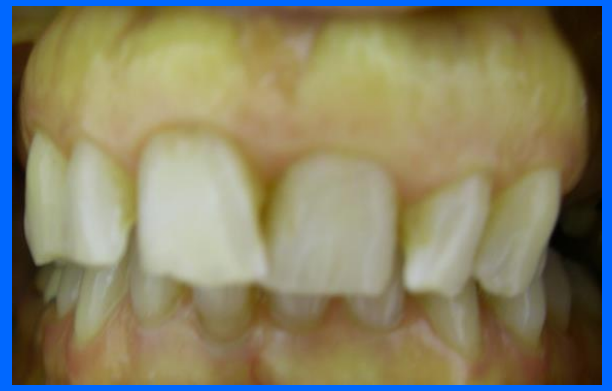
Jaundice: Understanding the Pathophysiology, Diagnosis, and Management

Agenda

I. Introduction
II. Pathophysiology of Jaundice
III. Clinical Features of Jaundice
IV. Diagnostic Evaluation
V. Differential Diagnosis
VI. Management of Jaundice
VII. Complications of Jaundice

Introduction

- Definition of Jaundice:
  - Jaundice is a clinical manifestation characterized by the yellow discoloration of the skin, sclera, and mucous membranes due to increased levels of bilirubin in the blood (HYPERBILIRUBINEMIA).
  - Jaundice is usually detectable clinically when the plasma bilirubin exceeds 40 µmol/L (~2.5 mg/dL)
  - It is not a disease itself, but a symptom of an underlying condition OR pathology.



Pathophysiology of Jaundice

Bilirubin Metabolism:

1-Heme Catabolism:

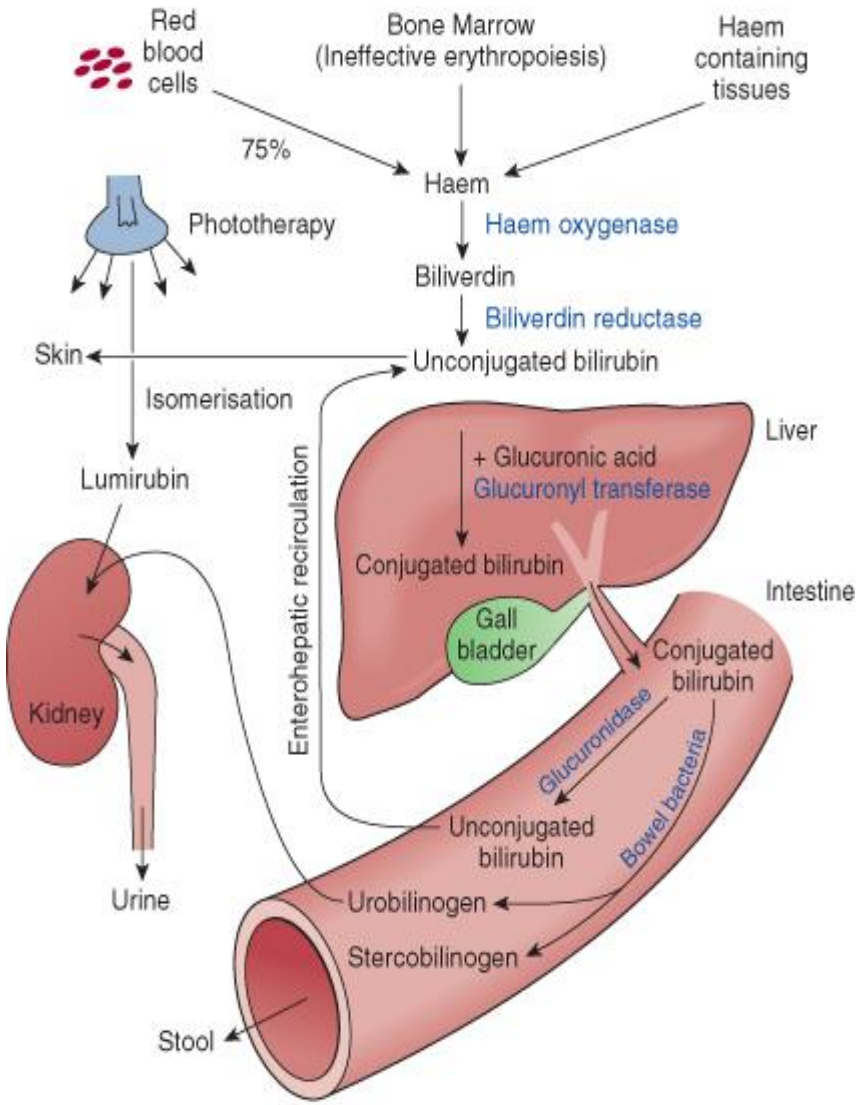
Bilirubin is formed from the breakdown of heme, which is derived from the degradation of hemoglobin from red blood cells.

2-Unconjugated Bilirubin:

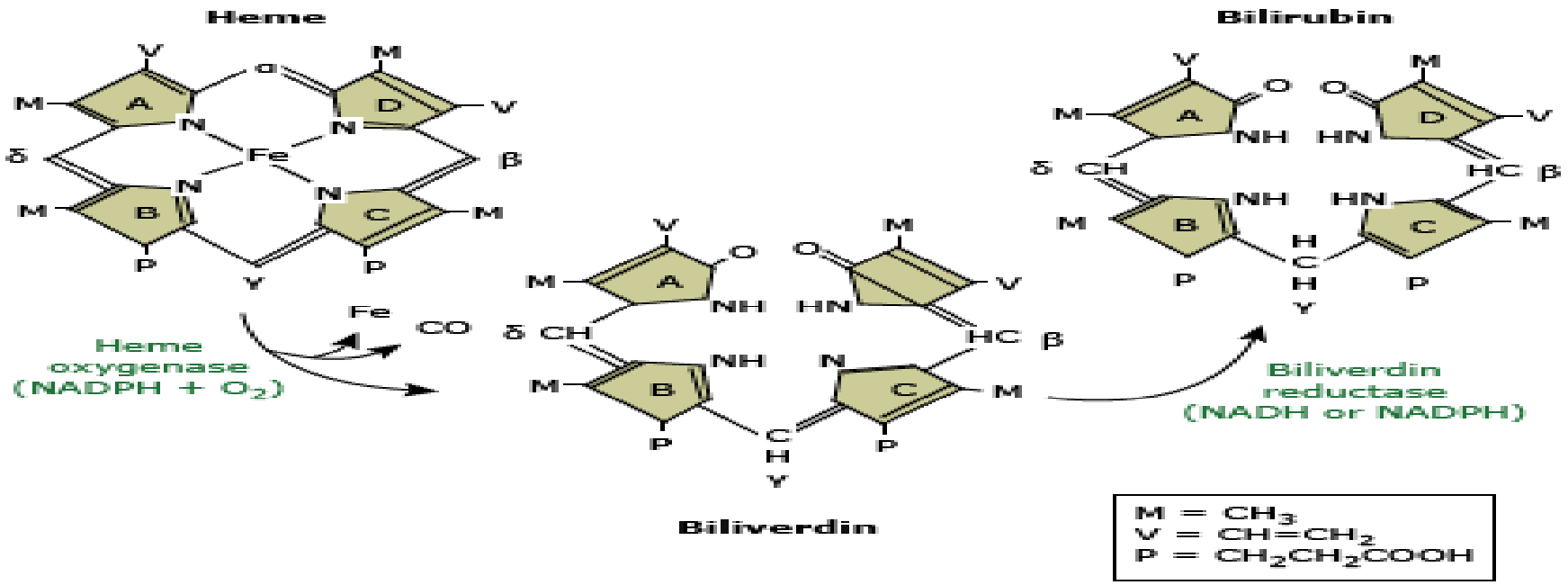
Unconjugated bilirubin is insoluble in water and is transported to the liver bound to albumin.

3-Conjugated Bilirubin:

In the liver, unconjugated bilirubin is conjugated with glucuronic acid, making it water-soluble and facilitating its excretion into bile.



