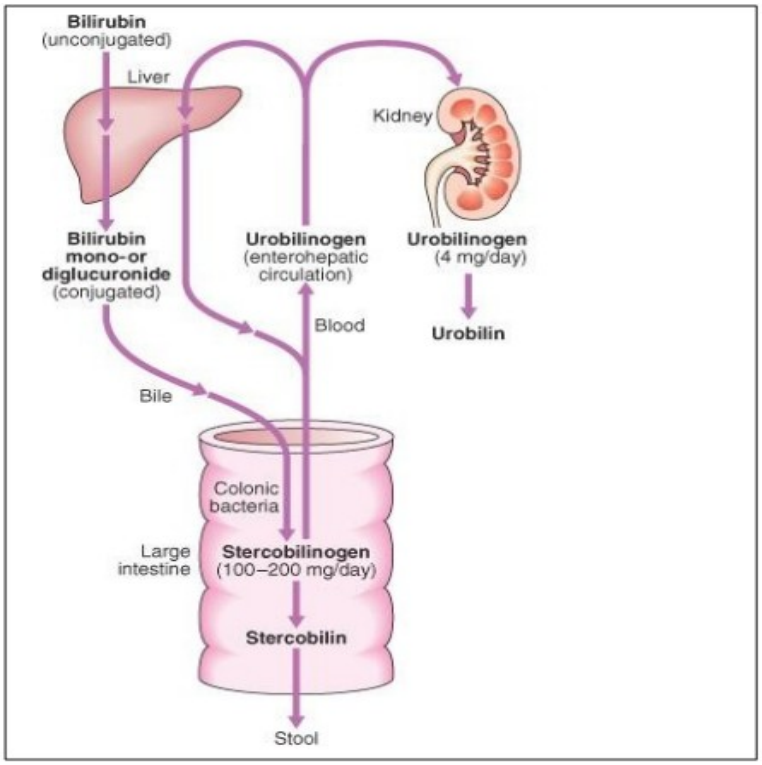
Internal Medicine
Jaundice (Icterus)

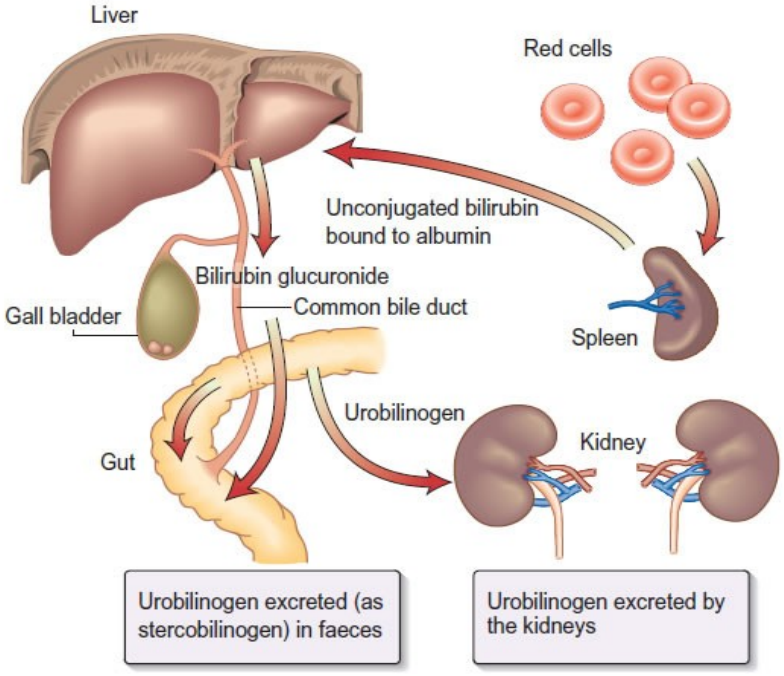
Objectives:
1. Understand how bilirubin is formed.
2. Sumarrize the causes and different features of each type of jaundice.
3. How to approach a patient with jaundice

Jaundice: is yellowish discoloration of the skin, sclera and mucous membrane, resulting from an increased bilirubin concentration in the body fluid (N: < 1mg/dl). It is usually detectable clinically when the plasma bilirubin exceeds 40µmol/l (~2.5mg/dl). Jaundice is a symptom or physical sign of a disease.

