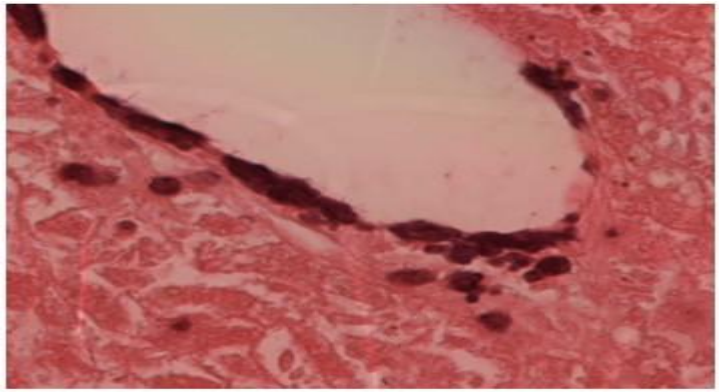
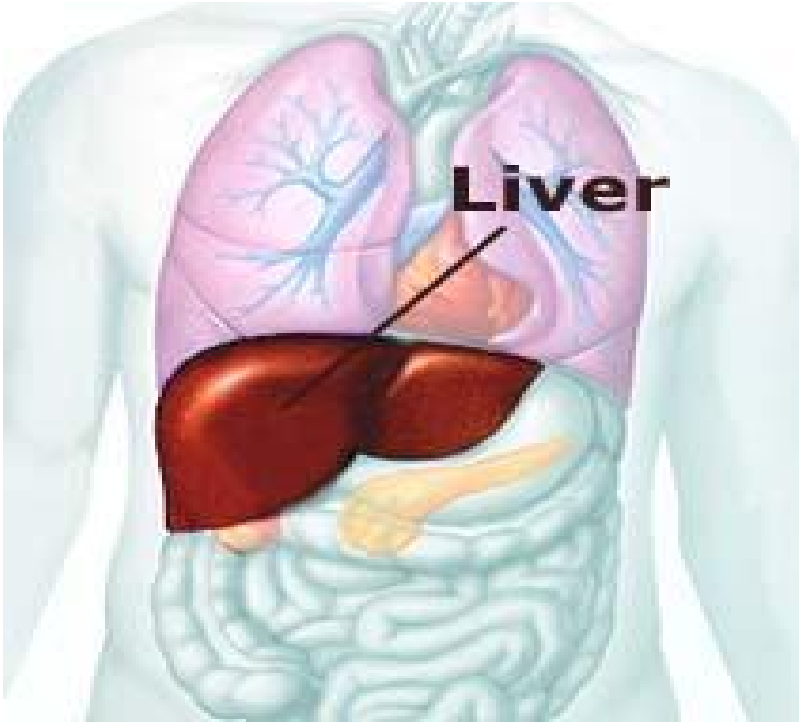
Definition