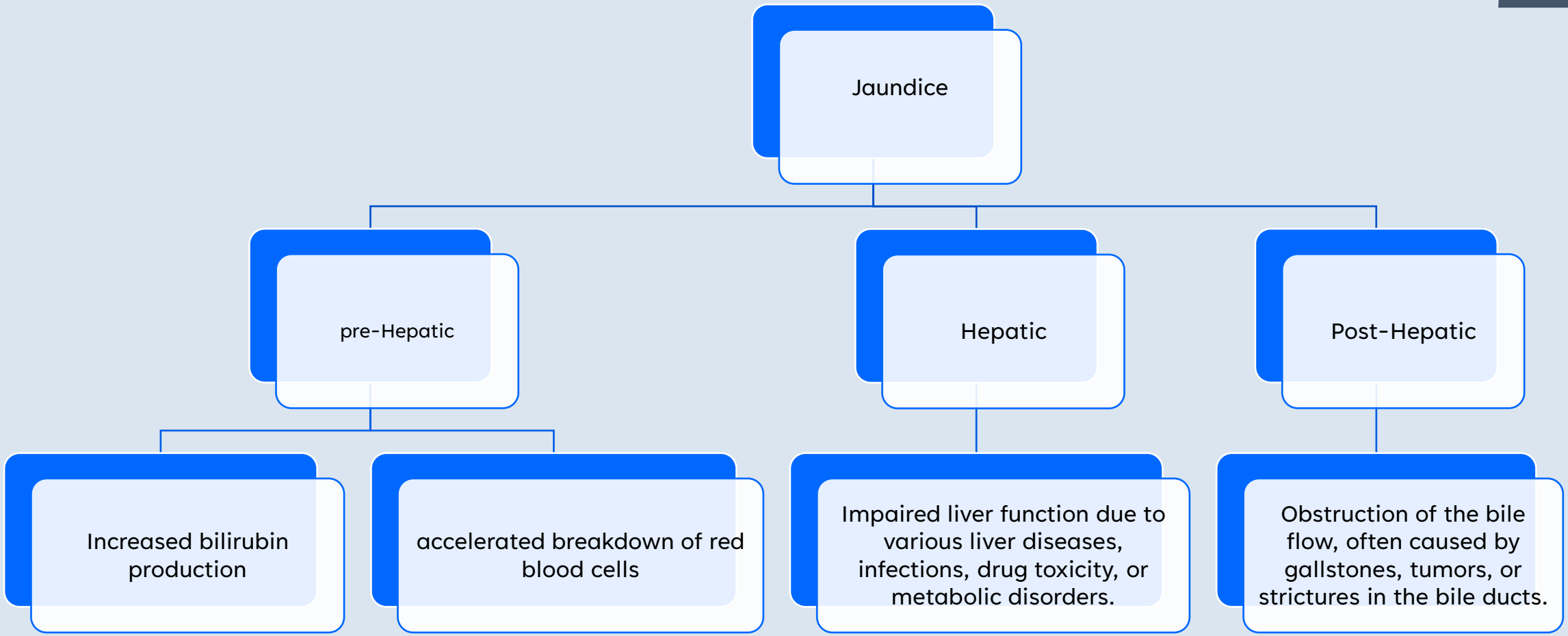
Bilirubin synthesis



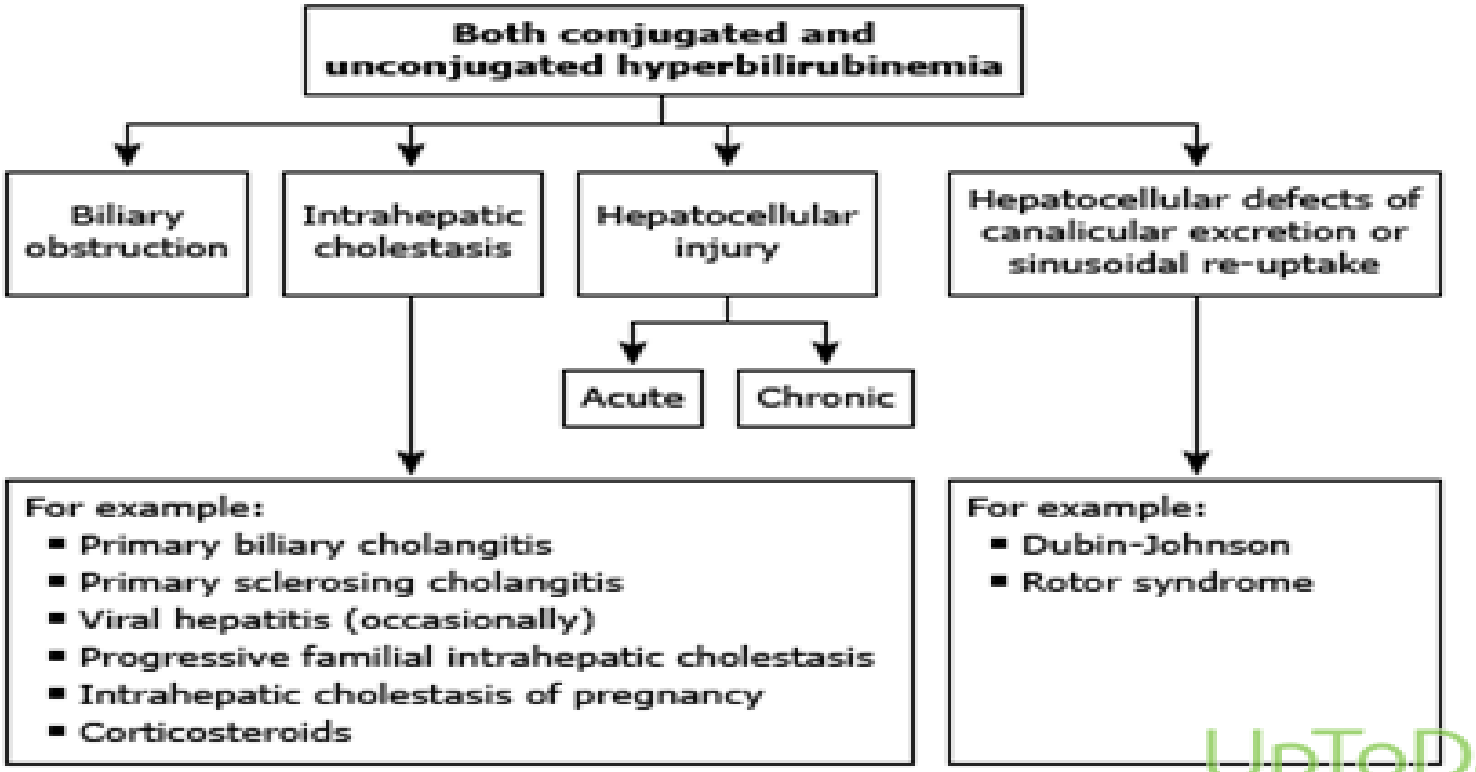
Conversion of heme to biliverdin and then bilirubin. Heme ring-opening at the alpha-carbon bridge of heme is catalyzed by heme oxygenase, resulting in the formation of biliverdin. This is followed by reduction of biliverdin to bilirubin in a reaction catalyzed by biliverdin reductase.

NADH: reduced nicotinamide adenine dinucleotide; NADPH: reduced nicotinamide adenine dinucleotide phosphate.

Causes of Jaundice:



Classification of jaundice due to both conjugated and unconjugated hyperbilirubinemia



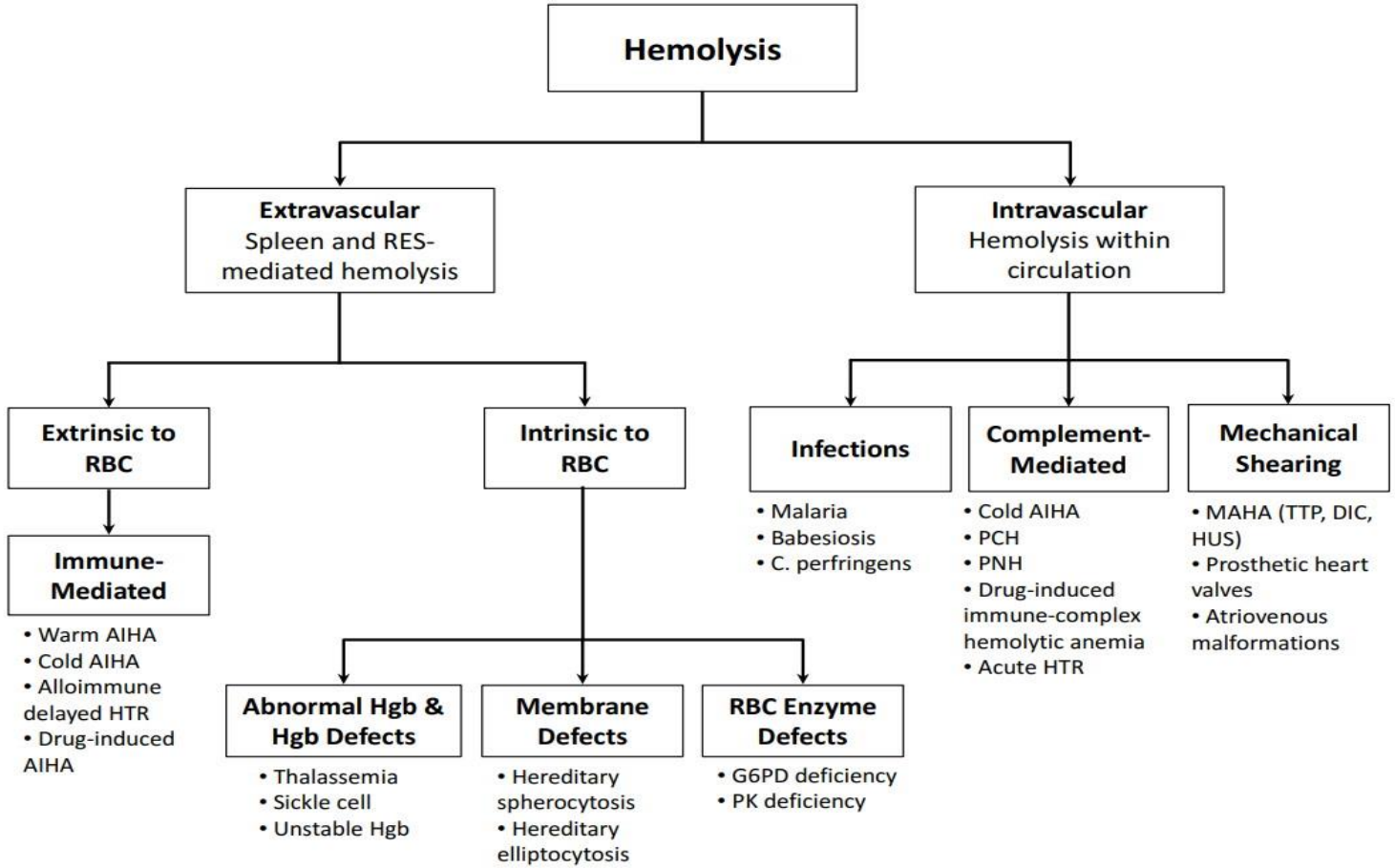
CLASSIFICATION OF JAUNDICE ACCORDING TO TYPE OF BILE PIGMENT

Unconjugated hyperbilirubinemia
Increased bilirubin production*
Extravascular hemolysis
Extravasation of blood into tissues
Intravascular hemolysis
Dyserythropoiesis
Wilson disease
Impaired hepatic bilirubin uptake
Heart failure
Portosystemic shunts
Some patients with Gilbert syndrome
Certain drugs¶ – Rifampin, probenecid, flavaspadic acid, bunamiodyl
Impaired bilirubin conjugation
Crigler-Najjar syndrome types I and II
Gilbert syndrome
Neonates
Hyperthyroidism
Ethinyl estradiol
Liver diseases – Chronic hepatitis, advanced cirrhosis

Conjugated hyperbilirubinemia
Defect of canalicular organic anion transport
Dubin-Johnson syndrome
Defect of sinusoidal reuptake of conjugated bilirubin
Rotor syndrome

Extrahepatic cholestasis (biliary obstruction)
Choledocholithiasis
Intrinsic and extrinsic tumors (eg, cholangiocarcinoma, pancreatic cancer)
Primary sclerosing cholangitis
AIDS cholangiopathy
Acute and chronic pancreatitis
Strictures after invasive procedures
Certain parasitic infections (eg, *Ascaris lumbricoides*, liver flukes)
Intrahepatic cholestasis
Viral hepatitis
Alcohol-associated hepatitis
Non-alcohol-associated steatohepatitis
Chronic hepatitis
Primary biliary cholangitis
Drugs and toxins (eg, alkylated steroids, chlorpromazine, herbal medications [eg, Jamaican bush tea], arsenic)
Sepsis and hypoperfusion states
Infiltrative diseases (eg, amyloidosis, lymphoma, sarcoidosis, tuberculosis)
Total parenteral nutrition
Postoperative cholestasis
Following organ transplantation
Hepatic crisis in sickle cell disease
Pregnancy
End-stage liver disease

Hemolysis


Hemolysis
Extravascular
Spleen and RES-mediated hemolysis
Intravascular
Hemolysis within circulation
Extrinsic to RBC
Intrinsic to RBC
Infections
Complement-Mediated
Mechanical Shearing
Immune-Mediated
• Warm AIHA
• Cold AIHA
• Alloimmune delayed HTR
• Drug-induced AIHA
Abnormal Hgb & Hgb Defects
• Thalassemia
• Sickle cell
• Unstable Hgb
Membrane Defects
• Hereditary spherocytosis
• Hereditary elliptocytosis
RBC Enzyme Defects
• G6PD deficiency
• PK deficiency
• Malaria
• Babesiosis
• C. perfringens
• Cold AIHA
• PCH
• PNH
• Drug-induced immune-complex hemolytic anemia
• Acute HTR
• MAHA (TTP, DIC, HUS)
• Prosthetic heart valves
• Atriovenous malformations

