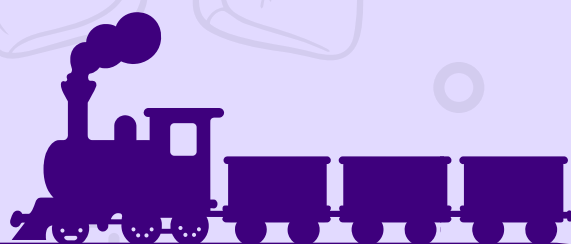




**HISTORY
TAKING
SERIES**



APPROACH TO JAUNDICE



**MUM
IM'S**

aka Hyperbilirubinemia

Definition of *Jaundice*

A yellow discolouration of the body tissue resulting from the accumulation of excess bilirubin



Some facts about



Jaundice

Normal range for
total bilirubin

3.4 to 20.0 $\mu\text{mol/L}$
(0.2 to 1.2 mg/dL)

Scleral icterus is detectable before
jaundice of the skin

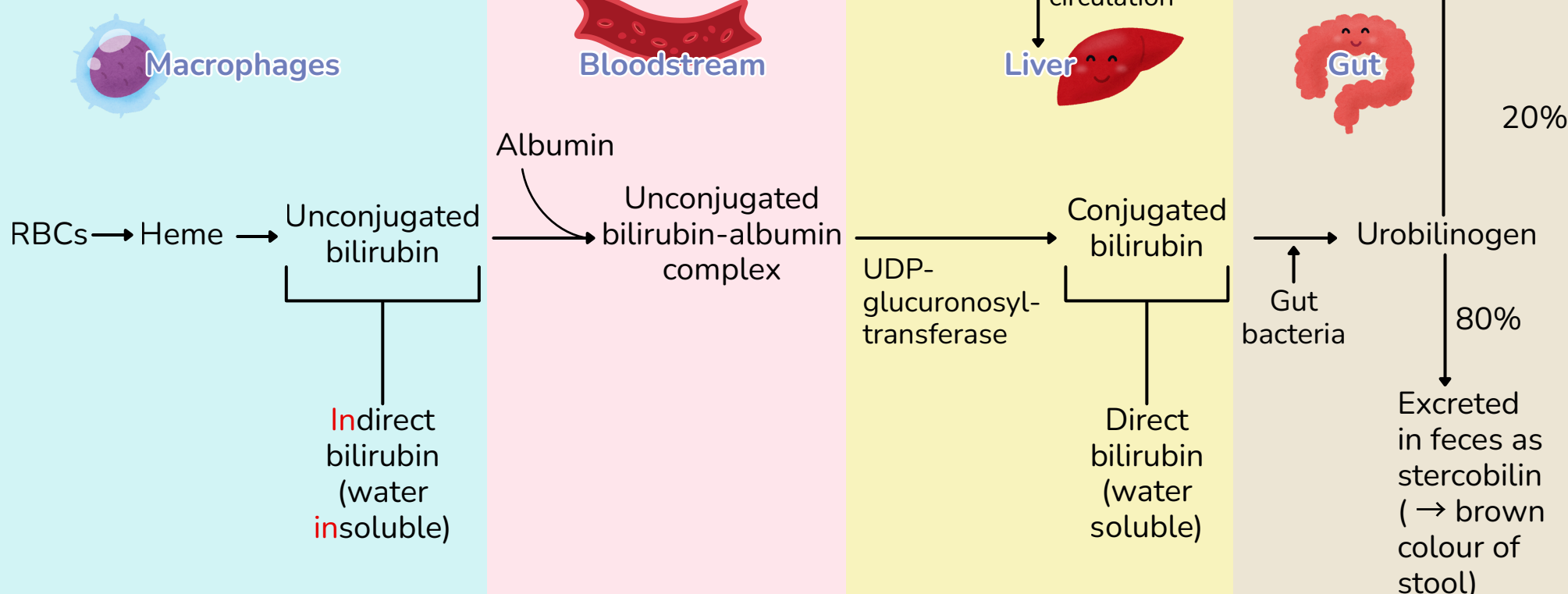
A cardinal symptom of hepatobiliary
disease and hemolysis