Bilirubin Metabolism للاطلاع فقط
About 250mg of unconjugated bilirubin is produced from the catabolism of **Haem** every day. Bilirubin in the blood is almost all unconjugated and, because it is not water – soluble, it is bound to albumin and does not pass into the urine. Unconjugated bilirubin is conjugated by the glucuronyl transferase into mono and diglucuronide bilirubin. These are water soluble and by specific carriers enter the bile and reach intestine.



Conjugated bilirubin is metabolized by colonic bacteria to form stercobilinogen which may be oxidized to stercobilin and both are excreted in the stool. A small amount of stercobilinogen (4mg/day) is absorbed from the bowel and go to the blood and excreted through the kidney (colorless urobilinogen).



Clinical types of Jaundice: for description purpose the jaundice is divided into: **pre-hepatic** (hemolytic anaemia and congenital non-hemolytic jaundice like Gilbert disease, **hepatic** or **hepatocellular** due to many causes and lastly **obstructive (cholestatic)** either intrahepatic (medical) which may be a consequences of hepatocellular damage or the causes may be due to extra-hepatic biliary obstruction like stone, strictures, pancreatic cancer, cancer of papilla of Vator, etc.

1. Haemolytic anaemia (Pre-hepatic): This is is characterised by an isolated raised bilirubin level (usually unconjugated). (unconjugated hyperbilirubinaemia) Increased destruction of RBCs or their precursors in the marrow, causing increasing production of bilirubin.

Features

A. Jaundice is usually mild (<100μmol/l) as healthy liver can excrete bilirubin six times greater than normal before unconjugated bilirubin accumulates in the plasma. This is not applied to new born (Kernicterus may occur).

B. There are no features of liver disease other than jaundice. Also liver function tests (LFTs) are normal.

C. There are no stigmata of chronic liver disease other than jaundice.

D. Normal or dark colored stool (stercobilinogen). Also urine may turn dark on standing as urobilin is formed through the oxidation of urobilinogen but a newly voided urine is colorless because no bilirubinuria.

E. Pallor due to anaemia and splenomegaly are maybe (usually) present.

F. No bilirubinuria.

G. Blood count and film may show evidence of haemolytic anaemia

2. Congenital non-haemolytic hyperbilirubinaemia:

Are inherited either as autosomal dominant like Gilbert (unconjugated) or autosomal recessive like Crigler-Najar (type1 & 2) also unconjugated and type 1 is more serious and cause death in neonate. There are other types of congenital non-hemolytic (Rotors & Dubin Jonson) which are causing conjugated hyperbilirubinaemia.

Gilbert Disease: This is the comments type and benign condition causes mild unconjugated hyperbilirubinaemia due to decrease in the level of glucuronyl transferase or decrease bilirubin uptake inherited as (AD). Usually follows viral infection or fasting well respond to phenobarbital. Clinical examination is normal, except for mild jaundice.

Note: In Dubin Jonson syndrome , and Rotor disease, the bilirubin is conjugated, whilist is unconjugated in Gilbert's disease (syndrome).

Hepatic (Hepatocellular jaundice):
Results from inability of liver to transport bilirubin into the bile as a result of parenchymal liver disease.
Swelling and oedema of cells may cause obstruction to the biliary canaliculi. Both conjugated and unconjugated bilirubin is increased.

Examples of Causes:
A large number of conditions (acute & chronic parenchymal liver diseases) can cause this type of jaundice:
- **Viral hepatitis** (A, B, C, D E).
- EBV, CMV.
- **Drugs** that cause hepatocellular damage like tetracycline, erythromycin, anti-tuberculosis, etc.
- Alcohol consumption,
- Autoimmune liver disease (autoimmune hepatitis)
- Hereditary liver diseases.
- Ischaemia.

The severity of jaundice, the other clinical features, investigation, treatment, and prognosis vary with underlying causes.

Characteristically, jaundice due to parenchymal liver disease is associated with increases in transaminases (AST, ALT), but increases in other LFTs, including cholestatic enzymes (GGT, ALP), may occur and suggest specific aetiologies.