22.17 Congenital non-haemolytic hyperbilirubinaemia

Syndrome	Inheritance	Abnormality	Clinical features	Treatment
Unconjugated hyperbilirubinaemia				
Gilbert's	Can be autosomal recessive or dominant	↓Glucuronyl transferase ↓Bilirubin uptake	Mild jaundice, especially with fasting	None necessary
Crigler–Najjar:				
Type I	Autosomal recessive	Absent glucuronyl transferase	Rapid death in neonate (kernicterus)	
Type II	Autosomal recessive	↓↓Glucuronyl transferase	Presents in neonate	Phenobarbital, phototherapy or liver transplant
Conjugated hyperbilirubinaemia				
Dubin–Johnson	Autosomal recessive	↓Canalicular excretion of organic anions, including bilirubin Pigmentation of liver biopsy tissue	Mild jaundice	None necessary
Rotor's	Autosomal recessive	↓Bilirubin uptake ↓Intrahepatic binding	Mild jaundice	None necessary

Clinical Features of Jaundice

1) Yellow Discoloration of the Skin and Sclera:

2) Dark Urine and Pale Stools:

3) Pruritus:

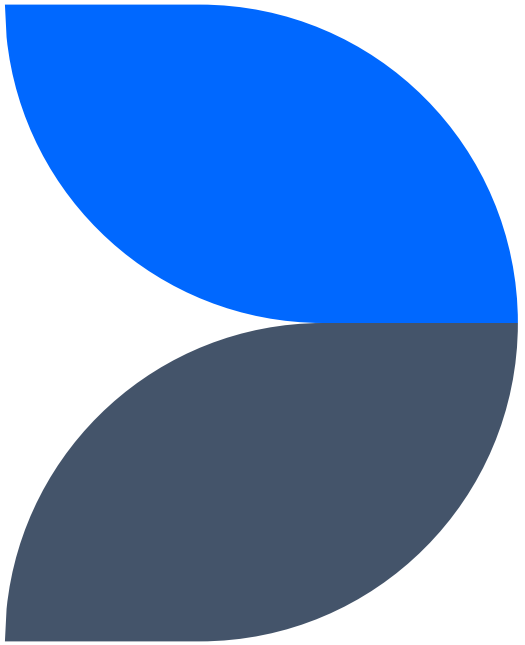
4) Abdominal Pain and Distension (ascites):

5) Fatigue and Weakness:

6) Nausea and Vomiting:

7) Loss of Appetite and Weight Loss :

Diagnostic Evaluation



History taking

History Taking

A detailed history is essential to identify potential risk factors, medication use, previous medical conditions, and family history of liver disease.

History:

- History of presenting illness (HOPI) :
  - Onset
  - Duation
  - Course (progression).
  - Associated symptoms: abdominal pain, fever (w/o chills), weight loss, itching (pruritis), steatorrhea, signs of anemia, bleeding tendency, fatigue, appetite, GI disturbances, vomiting and nausea.
  - Color of stool (normal or pale) and urine (normal or dark)..
  - Relieving and exacerbating factors (fasting, mild diseases, food, drugs)

Possible Risk Factors for Jaundice

Age related:

Newborns: Physiological jaundice is common in newborns due to immature liver function and increased breakdown of fetal red blood cells.

Liver Disease:

Drug abuse →(needle sticks)→hepatitis B, C
Obesity, diabetes, and metabolic syndrome →Non-Alcoholic Fatty Liver Disease (NAFLD)
Tattooing
Medications, herbal, dietary supplement and Toxins
Biliary Strictures →after abdominal surgery
Blood Disorders: hemophilia, sickle cell, ITP, ...
Family History: Gilbert, crigler-Najjar type 1 or 2, Rotor, or Dubin-johnoson syndromes
HIV status

Associated symptoms often help narrow the differential diagnosis

As examples:

A history of jaundice, fever, particularly when associated with chills or right upper quadrant pain and/or a history of prior biliary surgery, is suggestive of acute ascending cholangitis.((Charcot's triad))

Symptoms such as anorexia, malaise, and myalgias may suggest viral hepatitis.

Isolated right upper quadrant pain suggests extrahepatic biliary obstruction.

Development/worsening of jaundice during times of stress is suggestive of Gilbert syndrome. (See "Gilbert syndrome".)

To determine the cause of the Jaundice whither it is (prehepatic, hepatic or posthepatic):

TYPES OF JAUNDICE

TYPE	PRE HEPATIC	HEPATIC	POST HEPATIC
Urine color	normal	dark	dark
Stool color	normal	normal	acholic
Pruritus	no	No	yes

Past medical/ surgical history

Does patient have any chronic illnesses? (HTN, DM, autoimmune, sickle cell anemia, malignancy)

Liver diseases (hepatitis, malignancy)

Pancreatic or biliary diseases/procedures (gallstones, MRCP, ERCP)

If yes, what are they? Since when? Controlled?

Did the patient have similar attacks/episodes?

Previous admissions to the hospital.

Previous surgeries(biliary, hepatic, pancreatic, other)(what, when, why, outcomes, complications).

Previous blood transfusion.

Drug History:

6.8 Examples of drug-induced gastrointestinal conditions	
Symptom	**Drug**
Weight gain	Oral glucocorticoids
Dyspepsia and gastrointestinal bleeding	Aspirin Non-steroidal anti-inflammatory drugs
Nausea	Many drugs, including selective serotonin reuptake inhibitor antidepressants
Diarrhoea (pseudomembranous colitis)	Antibiotics Proton pump inhibitors
Constipation	Opioids
Jaundice: hepatitis	Paracetamol (overdose) Pyrazinamide Rifampicin Isoniazid
Jaundice: cholestatic	Flucloxacillin Chlorpromazine Co-amoxiclav
Liver fibrosis	Methotrexate

Family history:

Jaundice.

Malignancy.

Diseases of liver.

Hereditary spherocytosis.

Gilbert syndrome.

Contacted jaundiced patients (e.g. Hep. A)

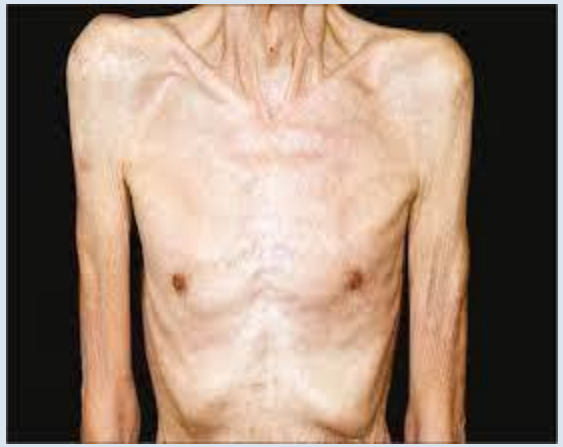
Social History

Alcohol intake.
Occupation.
Smoking.
Travel history.
Vaccinations.
Use of illicit or intravenous drugs. (sharing needle)
Sexual history.
Tattoos.

Physical examination

Physical Examination:

•<u>General</u>:
Evaluate the patient's general appearance, signs of distress, fatigue, or cachexia.
Examine the skin for jaundice (skin, sclera, and mucosa) and pallor (conjunctiva)
Evaluate for signs of encephalopathy, including altered mental status, confusion, or cognitive impairment.
Assess the presence of signs related to cholestasis, such as scratch related pruritus
Any smell, including alcohol, sweet smell on breath of Fetor hepaticus (release of dimethyl sulfide)
Assess for parotid gland enlargement, or goiter



Vital Signs :

- Vitals signs of patients with jaundice due to viral hepatitis include:
  - Fever
  - Tachycardia
  - Hypotension
  - Tachypnea

-A high fever and chills suggest a coexisting cholangitis

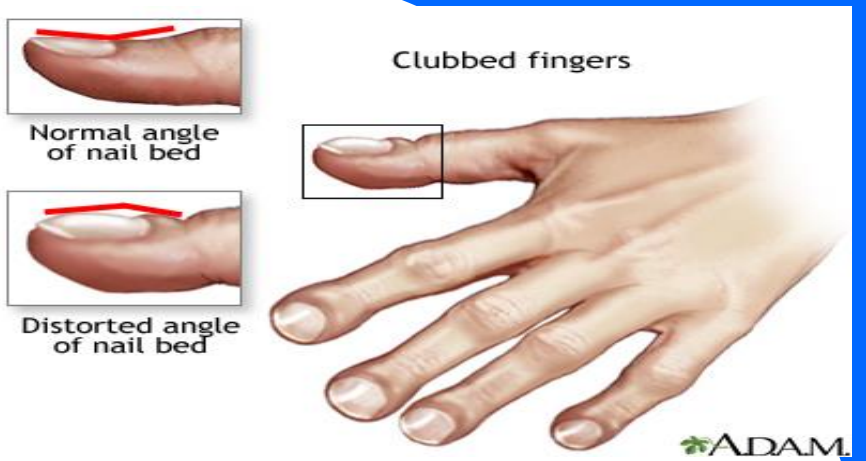
Hand :

-Palmar erythema.

-Dupuytrens contracture.

-Finger clubbing,koilonychia&leukonychia.

-Astrexis in hepatoencephalopathy.

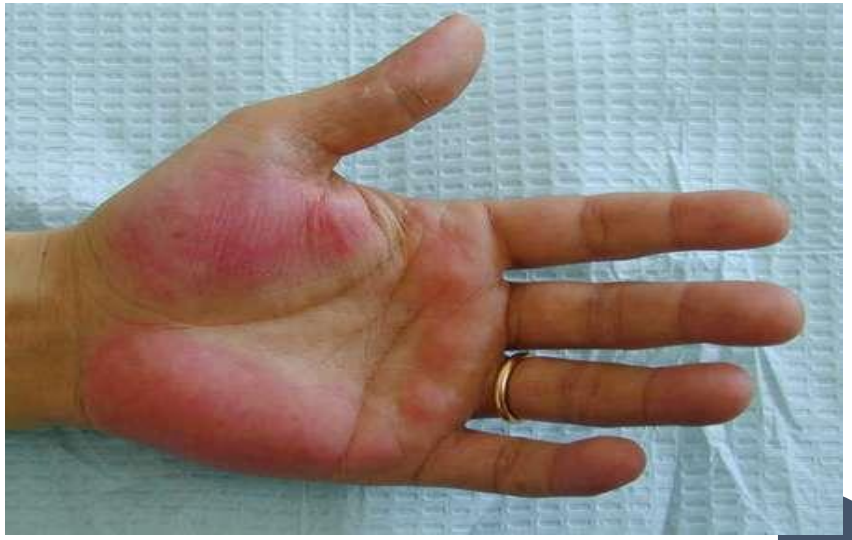


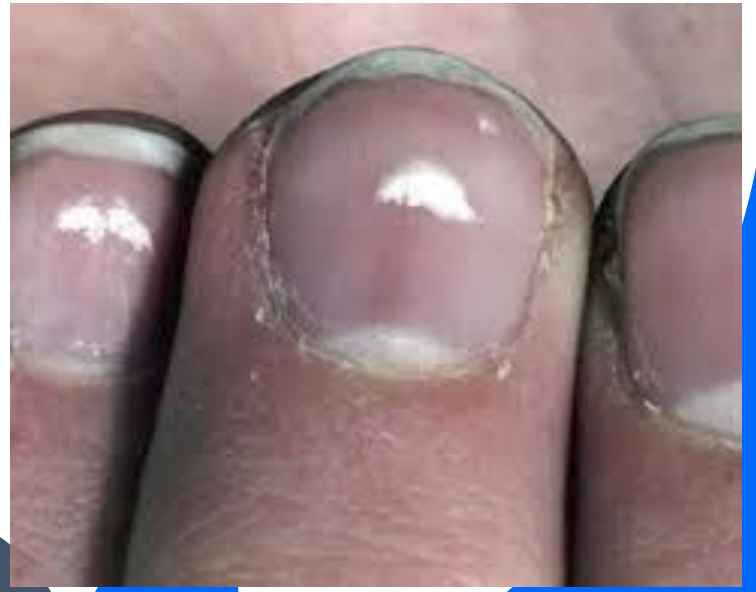
Chest :

