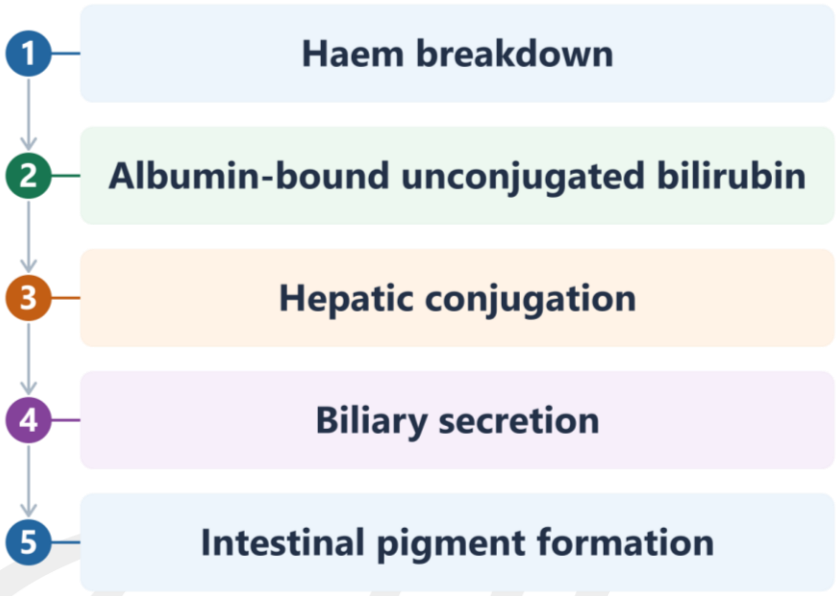
Pathology - Topic 24 - Hepatobiliary system

Bilirubin Metabolism

- Bilirubin metabolism converts haem breakdown products into forms that can be transported, processed by the liver and excreted.

Production, Conjugation and Excretion



1. Haem Breakdown and Plasma Transport

- Most bilirubin comes from the breakdown of haem in ageing red cells, with a smaller contribution from other haem proteins and ineffective erythropoiesis.
- Macrophages convert haem to biliverdin and then to **unconjugated bilirubin**.
  - Unconjugated bilirubin is poorly water soluble and travels in plasma bound to albumin.

2. Hepatic Conjugation and Biliary Excretion

- Hepatocytes take up bilirubin and conjugate it with glucuronic acid using UGT1A1.
  - Conjugation increases water solubility and permits active secretion into bile.

3. Intestinal Conversion and Pigment Excretion

- Intestinal bacteria convert conjugated bilirubin into urobilinogen and related pigments.
  - Most pigment leaves in stool, while some is reabsorbed and a small amount is excreted in urine.

Urine, Stool and Direct-bilirubin Interpretation

- Unconjugated albumin-bound bilirubin is not normally filtered into urine, while conjugated bilirubin can appear in urine when its blood concentration rises.
- Stercobilin and related pigments provide the brown colour of stool, so substantially reduced pigment delivery contributes to pale stools in complete obstruction.

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- Albumin-bound delta bilirubin can contribute to the measured direct fraction in prolonged cholestasis and persist after bile drainage improves.

Jaundice

- Jaundice is yellow discoloration of the skin and sclera caused by increased bilirubin in the blood.

Patterns of Hyperbilirubinaemia

1. Predominantly Unconjugated Hyperbilirubinaemia

- Increased bilirubin production occurs in haemolysis and ineffective erythropoiesis.
- Reduced hepatic uptake or conjugation can occur with selected drugs, neonatal immaturity and inherited conjugation disorders.
    - Gilbert syndrome causes a mild intermittent unconjugated increase, while severe UGT1A1 deficiency produces a more serious inherited syndrome.
- The urine does not usually contain bilirubin in a purely unconjugated pattern.
    - Marked unconjugated bilirubin can be dangerous in vulnerable neonates because unbound pigment can enter the brain.

2. Predominantly Conjugated Hyperbilirubinaemia

- Impaired hepatocellular secretion or obstruction to bile flow raises the conjugated fraction.
- Causes include hepatitis, intrahepatic cholestasis, bile-duct stones and obstructing tumours.
    - Dark urine may result from excretion of water-soluble bilirubin.
- Inherited canalicular excretion disorders can also produce a conjugated pattern without major hepatocellular injury.

3. Mixed Patterns

- Many hepatocellular diseases impair several bilirubin-handling steps and produce mixed direct and indirect increases.
    - The laboratory direct fraction approximates conjugated bilirubin but can include albumin-bound delta bilirubin in prolonged cholestasis.

Inherited Mechanistic Examples

1. Reduced Conjugation

- Crigler–Najjar syndromes result from severe UGT1A1 defects, with greatest neurological risk when conjugating activity is absent or nearly absent.

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2. Defective Hepatic Handling

- Dubin–Johnson syndrome causes predominantly conjugated hyperbilirubinaemia with impaired canalicular transport and characteristic dark hepatic pigmentation.
- Rotor syndrome produces a usually benign conjugated pattern through altered hepatic uptake and storage and lacks this dark pigmentation.