Common causes
of raised
bilirubin level

Hemolysis
Obstruction
Tumor
Liver disease



Bilirubin metabolism

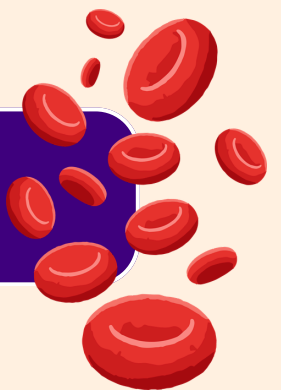


Causes of

Unconjugated Hyperbilirubinemia

Increased bilirubin production

1. Hemolysis
2. Dyserthropoiesis



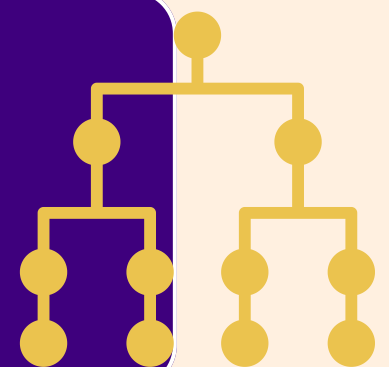
Impaired hepatic bilirubin uptake

1. Drug
2. Fasting

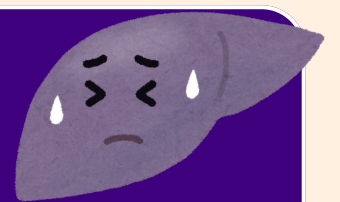


Impaired bilirubin conjugation
(↓ hepatic glucuronosyltransferase activity)

1. Hereditary
• Gilbert syndrome
• Crigler-Najjar syndrome



2. Acquired
• Neonates
• Liver disease (causes mixed hyperbilirubinemia; predominantly conjugated)



Causes of

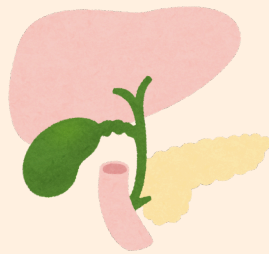
Unconjugated Hyperbilirubinemia



Thalassemia	• Thalassemic facies • Hepatosplenomegaly • Positive family history	
Sickle cell disease	• Painful vaso-occlusive crisis (acute severe bone pain, tachycardia, sweating, fever) • Positive family history	
G6PD deficiency	• Routinely screened in all newborns across Malaysia • Episodic jaundice after infections/drugs/fava beans • Positive family history	
Autoimmune hemolytic anemia	• Positive Coombs test • Warm AIHA: Personal history of cancer etc. • Cold AIHA: Personal history of mononucleosis, Mycoplasma infection etc.	
 Malaria	• Fever, malaise, headaches, myalgias, arthralgias, chills, and sweats • Travel history to endemic areas • Thrombocytopenia	
Transfusion reaction	• Recent blood transfusion	
Gilbert syndrome	• Asymptomatic or mild intermittent jaundice during fasting/stress/illness	

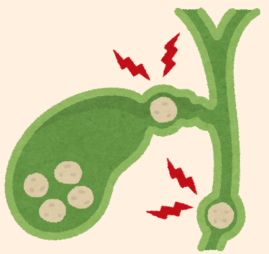
Causes of Conjugated Hyperbilirubinemia

Impaired hepatic secretion

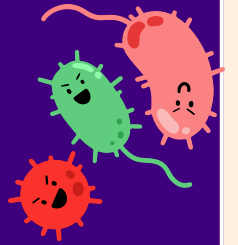


- Hepatocellular disease
 - Hepatitis
- Primary biliary cholangitis
- Cholestasis of pregnancy
- Familial disorders
 - Rotor's syndrome
 - Dubin-Johnson syndrome