-Gynecomastia(in men)

-Breast atrophy (in women)

- Spider naevi.(upper trunk, head , neck & arms)



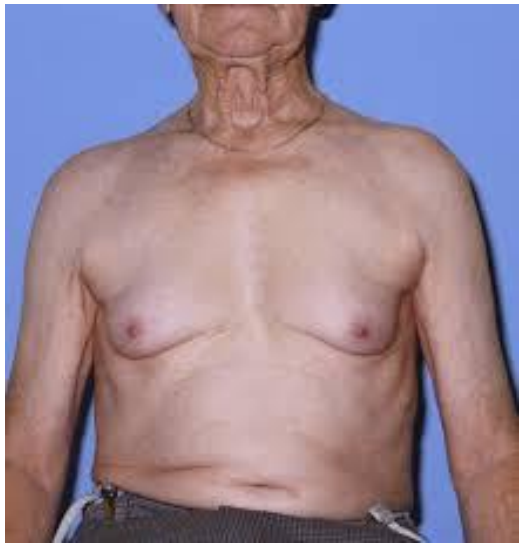


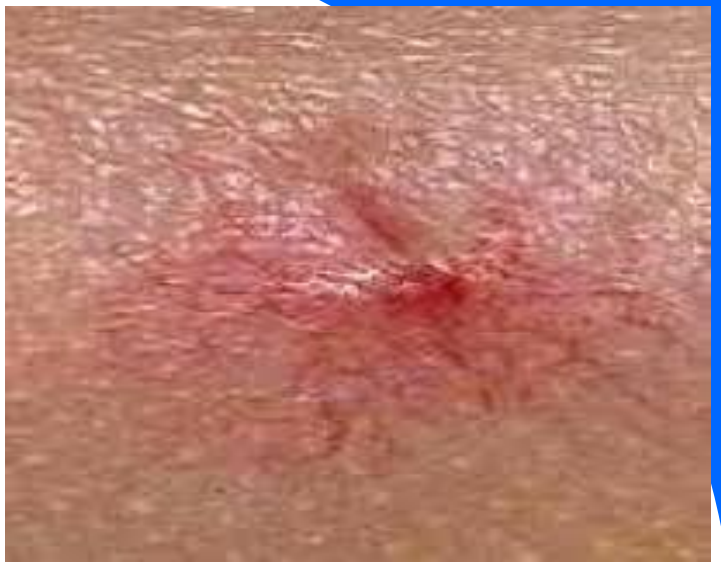
Lymph Nodes :

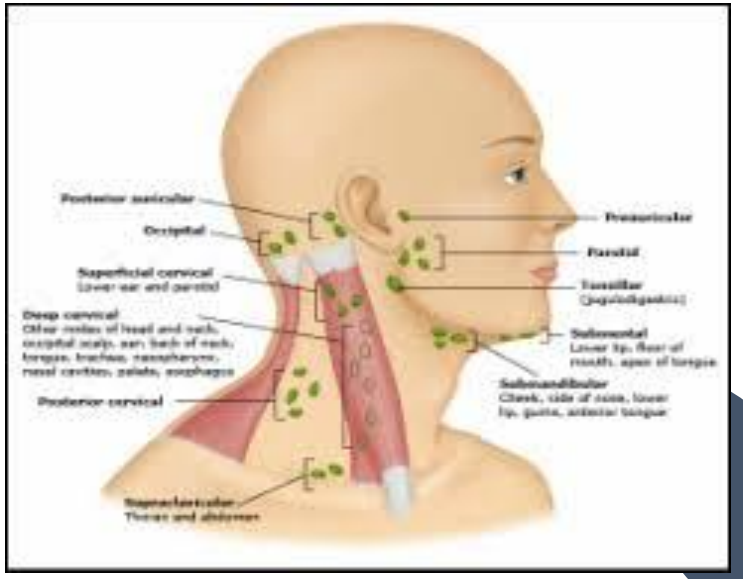
- Examine the cervical, axillary and inguinal lymph nodes.

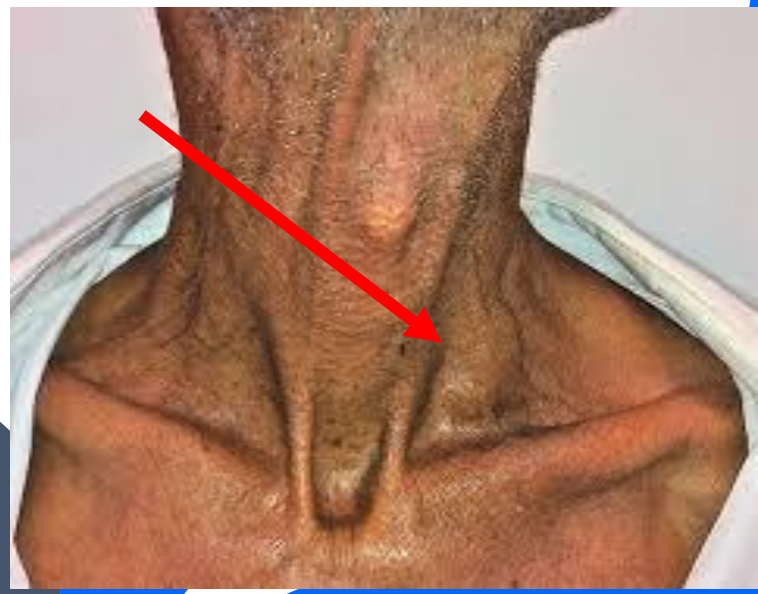
- Viral hepatitis can cause Cervical lymphadenopathy

- Metastatic pancreatic cancer : Left supraclavicular lymphadenopathy (Virchow's node)









- Check legs for oedema, hair loss.
- And general for skin pigmentation ,loss of body hair and bruising.
- And genetlia for testicular atrophy.

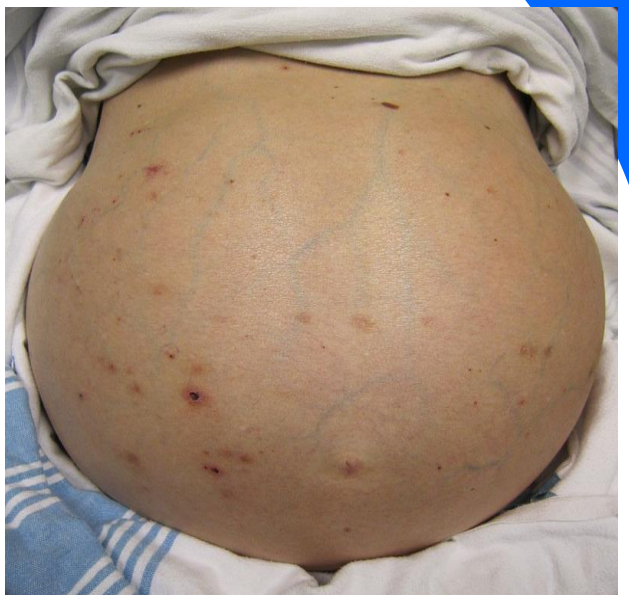
Abdominal examination

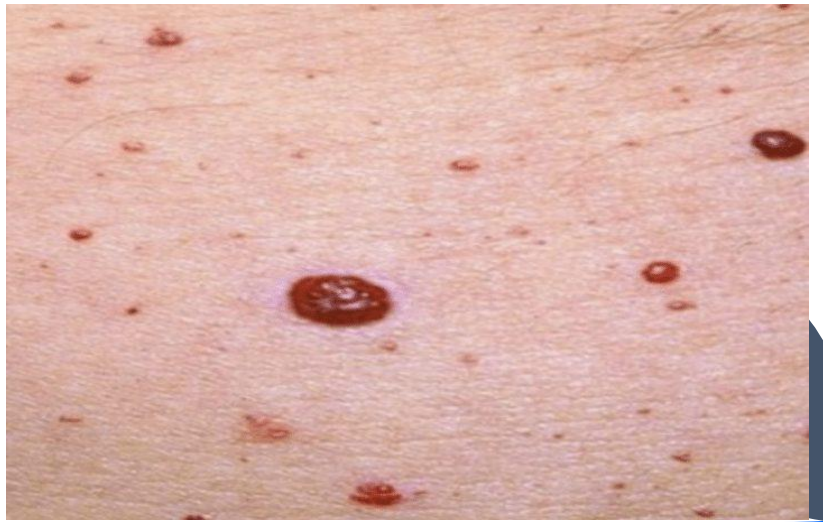
Inspection (Expose the abdomen from the xiphisternum to the symphysis pubis) :

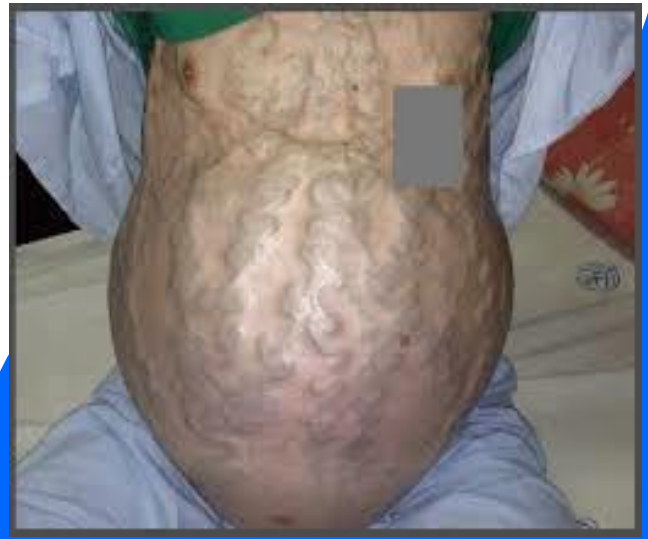
-Abdominal distension ,Ascites , visible veins and caput medusae.

-Check skin; in older patients, seborrhoeic warts, ranging from pink to brown or black, and haemangiomas (Campbell de Morgan spots) are common and normal,but note any striae, bruising or scratch marks.

-Abdominal scars and stoma.