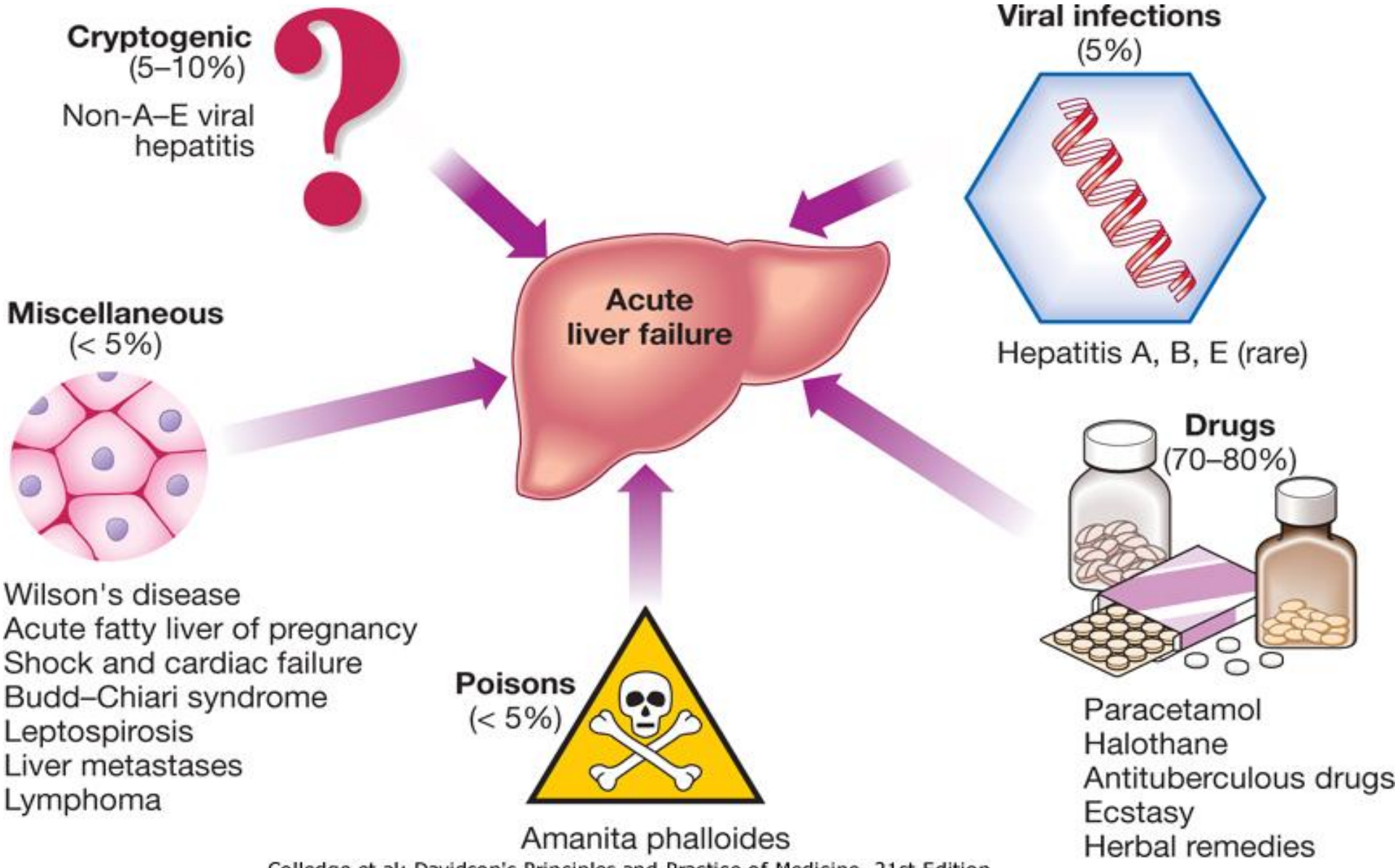
- () It is an uncommon but serious syndrome, define as a disease occurring within 8 weeks of onset of the precipitating illness, in the absence of evidence of pre-existing liver disease.
- () The presentation is with mental changes progressing from confusion to stupor and coma, and a progressive deterioration in liver function.
- () This distinguishes it from instances in which hepatic encephalopathy represents adeterioration in chronic liver disease
- () Acute viral hepatitis is the most common cause world-wide, In 10% of cases the cause of acute liver failure remains unknown and these patients are often labelled as having non-A-E viral hepatitis or cryptogenic acute liver failure.

Classification

Type	Time: jaundice to encephalopathy	Cerebral oedema	Common causes
Hyperacute	< 7 days	Common	Viral, paracetamol
Acute	8-28 days	Common	Cryptogenic, drugs
Subacute	29 days-12 weeks	Uncommon	Cryptogenic, drugs