Obstructive and Non-obstructive Patterns

Predominant mechanism	Common biochemical pattern	Urinary bilirubin
Excess production or impaired conjugation	Predominantly unconjugated bilirubin	Usually absent
Hepatocellular injury	Mixed bilirubin; aminotransferase-predominant injury	May be present
Cholestasis or obstruction	Conjugated bilirubin; often ALP/GGT predominance	Often present

- Pale stool, dark urine and pruritus support impaired bile delivery, especially when cholestasis is substantial.
- A disproportionate ALP and GGT increase supports a cholestatic pattern, while a disproportionate ALT or AST increase supports hepatocellular injury.
    - Early acute obstruction can sometimes produce a marked aminotransferase rise, so timing matters.
- Ultrasound and other appropriate imaging assess duct dilatation, stones or masses when obstruction is suspected.
    - Biochemistry alone cannot locate the blockage or reliably distinguish every intrahepatic from extrahepatic cause.

Hepatic Failure

- Hepatic failure occurs when liver function becomes inadequate to meet metabolic, synthetic and detoxifying needs.

Acute Liver Failure Criteria

- Acute liver failure usually involves severe recent injury with coagulopathy and encephalopathy in a patient without established cirrhosis.
    - The commonly used AASLD definition requires an INR of at least 1.5 and any degree of hepatic encephalopathy, with an illness lasting less than 26 weeks and no pre-existing cirrhosis.

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- The Indian National Association for the Study of the Liver generally uses a shorter interval: encephalopathy with jaundice and coagulopathy develops within four weeks of symptom onset in a person without pre-existing liver disease.

Causes and Acute-on-chronic Deterioration

- Extensive hepatocyte necrosis or dysfunction can follow toxins, drugs, viruses, ischaemia and other causes.
- Chronic failure commonly develops in cirrhosis, where fibrosis and regenerative nodules distort tissue and vascular relationships.
    - Acute deterioration can also occur on top of chronic disease and should be assessed separately from a first acute episode.

Morphological Patterns of Severe Injury

- Microscopy may show massive or submassive necrosis in acute disease and bridging fibrosis with nodules in chronic disease.
    - The amount and distribution of injury depend on the cause and timing of the biopsy.
- Massive necrosis may leave a small soft liver with collapse of the reticulin framework; surviving hepatocytes may proliferate at the edges of viable regions.

Major Clinical Consequences

Synthetic Failure and Fluid Changes

- Reduced coagulation-protein synthesis prolongs PT/INR and can contribute to bleeding risk.
    - Liver disease also lowers natural anticoagulants, so an elevated INR does not mean that thrombosis cannot occur.
- Reduced albumin synthesis contributes to oedema and ascites, together with portal and renal haemodynamic changes.
    - A low albumin level can have non-hepatic causes and changes slowly compared with many injury markers.

Detoxification and Metabolic Failure

- Accumulation of ammonia and other substances, together with inflammation and altered brain function, contributes to hepatic encephalopathy.
    - Confusion, altered sleep, asterixis and reduced consciousness may develop, but an ammonia value alone does not grade the syndrome reliably.
- Severe acute failure can cause hypoglycaemia and cerebral oedema.
- Impaired bilirubin handling causes jaundice, while altered hormone metabolism can contribute to endocrine and vascular signs in chronic disease.

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Renal and Infective Complications

- Advanced liver disease can cause circulatory changes that reduce effective renal perfusion and contribute to hepatorenal syndromes.
    - Infection, hypovolaemia, nephrotoxins and intrinsic kidney disease must also be considered when creatinine rises.
- Immune dysfunction and ascites increase susceptibility to serious infection.
    - Infection may precipitate encephalopathy, kidney dysfunction or acute decompensation.

Interpreting Severity

- Assess the clinical state and serial bilirubin, INR, renal function, glucose and other relevant results.
- ALT and AST measure injury rather than the amount of remaining functional reserve.
    - A falling aminotransferase value can accompany either recovery or loss of viable hepatocytes, so the direction must be interpreted with other findings.

Viral Hepatitis

- Viral hepatitis is liver inflammation caused by a virus, with patterns of injury that vary according to the organism and host response.

Shared Histological Patterns

1. Acute Hepatitis Patterns

- **Hepatitis** means inflammation of the liver and has viral, immune, toxic and other causes.
- Acute injury can show hepatocyte swelling, apoptotic acidophilic bodies, lobular inflammation and variable cholestasis.
    - Confluent or bridging necrosis indicates more extensive injury than scattered individual-cell death.

2. Chronic Hepatitis and Fibrosis

- Chronic hepatitis often has portal inflammation, interface activity and variable fibrosis.
    - Interface hepatitis describes inflammatory injury at the border between portal tissue and adjacent hepatocytes.
- Fibrosis may bridge portal and central regions and eventually produce cirrhosis.

Activity Grade and Fibrosis Stage

- Histological activity grades ongoing inflammatory injury, while fibrosis stage records accumulated structural remodelling; severe activity and advanced stage are different observations.

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