Palpation (examination sequence)

Ensure your hands are warm and clean.

If the bed is low, kneel beside it but avoid touching the floor to prevent infection.

Ask the patient to show you where any pain is and to report any tenderness during palpation.

Ask the patient to place their arms by their sides to help relax the abdominal wall.

Use your right hand, keeping it flat and in contact with the abdominal wall.

Observe the patient’s face throughout for any sign of discomfort.

Begin with light superficial palpation away from any site of pain.

• Palpate each region in turn, and then repeat with deeper palpation.

• Test abdominal muscle tone using light, dipping finger movements.

• Describe any mass. Describe its site, size, surface, shape and consistency, and note whether it moves on respiration. Is the mass fixed or mobile?

• To determine if a mass is superficial and in the abdominal wall rather than within the abdominal cavity, ask the patient to tense their abdominal muscles by lifting their head. An abdominal wall mass will still be palpable,
whereas an intra-abdominal mass will not.

• Decide whether the mass is an enlarged abdominal organ or separate from the solid organs.

Palpation cont.

Abnormal Findings:

- Tenderness.
- Palpable mass.
- Enlarged organs.(Examine the liver, gallbladder, spleen and kidneys in turn during deep inspiration)

If you feel a liver edge, describe:

- size
- surface: smooth or irregular
- edge: smooth or irregular; define the medial border
- consistency: soft or hard
- tenderness
- pulsatility.

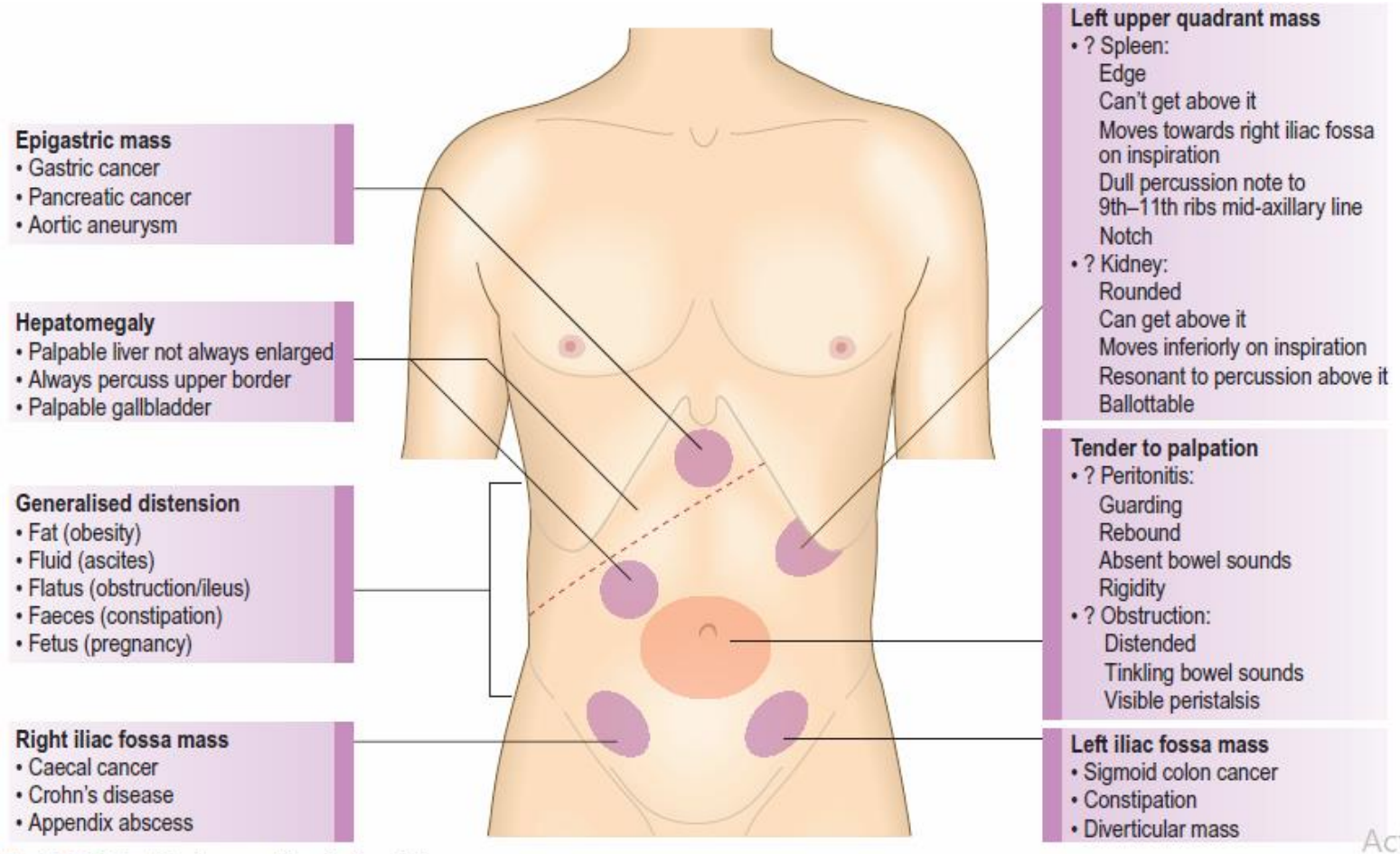


Fig. 6.12 Palpable abnormalities in the abdomen.

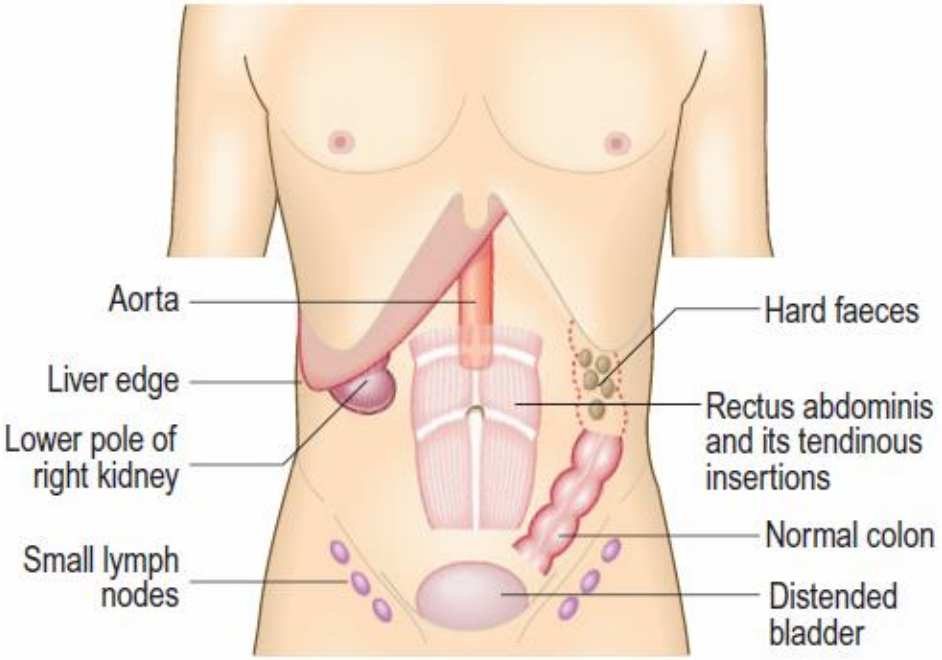


Fig. 6.13 Palpable masses that may be physiological rather than pathological.

Percussion (examination sequence)

Ask the patient to hold their breath in full expiration.

Percuss downwards from the right fifth intercostal space in the mid-clavicular line, listening for dullness indicating the upper border of the liver.

Measure the distance in centimeters below the costal margin in the mid-clavicular line or from the upper border of dullness to the palpable liver edge.

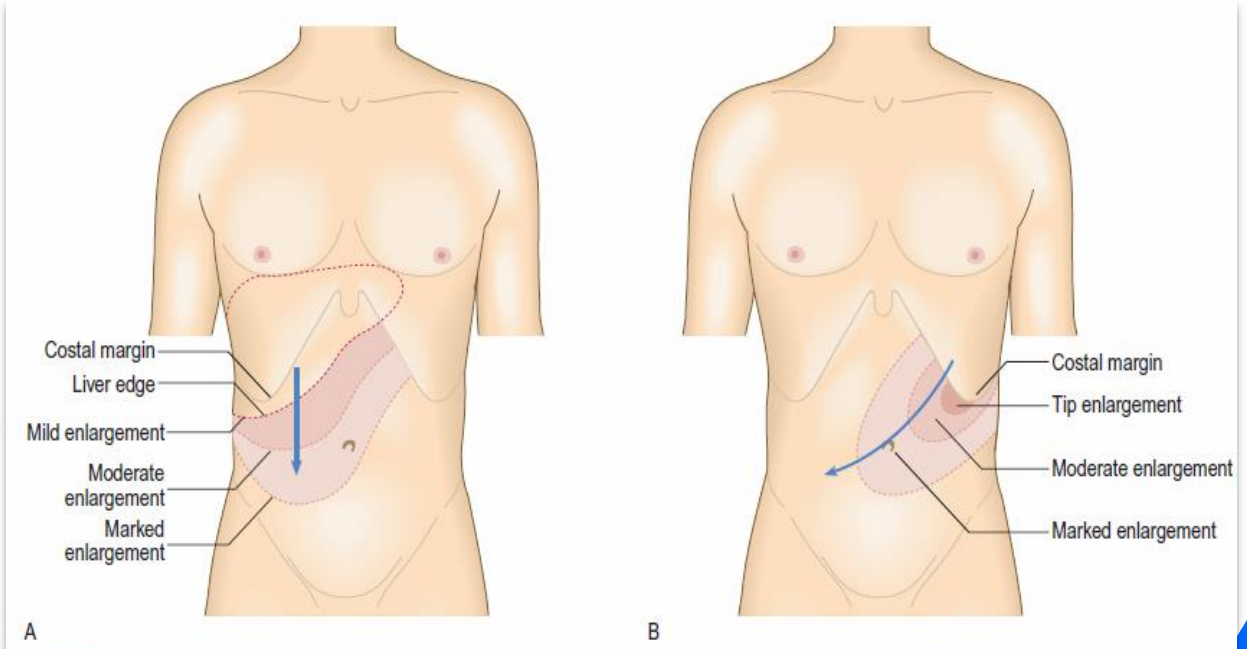


Fig. 6.15 Patterns of progressive enlargement of liver and of spleen. A Direction of enlargement of the liver. B Direction of enlargement of the spleen. The spleen moves downwards and medially during inspiration.

Percussion cont.

Shifting dullness.

Fluid thrill.

<u>Abnormal findings:</u>

Ascites.

Splenomegaly.

Auscultation

With the patient supine, place your stethoscope diaphragm to the right of the umbilicus and do not move it.

Listen for up to 2 minutes before concluding that bowel sounds are absent.

Listen above the umbilicus over the aorta for arterial bruits.

Now listen 2–3 cm above and lateral to the umbilicus for bruits from renal artery stenosis.

Listen over the liver for bruits.