Causes



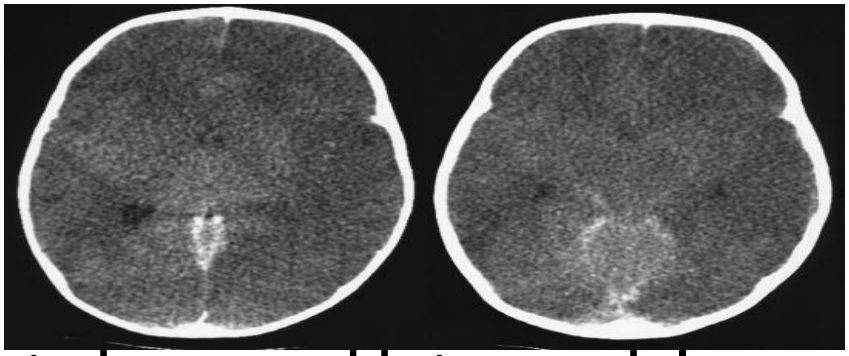
Various Causes of ALF

Cause	Examples	Comment
Drugs and Toxins	❖ Acetaminophen ❖ Amanita phalloides ❖ Isoniazid ❖ Halothane	Acetaminophen poisoning is the overall leading cause of ALF in the US
Viral Infection	❖ Hepatitis A ❖ Hepatiis B (+/-D) ❖ Hepatitis E ❖ Herpes simplex virus	Hepatitis C is a very rare cause of ALF
Vascular problems	❖ Shock ❖ Heat stroke ❖ Tumor infiltrating the liver	Most often seen after cardiac arrest, major blood loss, or iatrogenic ligation of the major blood vessels feeding the liver
Metabolic/Miscellaneous	❖ Wilson Disease ❖ Acute fatty liver of pregnancy ❖ Alpha-1 antitrypsin deficiency ❖ Autoimmune hepatitis	Family screening is appropriate for many metabolic/genetic causes of ALF
Indeterminate	❖ Unknown	Approximately 15%-20% of adult ALF cases, and up to 50% of ALF in children, cannot be attributed to a specific cause.

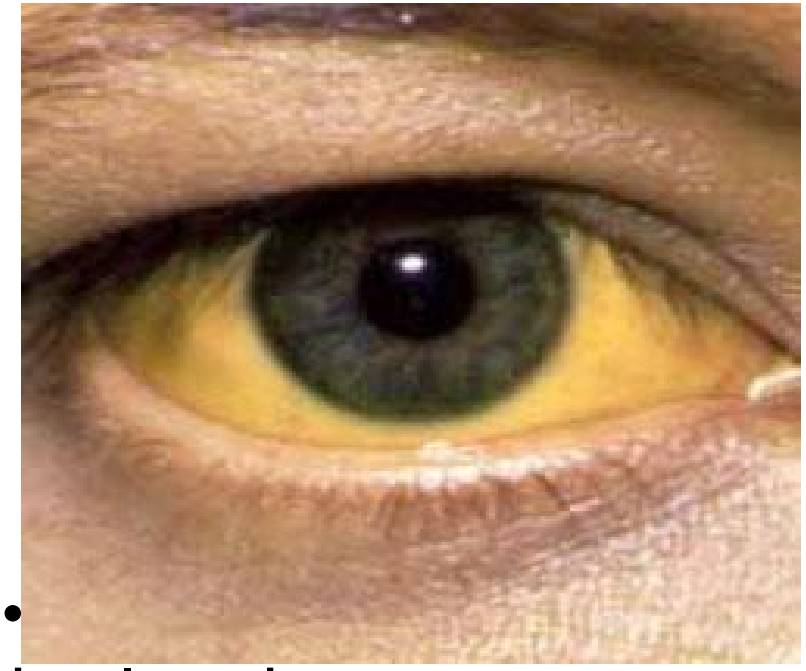
Clinical assessment

() cerebral disturbance (hepatic encephalopathy) is the cardinal feature of acute liver failure:

- *Grade 1:* Poor concentration, slurred speech, slow mentation, disordered sleep rhythm
- *Grade 2*: Drowsy but easily rousable, occasional aggressive behaviour, lethargic
- *Grade 3:* Marked confusion, drowsy, sleepy but responds to pain and voice, gross disorientation
- *Grade 4:* Unresponsive to voice, may or may not respond to painful stimuli, unconscious