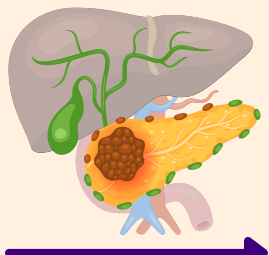
Biliary obstruction/
Intraductal obstruction



- Gallstones
- Biliary stricture
- Infection
 - Clonorchis
- Malignancy
 - Cholangiocarcinoma
- Primary sclerosing cholangitis



Extraductal obstruction



- Malignancy
 - Pancreatic adenocarcinoma
- Inflammation
 - Pancreatitis
- Lymphadenopathy

Causes of Conjugated Hyperbilirubinemia

Clinical Clues



Acute viral hepatitis	- Fever, malaise, anorexia, right upper quadrant discomfort - Contaminated food, sexual contact, IV drug use, blood transfusion
Alcoholic hepatitis	- Excessive alcohol consumption - AST/ALT ratio >2
Non-alcoholic Fatty Liver Disease (NAFLD)/Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)	- Obesity, diabetes, hypertension, hyperlipidemia - Independent of alcohol use (Usually asymptomatic or mild fatigue)
Liver cirrhosis	Ascites, upper gastrointestinal bleeding, hepatic encephalopathy, gynecomastia in males
Hepatocellular carcinoma/hepatoma	- Jaundice, tender hepatomegaly, ascites, polycythemia, anorexia, unexplained weight loss - Underlying liver cirrhosis
Liver metastases	Previous or underlying malignancy
Drug-induced liver injury	- Very high ALT - Common drugs: Paracetamol, antibiotics, anti-tuberculosis drugs
Autoimmune hepatitis	- Typically females - History of other autoimmune diseases (Eg thyroid disease, lupus)
Choledocholithiasis	- Pain in the right upper quadrant - Pruritus, dark urine, rigors

>>Continue next page

Causes of Conjugated Hyperbilirubinemia

Clinical Clues



Ascending cholangitis

- **Charcot's triad:** Right upper quadrant pain, fever, jaundice
- **Reynold's pentad:** Charcot's triad, shock, mental status changes

Benign biliary stricture

- Most commonly due to iatrogenic bile duct injuries (Eg cholecystectomy)



Pancreatic cancer (head)

- **Courvoisier sign:** Obstructive jaundice with palpable, nontender gallbladder
- Abdominal pain radiating to back
- **Weight loss** due to malabsorption and anorexia
- Migratory thrombophlebitis (Trousseau's syndrome)



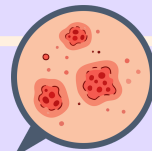
Cholangiocarcinoma

- Associated with gallstones, primary sclerosing cholangitis, Caroli's disease, choledochal cysts, chronic liver fluke infection (*Clonorchis sinensis*)

Primary biliary cholangitis (PBC)

- Autoimmune destruction of small intrahepatic bile ducts

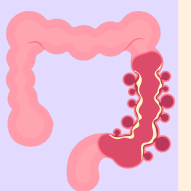
- Typically **middle-aged women**
- Pruritus, usually worse on the limbs
- Associated with other autoimmune conditions



Primary sclerosing cholangitis (PSC)

- Progressive inflammation & fibrosis of intrahepatic and extrahepatic bile ducts

- Typically middle-aged men
- **Inflammatory bowel disease especially ulcerative colitis**

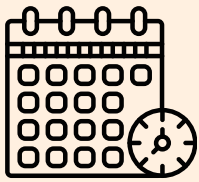


Leptospirosis (Weil's disease)

- Fever, myalgia, severe headache, conjunctival suffusion
- **Contact with urine of infected animals**
- Farmers, workers in the meat industry
- Recreational freshwater activities