Test for a succussion splash; this sounds like a half-filled water bottle being shaken. Explain the procedure to the patient, then shake their abdomen by rocking their pelvis using both hands.

DON'T FORGET.

Complete with rectal and hernia examination.

6.9 Specific signs in the 'acute abdomen'

Sign	Disease associations	Examination
Murphy's	Acute cholecystitis: Sensitivity 50–97% Specificity 50–80%	As the patient takes a deep breath in, gently palpate in the right upper quadrant of the abdomen; the acutely inflamed gallbladder contacts the examining fingers, evoking pain with the arrest of inspiration
Rovsing's	Acute appendicitis: Sensitivity 20–70% Specificity 40–96%	Palpation in the left iliac fossa produces pain in the right iliac fossa
Iliopsoas	Retroileal appendicitis, iliopsoas abscess, perinephric abscess	Ask the patient to flex their thigh against the resistance of your hand; a painful response indicates an inflammatory process involving the right psoas muscle
Grey Turner's and Cullen's	Haemorrhagic pancreatitis, aortic rupture and ruptured ectopic pregnancy (see Fig. 6.25)	Bleeding into the falciform ligament; bruising develops around the umbilicus (Cullen) or in the loins (Grey Turner)

Investigations

- Complete blood cell (CBC) count to screen for hemolysis.
- Serum bilirubin.
- Serum aminotransferases (aspartate aminotransferase [AST], alanine aminotransferase [ALT])
- Alkaline phosphatase (ALP)/GGT.
- Serum protein (albumin) – chronic liver disease.
- PT to exclude cirrhosis.
- Urinalysis.
- Stool analysis.
- Viral markers.
- Blood alcohol or acetaminophen levels upon admission (may be useful in certain cases).
- Antimitochondrial antibody when considering primary biliary cholangitis.
- Antinuclear antibodies (ANAs), smooth-muscle antibodies, and other serologic studies when considering autoimmune hepatitis.
- Iron and genetic studies when considering hemochromatosis.
- Copper studies when considering Wilson disease.
- Alpha-1 antitrypsin fractionation and other studies when considering hereditary liver diseases.
- Serum amylase/lipase to exclude pancreatitis.

Evaluation of isolated mild chronic elevation of serum aminotransferases*

Step 1: Initial evaluation
Review possible links to medications, herbal therapies, or recreational drugs
Screen for alcohol abuse (history, screening instruments, AST/ALT ratio >2:1)
Obtain serology for hepatitis B and C (HBsAg, anti-HBs, anti-HBc, anti-HCV)
Screen for hemochromatosis (Fe/TIBC >45%)
Evaluate for fatty liver (AST/ALT usually <1, obtain RUQ ultrasonography)
Step 2: Second-line evaluation (if initial evaluation is unrevealing)
Consider autoimmune hepatitis, particularly in women and in those with a history of other autoimmune disorders (check serum protein electrophoresis; obtain ANA and ASMA if positive)
Obtain thyroid function tests (TSH if hypothyroidism is suspected; otherwise, obtain serum TSH, free T4, and T3 concentrations)
Consider celiac disease (especially in patients with a history of diarrhea or unexplained iron deficiency: serum IgA anti-tissue transglutaminase antibodies)
Step 3: Evaluation for uncommon causes (if second-line evaluation is unrevealing)
Consider Wilson disease, especially in those <40 years of age (check serum ceruloplasmin, evaluate for Kayser-Fleischer rings)
Consider alpha-1 antitrypsin deficiency, especially in patients with a history of emphysema out of proportion to their age or smoking history (obtain alpha-1 antitrypsin level)
Consider adrenal insufficiency (8 am serum cortisol and plasma ACTH, high-dose ACTH stimulation test)
Exclude muscle disorders (obtain creatine kinase or aldolase)
Step 4: Obtain a liver biopsy or observe (if no source identified after steps 1 to 3)
Observe if ALT and AST are less than twofold elevated
Otherwise, consider a liver biopsy

Imaging studies

Ultrasonography.

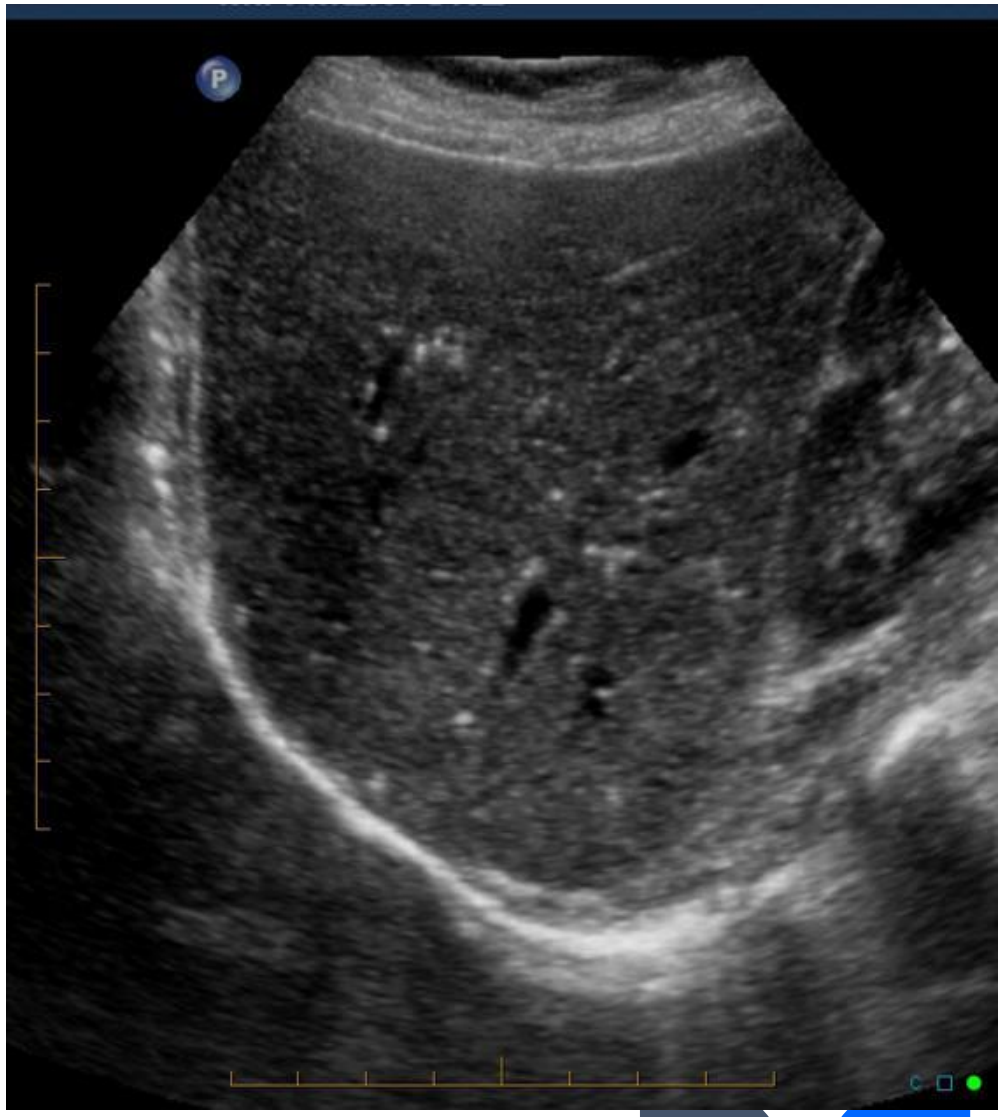
Computed tomography (CT) scanning.

Magnetic resonance imaging (MRCP).

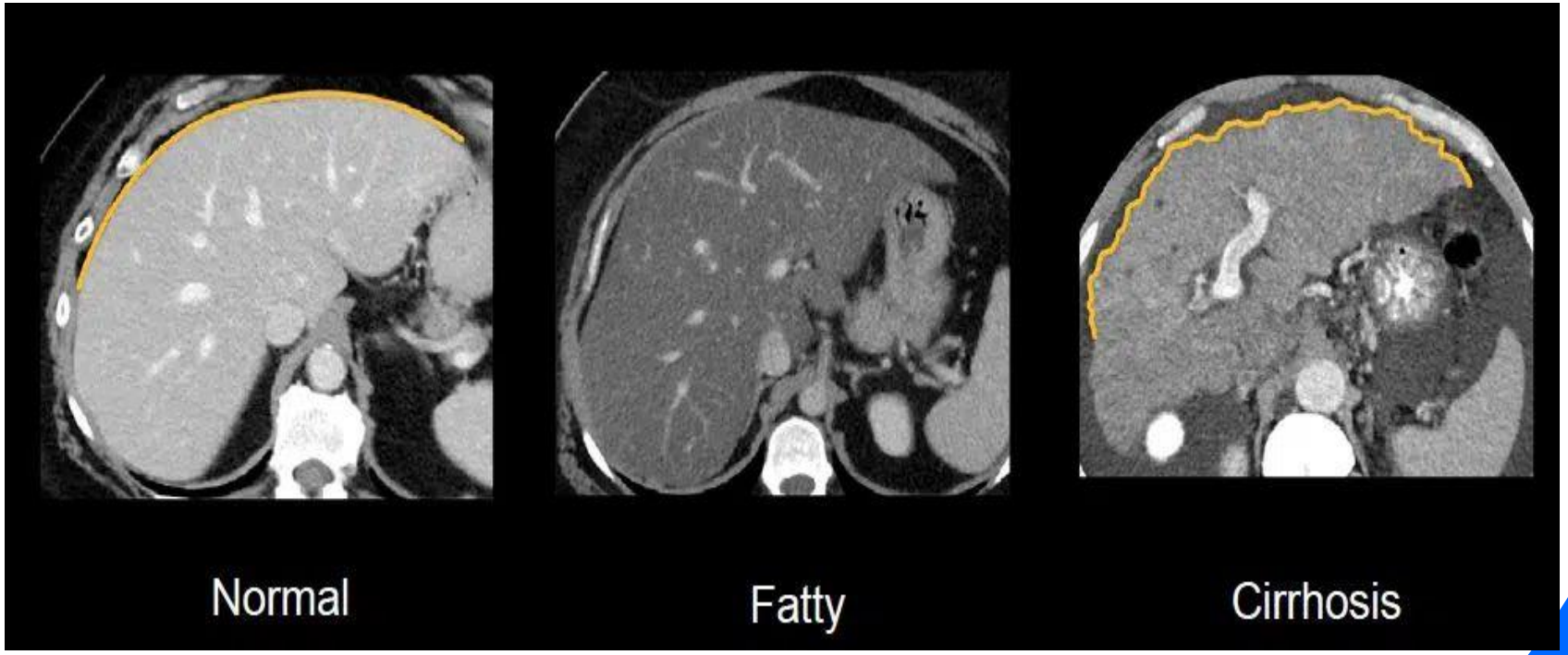
Endoscopic retrograde cholangiopancreatography (ERCP).

Percutaneous transhepatic cholangiography (PTC or PTHC).