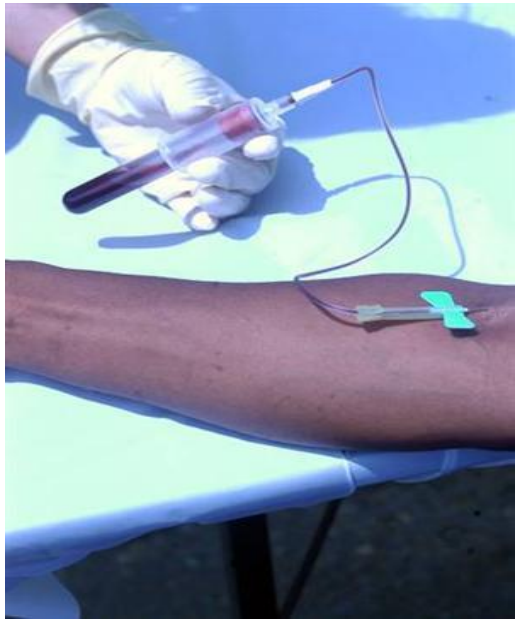


- (*)Cerebral oedema may occur due to increased intracranial pressure causing unequal or abnormally reacting pupils, fixed pupils, hypertensive episodes, bradycardia, hyperventilation, profuse sweating, local or general myoclonus, focal fits or decerebrate posturing.
- (*)Papilloedema occurs rarely and is a late sign.
- (*)More general symptoms include weakness, nausea and vomiting.
- (*)Right hypochondrial discomfort is an occasional feature.
- (*)The patient is usually jaundiced, except in Reye's syndrome when jaundice is rare.



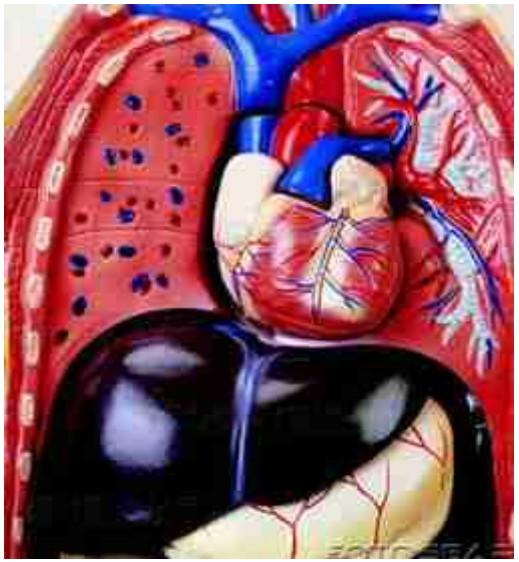
- (*)Occasionally, death may occur in fulminant cases of acute liver failure before jaundice develops.
- (*)Fetor hepaticus can be present.
- (*) The liver is usually of normal size but later becomes smaller.
- Hepatomegaly is unusual and, in the presence of a sudden onset of ascites, suggests venous outflow obstruction as the cause (Budd-Chiari syndrome).
- (*) Splenomegaly is uncommon and never prominent.
- (*)Ascites and oedema are late developments and may be a consequence of fluid therapy.