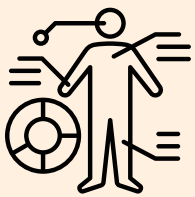


History of Presenting Illness



Duration of illness

- a. **Chronic** + Weight loss + Elderly: Consider malignancy
- b. **Acute** + Prodromal illness of malaise: Consider viral hepatitis



Associated symptoms

- a. **Dark urine & pale stools**: Consider causes of obstructive jaundice
- b. **Fatigue, dizziness, dyspnea**: Consider causes of hemolysis
- c. **Fever**: Cholangitis, liver abscess, hepatitis
- d. **Weight loss**: Malignancy, chronic liver disease
- e. **Pain in the right hypochondrium**: Gallstones, acute hepatitis
- f. **Anorexia, dark urine, fever**: Viral hepatitis, drug-induced hepatitis
- g. **Pruritus**: Suggests cholestasis
- h. **Arthralgia, rash**: Viral hepatitis, autoimmune hepatitis

RED FLAG

pointers for
Jaundice

1. Unexplained weight loss
2. Progressive jaundice, including painless jaundice
3. Oedema
4. Cerebral dysfunction (e.g.confusion, somnolence)
5. Marked abdominal pain
6. Gastrointestinal bleeding
7. Symptoms of coagulopathy

History of Presenting Illness

Past Medical History

1. Metabolic syndrome
2. History of malignancies
3. History of autoimmune diseases
4. Human immunodeficiency virus (HIV)
5. Surgery on the biliary tract or for carcinoma
6. Vaccination



Drug History



Mechanism	Example
Hemolysis	• Antimalarials (Eg primaquine)
Hepatitis	• Paracetamol overdose • Anti-tuberculosis drugs • Sodium valproate • Halothane • Statins
Cholestasis	• NSAIDs • Flucloxacillin (may be weeks after treatment) • Fusidic acid, co-amoxiclav, nitrofurantoin • Steroids (anabolic; the Pill) • Sulfonylureas • Prochlorperazine • Chlorpromazine

History of Presenting Illness

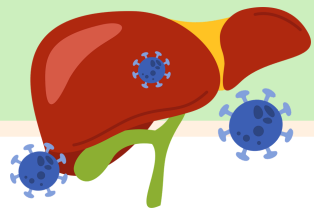


Substance History

1. IVDU, recent injections, blood transfusions: Hepatitis B or C
2. Excessive alcohol consumption: Alcoholic liver disease

Family History

1. Liver diseases
2. Autoimmune diseases
3. Metabolic syndrome
4. Hemolytic disorders



Social History

1. Tattoos, sex workers, men having sex with men: Hepatitis B or C
2. Travel history: Hepatitis A, malaria, leptospirosis (water activity)
3. Diet: Shellfish, drinking water





Physical Examination



Possible findings on examining the jaundiced patient

General

- Jaundice
- Loss of body hair
- Fever

Epstein-Barr mononucleosis

- Lymphadenopathy
- Tonsillitis

Spider naevi

Liver

- Large or small

Enlarged gall bladder (carcinoma head pancreas)

Tremor

- Wilson's syndrome
- Hepatic flap

Alcoholic facies

Parotid enlargement

Scratch marks (if obstructive jaundice)