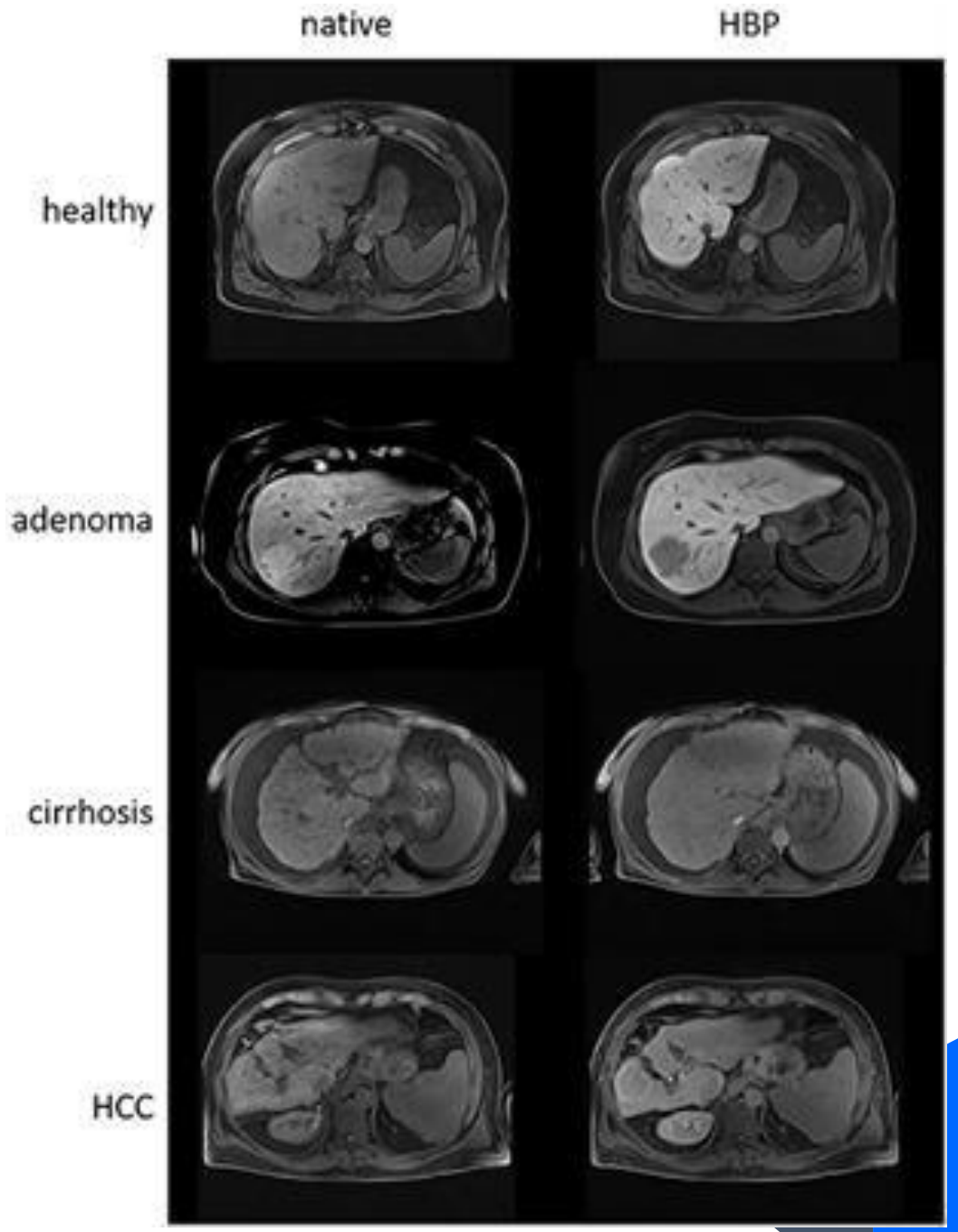
US-Scan



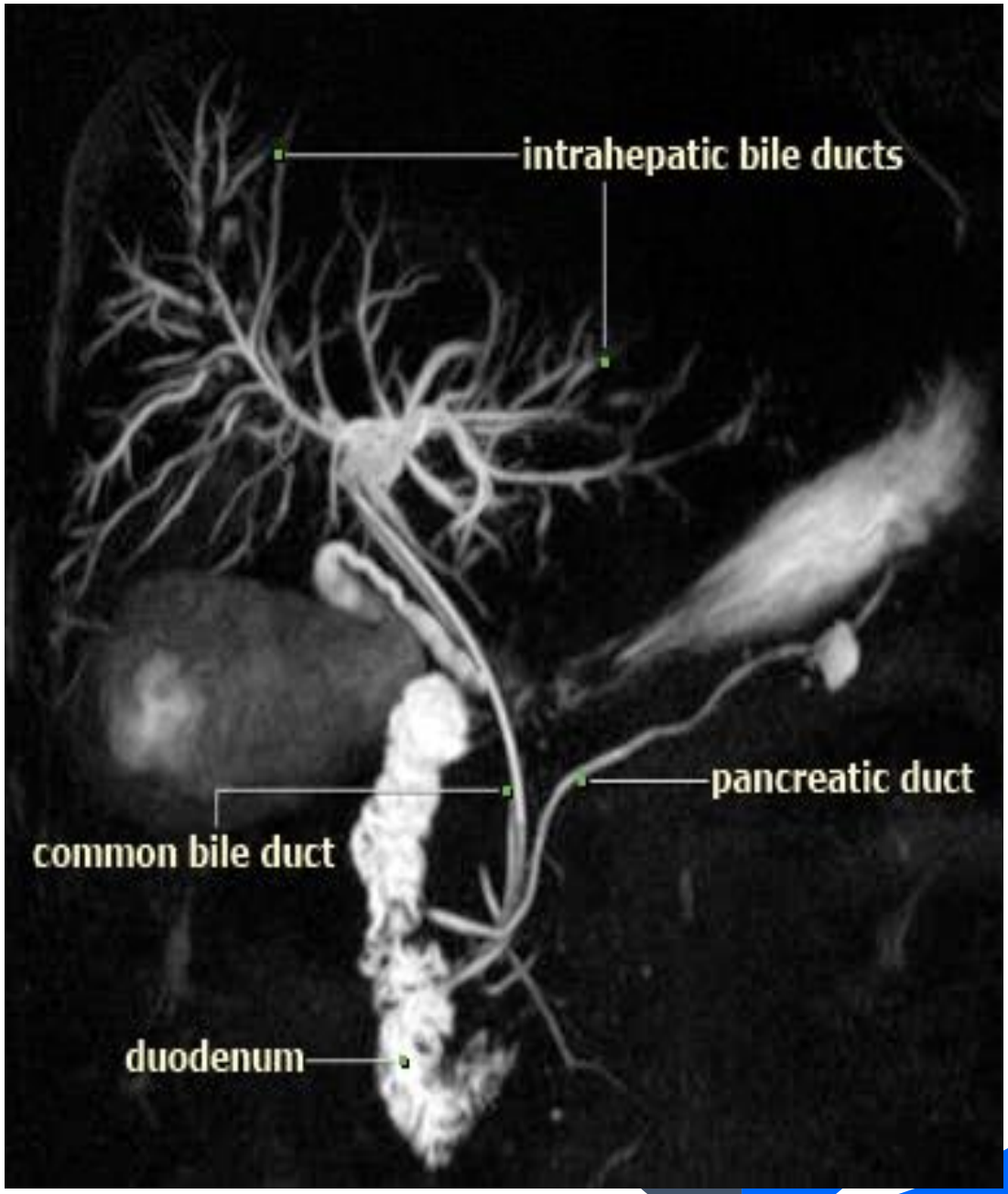
CT-scan



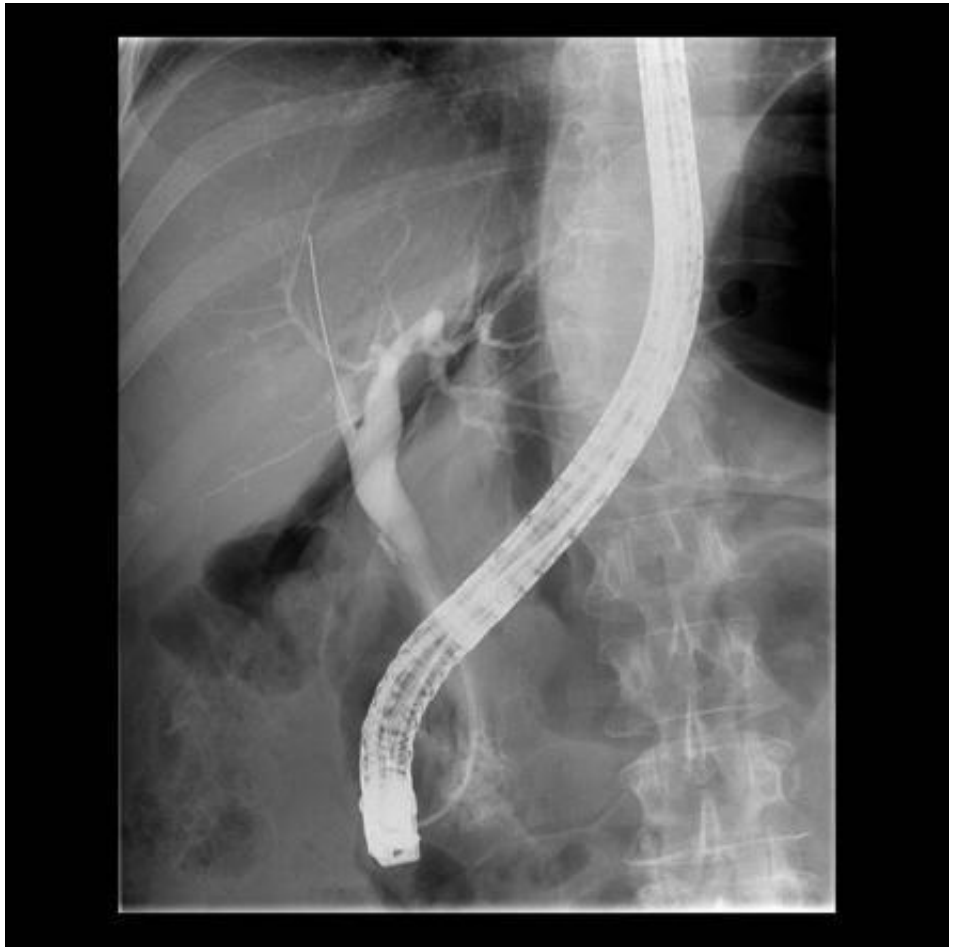
MRI



MRCP


intrahepatic bile ducts
pancreatic duct
common bile duct
duodenum

ERCP
*) diagnostic and therapeutic



Differential diagnosis of hepatocellular jaundice

Neoplasms
Hepatocellular carcinoma
Cholangio carcinoma
Metastases (bronchogenic, GI tract, breast, GU tract)
Lymphoma
Hemangioendothelioma
Hepatoblastoma
Metabolic/hereditary
Wilson disease
Alpha-1 antitrypsin deficiency
Hemochromatosis
Porphyrias
Congenital hepatic fibrosis
Fibropolycystic disease
Systemic
Acute ischemia
Severe heart failure
Tricuspid insufficiency
Constrictive pericarditis
Budd-Chiari syndrome
Venoocclusive disease
Telangiectasias
Sarcoidosis
Amyloidosis
Miscellaneous
Secondary biliary cirrhosis
Cryptogenic cirrhosis

Infections
Viral
Hepatitis viruses
Herpes viruses
"Hemorrhagic" viruses: yellow fever, Ebola, Marburg, Lassa
Adenoviruses, enteroviruses, etc
Bacterial
Tuberculosis, leptospirosis, syphilis, pyogenic abscess, *Brucella*, *Rickettsia*, *Tropheryma whippeli*, *Rochalimea*
Parasitic
Helminths: *Ascaris*, *Fasciola*, *Clonorchis*, schistosomiasis, echinococcosis
Protozoa: amebiasis, plasmodia, babesiosis, toxoplasmosis, leishmaniasis
Fungal
Candida, *Blastomyces*, *Coccidioides*, *Histoplasma*, *Cryptococcus*
Toxic/immunologic
Medications (allergic, idiosyncratic)
Alcohol
Chlorinated hydrocarbons (carbon tetrachloride, chloroform)
Amanita phalloides toxin
Aflatoxin B1
Vitamin A
Pyrrolizidine alkaloids
Arsenic
Phosphorous
Autoimmune hepatitis
Primary biliary cholangitis
Primary sclerosing cholangitis
Overlap syndrome
Autoimmune cholangiopathy
Nonalcoholic steatohepatitis

GI: gastrointestinal; GU: genitourinary.