Investigations

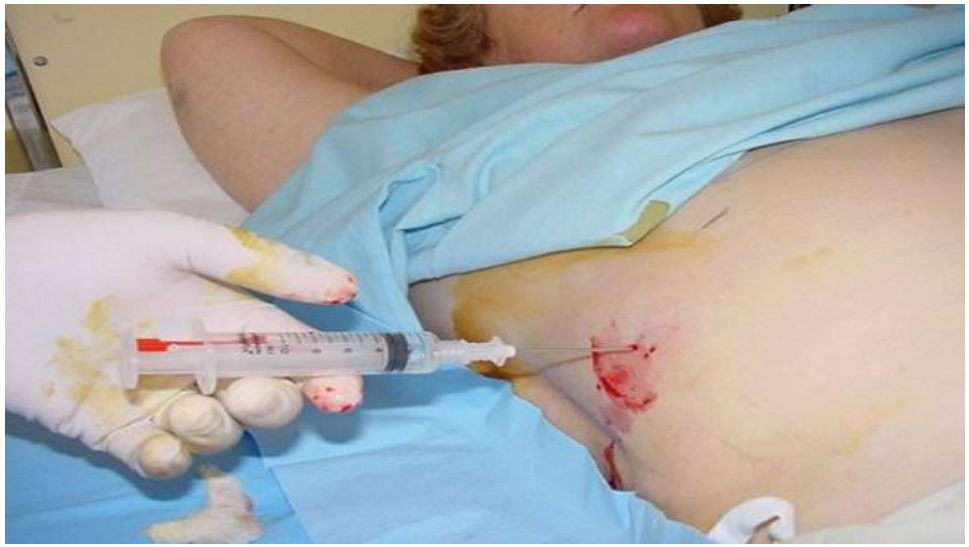


- Toxicology screen of blood and urine
- HBsAg, IgM anti-HBc
- IgM anti-HAV
- Anti-HEV, HCV, cytomegalovirus, herpes simplex, Epstein-Barr virus
- Ceruloplasmin, serum copper, urinary copper, slit-lamp eye examination
- Autoantibodies: ANF, ASMA, LKM
- Immunoglobulins
- Ultrasound of liver and Doppler of hepatic veins

- () Hepatitis B core IgM antibody is the best screening test for acute hepatitis B infection, as liver damage is due to the immunological response to the virus which has often been eliminated and the test for HBsAg may be negative.
- () The prothrombin time rapidly becomes prolonged as coagulation factor synthesis fails; this is the laboratory test of greatest prognostic value and should be carried out at least twice daily.
- () Factor V levels can be used instead of the prothrombin time to assess the degree of liver impairment.



- () The plasma bilirubin reflects the degree of jaundice.
- () Plasma aminotransferase activity is particularly high after paracetamol overdose, reaching 100-500 times normal, but falls as liver damage progresses and is not helpful in determining prognosis.
- () Plasma albumin remains normal unless the course is prolonged.
- () Percutaneous liver biopsy is contraindicated because of the severe coagulopathy, but biopsy can be undertaken using the transjugular route.



Adverse prognostic criteria in acute liver failure

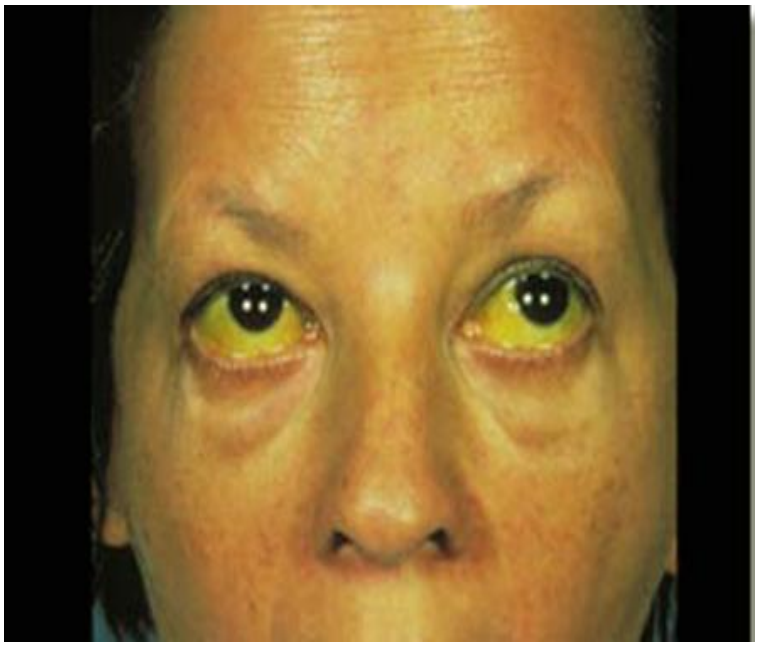
()Paracetamol cases

- H^+ > 50 nmol/L (pH < 7.3) at or beyond 24 hours following the overdose
  or
- Serum creatinine > 300 μmol/L (≅ 3.38 mg/dL) *plus* prothrombin time > 100 seconds *plus* encephalopathy grade 3 or 4

() Non-paracetamol cases

- Prothrombin time > 100 seconds
  or
- Any three of the following:
  - Jaundice to encephalopathy time > 7 days
  - Age < 10 or > 40 years
  - Indeterminate or drug-induced causes
  - Bilirubin > 300 μmol/L (≅ 17.6 mg/dL)
  - Prothrombin time > 50 seconds

  or
- Factor V level < 15% and encephalopathy grade 3 or 4



Managment

- () Patients with acute liver failure should be treated in intensive care unit as soon as progressive prolongation of the prothrombin time occurs or hepatic encephalopathy is identified .
- *()* *N*-acetylcysteine therapy may improve outcome, particularly in patients with acute liver failure due to paracetamol poisoning.
- ()Liver transplantation is an increasingly important treatment option for acute liver failure,
- Survival following liver transplantation for acute liver failure is improving, and 1-year survival rates of about 60% can be expected.