Gynecomastia

Needle marks

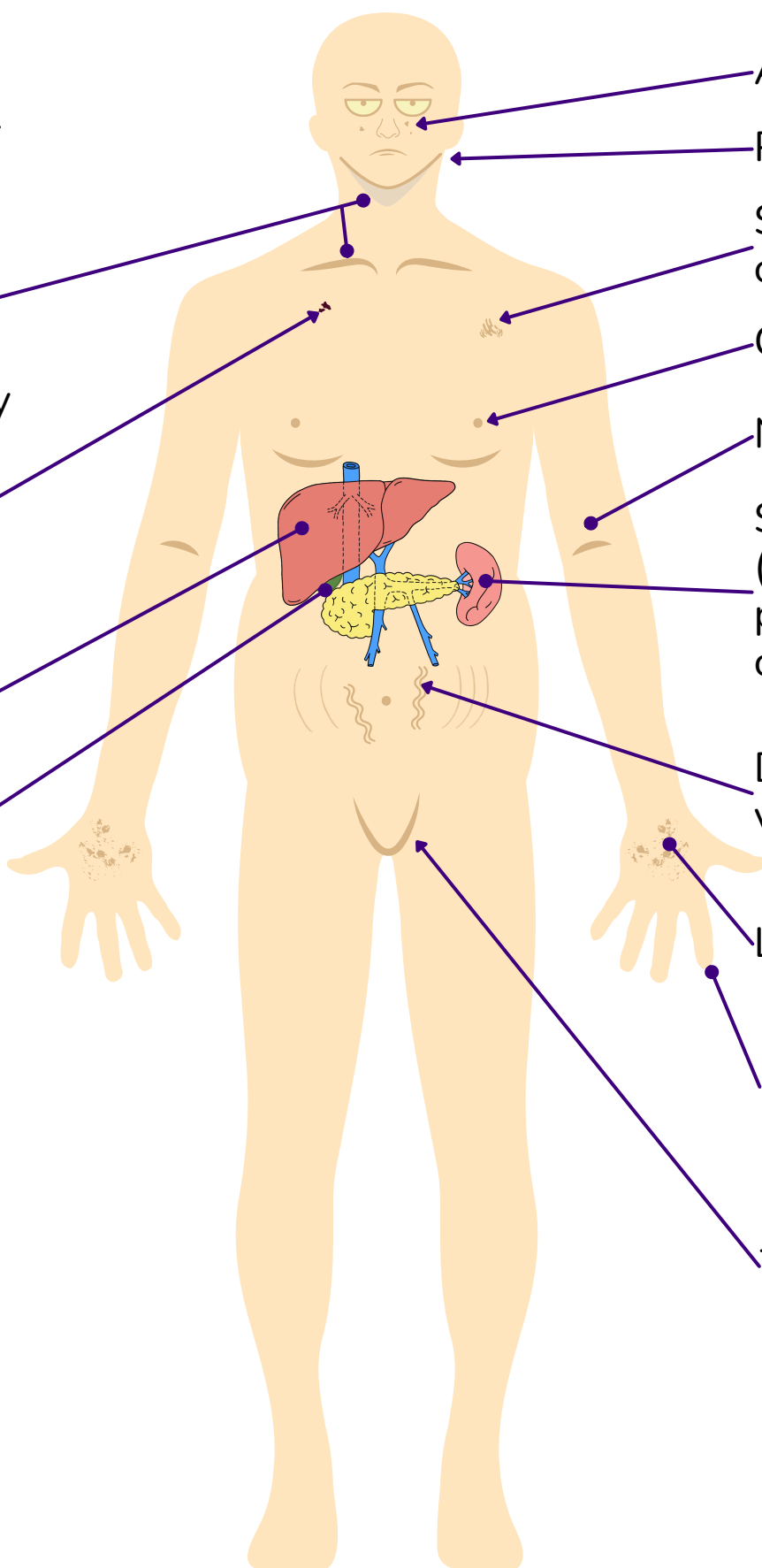
Splenomegaly (hemolytic anemia, portal hypertension, or viral hepatitis)

Dilated abdominal veins

Liver palms

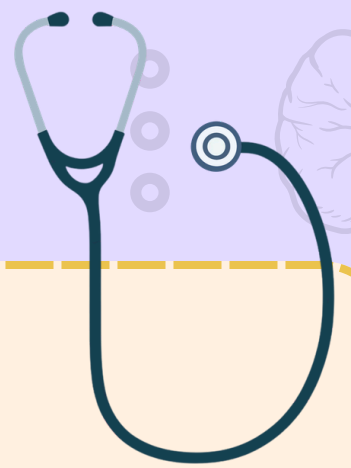
Leuconychia

Testicular atrophy





Diagnostic Approach to Hyperbilirubinemia



History

- Alcohol history / Metabolic Syndrome & BMI
- Drug history / Risk factors for viral hepatitis
- Personal family history / comorbidities