Approach

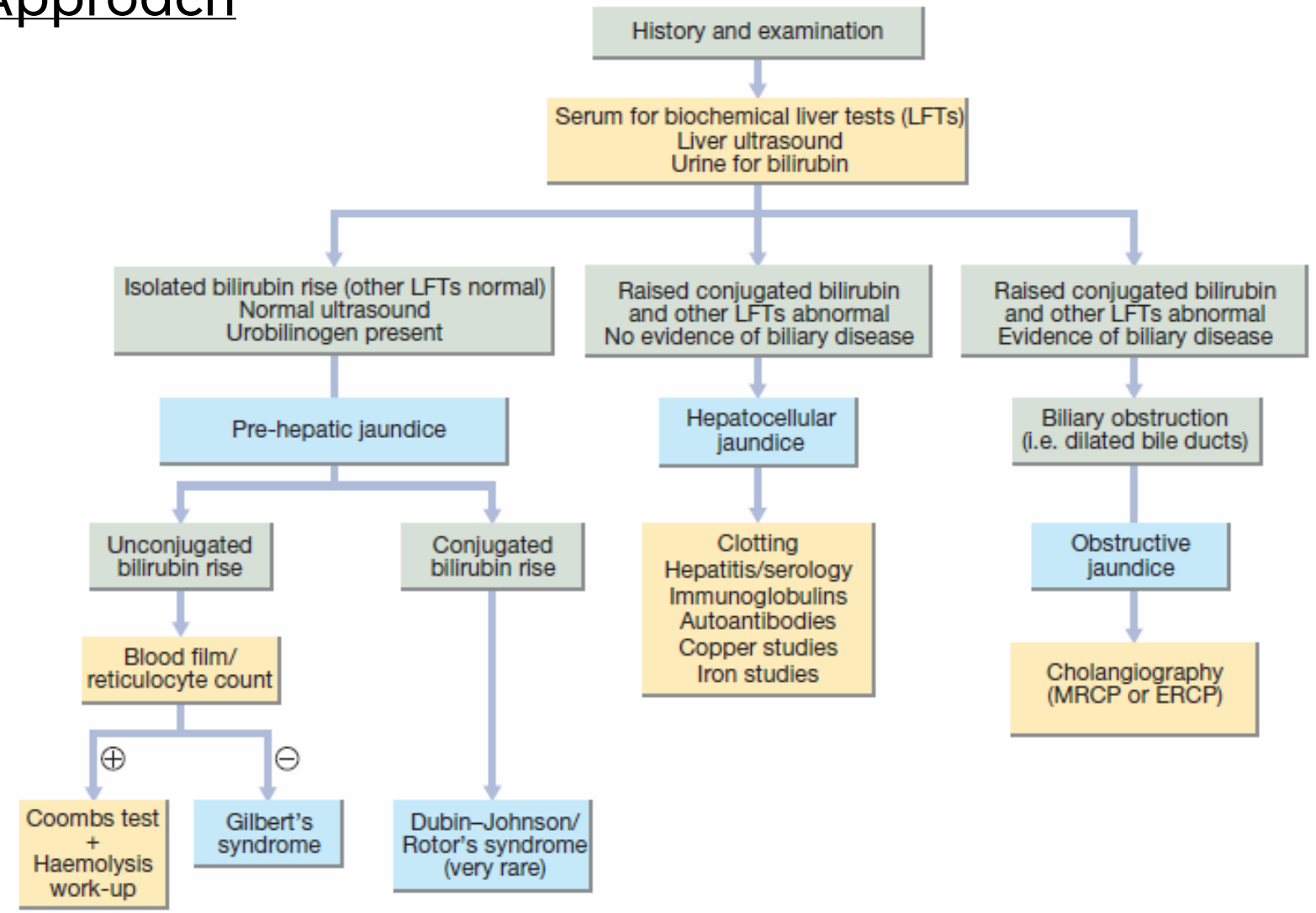


Fig. 22.15 Investigation of jaundice. (ERCP = endoscopic retrograde cholangiopancreatography; LFTs = liver function tests; MRCP = magnetic resonance cholangiopancreatography)

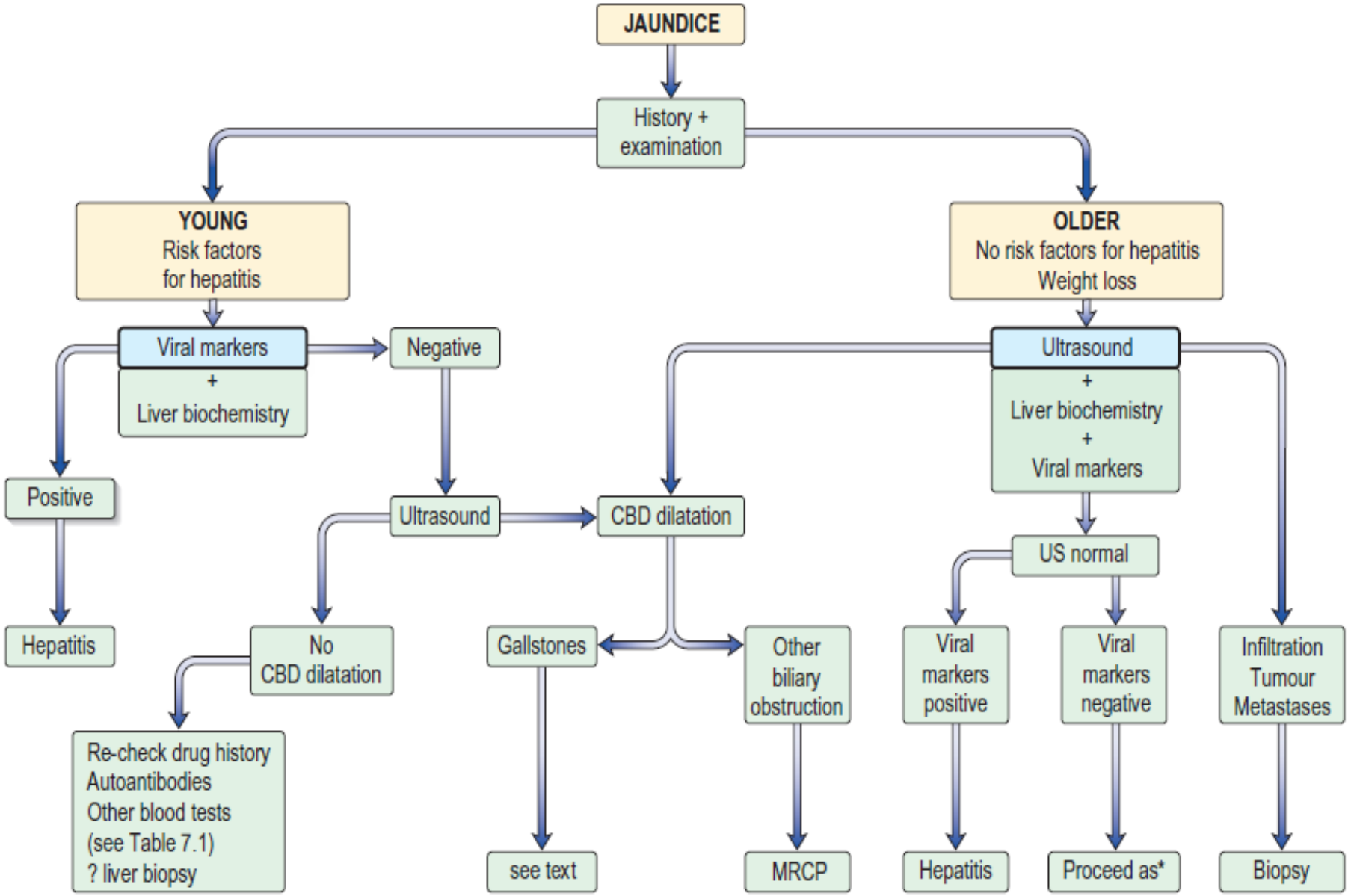


Figure 7.12 Approach to patient with jaundice. CBD, common bile duct; US, ultrasound; MRCP, magnetic resonance cholangiopancreatography. *Proceed as in bottom left box (Re-check drug history ...)

Management of Jaundice

Treatment Goals:

* Identify and treat the underlying cause of jaundice.
* Alleviate symptoms, manage complications, and prevent disease progression.
* Supportive care to optimize liver function and promote and maximize recovery.

Specific Management Approaches:

* Viral Hepatitis: Antiviral medications (e.g., interferon alpha, direct-acting antivirals: entecavir, tenofovir) for hepatitis B or C chronic infections.

* Alcoholic Liver Disease: Abstinence from alcohol, nutritional support.

* Biliary Obstruction: Endoscopic or surgical interventions to relieve the obstruction.

* Medication-Induced Jaundice: Discontinuation of the offending medication, supportive care, and monitoring liver function.

Symptom Relief

Itching management with antihistamines,

bile acid sequestrants, or ursodeoxycholic acid.

Nutritional Support: Adequate calorie and hydration, vitamin supplementation (especially vitamin K),thiamine(vitB1) for (alcoholic), and avoidance of hepatotoxic substances.

Complications if lifted untreated

Liver Failure: leading to hepatic encephalopathy, coagulopathy, and multi-organ failure.

Portal Hypertension: due to Liver fibrosis and cirrhosis

Cholangitis: Biliary obstruction can predispose to bacterial infection, leading to cholangitis, sepsis, or abscess formation.

Hepatocellular Carcinoma.

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Thank you