Monitoring in acute liver failure

Neurological

- Intracranial pressure monitoring
- Conscious level

Cardiorespiratory

- Pulse
- Blood pressure
- Central venous pressure
- Respiratory rate

Fluid balance

- Hourly output (urine, vomiting, diarrhoea)
- Input: oral, intravenous

Blood analyses

- Arterial blood gases
- Peripheral blood count (including platelets)
- Sodium, potassium, HCO^{3-}, calcium, magnesium
- Creatinine, urea
- Glucose (2-hourly in acute phase)
- Prothrombin time

Infection surveillance

- Cultures: blood, urine, throat, sputum, cannula sites
- Chest X-ray
- Temperature

Complications of acute liver failure

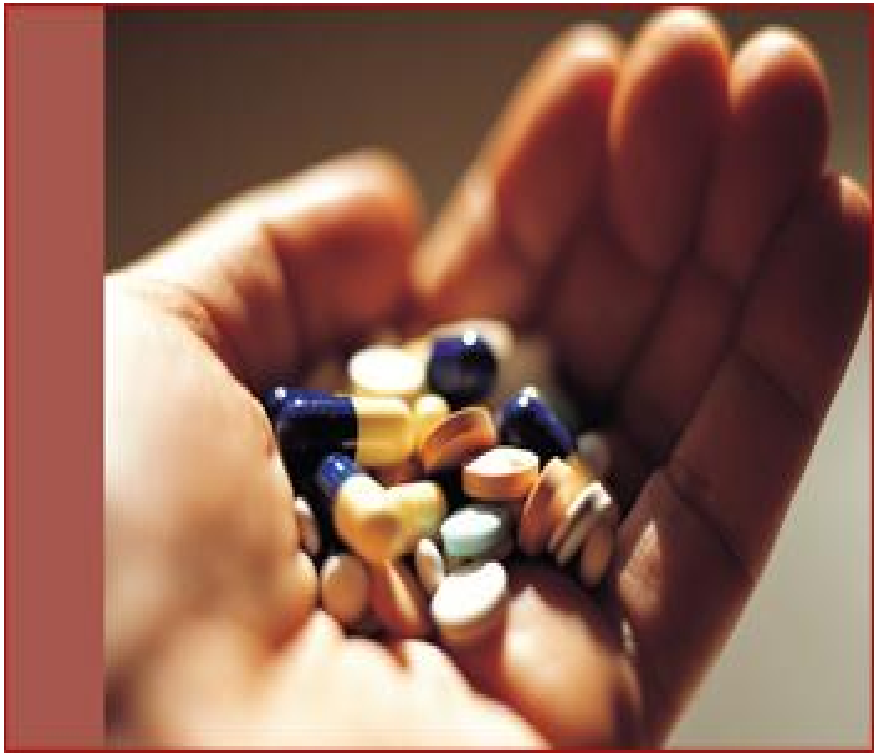
- Encephalopathy and cerebral oedema
- Hypoglycaemia
- Metabolic acidosis
- Infection (bacterial, fungal)
- Renal failure
- Multi-organ failure (hypotension and respiratory failure)

DRUGS, TOXINS AND THE LIVER

- () The liver is the primary site of drug metabolism
- () the most common picture is of a mixed cholestatic hepatitis.
- () The presence of jaundice indicates more severe liver damage.
- () Although acute liver failure can occur, most drug reactions are self-limiting and chronic liver damage is rare.
- () Abnormal LFTs often take weeks to normalise following a drug-induced hepatitis, and it may take months for them to normalise following a cholestatic hepatitis.
- () Occasionally permanent bile duct loss (ductopenia) follows a cholestatic drug reaction, such as that due to co-amoxiclav, resulting in chronic cholestasis with persistent symptoms such as itching.