Acute jaundice in the presence of an ALT of > 1000 U/L is highly suggestive of an infectious cause (e.g. hepatitis A or B), drugs (e.g. paracetamol) or hepatic ischaemia.

Imaging is essential, in particular to identify features suggestive of cirrhosis, define the patency of the hepatic vasculature and obtain evidence of portal hypertension. Liver biopsy has an important role in defining the aetiology of hepatocellular jaundice and the extent of liver injury.

Obstructive (Cholestatic) jaundice: It is due biliary passage obstruction (intra & extrahepatic). Tend to become progressive and severe because conjugated bilirubin is unable to enter the bile canaliculi and passes back into the blood and because failure of clearence of unconjugated bilirubin arriving at the liver cells.

Causes of Obstructive Jaundice:

A. Intrahepatic cholestasis: examples of causes:

1. Primary biliary cholangitis (PBC),
2. Primary sclerosing cholangitis (PSC), it also cause extrahepatic biliary passage obstruction.
3. Intrahepatic cholestasis of pregnancy.
4. Benign recurrent intrahepatic cholestasis (BRIC).
5. Drugs like contraceptive pills, chlorpromazine.
6. Hodgkin's lymphoma.
7. Other parenchymal liver disease like viral hepatitis.

B. Extrahepatic:

1. Choledocholithiasis.
2. Carcinoma (ampullary, pancreatic,bile duct).
3. Parasitic infection.
4. Traumatic biliary stricture.

i 22.15 Causes of cholestatic jaundice

Intrahepatic

- Primary biliary cholangitis
- Primary sclerosing cholangitis
- Alcohol
- Drugs
- Hepatic infiltrations (lymphoma, granuloma, amyloid, metastases)
- Cystic fibrosis
- Severe bacterial infections
- Pregnancy (p. 899)
- Inherited cholestatic liver disease, e.g. benign recurrent intrahepatic cholestasis
- Chronic right heart failure

Extrahepatic

- Carcinoma:
  - Ampullary
  - Pancreatic
  - Bile duct (cholangiocarcinoma)
  - Liver metastases
- Choledocholithiasis
- Parasitic infection
- Traumatic biliary strictures
- Chronic pancreatitis

Clinical Features in Cholestatic Jaundice

A. Early features:

1. Jaundice.
2. Dark urine.
3. Pale stool.
4. Pruritis.

B. Late features:

1. Xanthelasma and xanthomas.
2. Malabsorption (weight loss, steatorrhea, osteomalacia, bleeding tendency).

Features of choleangitis:

1. Fever **2.** Rigor **3.** Pain.

Early Investigations of Obstructive Jaundice

The history and clinical examination determine the investigation in individual patients.

- Usually biochemistry tests show greater elevation of the alkaline phosphatase and GGt compared with aminotransferases (ALT, AST).
- Ultrasound is performed to identify any biliary dilatation.
- Subsequent investigation is shown in next Schema.