Factors influencing drug induced hepatotoxicity

1- Age
2- Ethnicity and race
3-Gender
4-Nutritional status
5-Underlying liver disease
6-Renal function
7-Pregnancy
8- Duration and dosage of drug
9-Enzyme induction
10-Drug-to-drug interaction



diagnosis

- Tabulate drugs taken
  - Prescribed
  - Self-administered
- Establish if reported hepatotoxicity in the literature
- Relate time drugs taken to onset of illness
  - 4 days-8 weeks (usual)
- Effect of stopping drugs on normalisation of liver biochemistry
  - Hepatitic LFTs (2 months)
  - Cholestatic/mixed LFTs (6 months)
- Exclude other causes
  - Viral hepatitis
  - Biliary disease
- Consider liver biopsy ：A liver biopsy should be considered if there is suspicion of pre-existing liver disease or if blood tests fail to improve when the suspect drug is withdrawn.

Types of liver injury

1- Cholestasis

- Pure cholestasis (selective interference with bile flow in the absence of liver injury) can occur with oestrogens; this was seen quite frequently when high concentrations of oestrogens (50 μg/day) were used as contraceptives. Both the current oral contraceptive pill and hormone replacement therapy can be safely used in chronic liver disease.
- Chlorpromazine and antibiotics such as flucloxacillin are examples of drugs that cause cholestatic hepatitis, which is characterised by inflammation and canalicular injury.
- Co-amoxiclav is the most common antibiotic to cause abnormal LFTs but, unlike other antibiotics, it may not produce symptoms until 10-42 days after it is stopped.
- Anabolic steroids used by body-builders may also cause a cholestatic hepatitis.
- In some cases (e.g. NSAIDs and COX-2 inhibitors) there is overlap with acute hepatocellular injury.

2- Hepatocyte necrosis :

- Many drugs cause an acute hepatocellular necrosis with high serum transaminase concentrations; paracetamol is the best known. Inflammation is not always present but does accompany necrosis in liver injury due to diclofenac (an NSAID) and isoniazid (an anti-tuberculous drug).
- Recreational drugs, including cocaine and ecstasy, can also cause severe acute hepatitis. Ex : Allopurinol, Amiodarone HAART, NSAID

3- mixed: neither aminotransferase nor alkaline phosphatase elevations are clearly predominant. Symptoms may also be mixed. Drugs such as phenytoin, Amitryptyline,Enalapril, Carbamazepine Sulfonamide

Type of injury:	Hepatocellular	Cholestatic	Mixed
• ALT	≥ Twofold rise	Normal	≥ Twofold rise
• ALP	Normal	≥ Twofold rise	≥ Twofold rise
• ALT: ALP ratio	High, ≥5	Low, ≤2	2-5

4- Steatosis :

- Microvesicular hepatocyte fat deposition, due to direct effects on mitochondrial beta-oxidation, can follow exposure to tetracyclines and sodium valproate
- Macrovesicular hepatocyte fat deposition has been described with tamoxifen, and amiodarone toxicity can produce a similar histological picture to NASH.

5- Vascular/sinusoidal lesions :

- Drugs such as alkylating agents used in oncology can damage the vascular endothelium and lead to hepatic venous outflow obstruction.
- Chronic overdose of vitamin A can damage the sinusoids and trigger local fibrosis that can result in portal hypertension.

6- Hepatic fibrosis :

- Most drugs cause reversible liver injury and hepatic fibrosis is very uncommon.
- Methotrexate, however, as well as causing acute liver injury when it is started, can lead to cirrhosis when used in high doses over a long period of time. Risk factors for drug-induced hepatic fibrosis include pre-existing liver disease and a high alcohol intake.

7- Neoplasms:

- Neoplasms have been described with prolonged exposure to some medications or toxins.
- Hepatocellular carcinoma, angiosarcoma, and liver adenomas are the usually reported.
- Causes: Vinyl chloride, combined oral contraceptive pill, anabolic steroid, arsenic, thorotrast

8- Drug-induced hepatic granulomas are usually associated with granulomas in other tissues and patients typically have features of systemic vasculitis and hypersensitivity.

- Causes: Allopurinol, phenytoin, isoniazid, quinine, penicillin, quinidine