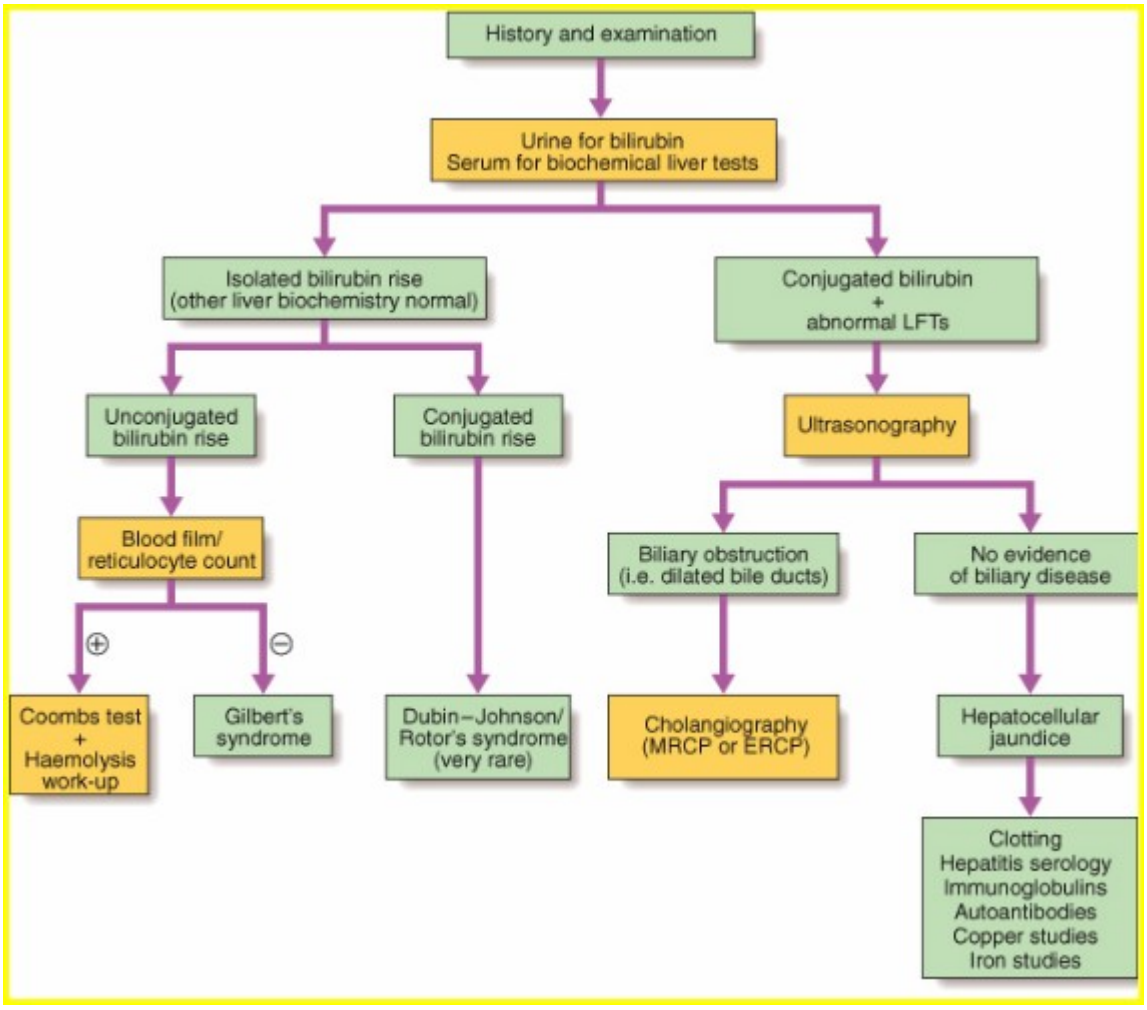
Clinical Features suggesting an underlying cause of obstructive jaundice:

1. Progressive, static or flacuating jaundic (carcinoma, stone, stricture, pancreatitis).
2. Abdominal pain: (stone, pancreatitis, choedochal cyst).
3. Irregular hepatomegaly: (hepatic ca.)
4. Palpable gallbladder: (cancer below custic duct (usually pancreas))
5. Abdominal mass: (Ca, Pancreatic cyst, choledochal cyst)
6. Occult blood: Papillary tumour.

Take-home message

1. The history and clinical exam determine the investigations in individual patients.
2. Obstructive jaundice shows greater elevation of the alkaline phosphatase (ALP) and gama-glutamyltransferase (GGT) compared with aminotransferases (ALT, AST) which are elevated in hepatocellular jaundice.
3. Ultrasound is performed to identify any biliary dilatation in patients with jaundice and an abnormal liver function test.
4. In isolated hyperbilirubinaemia, you must exclude hemolytic and congenital non-hemolytic hyperbilirubinemia like Gilbert disease.

How to approach to a patient with jaundice?



22.16 Key history points in patients with jaundice

Symptoms*

- Itching preceding jaundice
- Abdominal pain (suggests stones)
- Weight loss (chronic liver disease and malignancy)
- Dark urine and pale stools
- Fever ± rigors
- Dry eyes/dry mouth
- Fatigue

Recent drug history

Other

- Exposure to intravenous drug or blood transfusions
- Travel history and country of birth
- Metabolic syndrome (increased body mass index ± type 2 diabetes/hypertension)
- Autoimmune disease history
- Alcohol history
- Inflammatory bowel disease
- Family history of liver disease, autoimmune disease or the metabolic syndrome

*Symptoms may be absent and abnormal liver function tests detected incidentally.