Clinical Pattern Recognition

Suspected alcohol risk
→ **Alcohol-related liver disease**
AST/ALT ratio

Hepatic liver enzymes
↑ AST or ALT

- Liver function test +
- FBC +
- Ultrasound +
- Liver etiology screen
 - HBV
 - HCV
 - Autoantibodies & immunoglobulins
 - Ferritin & transferrin saturation
 - HbA1c

Synthetic Failure

- Low albumin
- Prolonged INR

OR

Suggested Malignancy

- Weight loss
- Marked cholestasis

Urgent Referral

- Urgent ultrasound +
- Consider urgent referral to secondary care or admission

Isolated Raised Unconjugated Bilirubin with otherwise normal liver function tests

- Gilbert syndrome
- Hemolysis (Consider reticulocyte count, LDH, haptoglobin)

Cholestatic liver enzymes
↑ ALP or GGT

- Liver function test +
- FBC +
- Ultrasound +
- Liver etiology screen
 - Autoantibodies & immunoglobulins
 - Ferritin & transferrin saturation

NAFLD

- T2DM
- BMI >25
- Dyslipidemia
- Hypertension

NAFLD Fibrosis Score

- Normal ultrasound +
- Negative liver etiology screen +
- No NAFLD risk factors

Refer for further diagnostic evaluation

Abnormal Usg and/or positive liver etiology screen

Refer for further specialist management / investigation as defined by tests

Normal Usg and negative liver etiology screen but abnormal ALP & GGT

Investigations



Bedside Test

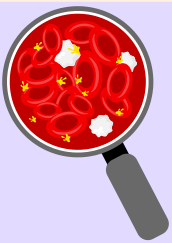
Urine dipstick

- Bilirubin
- Urobilinogen

Lab Test

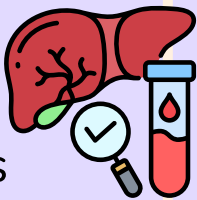


Full blood count



- Anemia
- Infections
- Thrombocytopenia: Common in cirrhosis
- Hemolysis (reticulocyte count)

Liver function tests



- Levels of bilirubin: Unconjugated or conjugated hyperbilirubinemia
- Hepatocellular pattern: ALT/AST elevated out of proportion to ALP
- Cholestatic pattern: ALP elevated out of proportion to ALT/AST

Haptoglobin & lactate dehydrogenase (LDH)

- Hemolytic anemia

Viral hepatitis serology

- Viral hepatitis

Coagulation profile

- Prolonged prothrombin time in acute and chronic liver diseases

HbA1c

- Diabetes (associated with NAFLD)



>>Continue next page

Investigations



Imaging



Transabdominal ultrasound

- Gallstones
- NAFLD
- Liver cirrhosis
- Splenomegaly
- Thrombosis in the hepatic vasculature

CT TAP

- Suspected malignancy

ERCP/MRCP

- Choledocholithiasis
- Ascending cholangitis
- PSC

Fibroscan (vibration-controlled transient elastography)

- Liver cirrhosis (measures liver stiffness)

Special Test

Peripheral blood smear

- Evaluation of the causes of hemolysis

ASMA, ANA, LKM-1, immunoglobulin

- Autoimmune hepatitis

AMA

- Primary biliary cholangitis

Alpha-fetoprotein (AFP)

- Hepatocellular carcinoma

Serum ceruloplasmin

- Low in Wilson's disease

Anti-nuclear cytoplasmic antibodies (ANCA)

- PSC

Ferritin & iron studies

- Hemochromatosis



ANA: antinuclear antibody; AMA: anti-mitochondrial antibody; ASMA: anti-smooth muscle antibody; CT TAP: CT thorax, abdomen, and pelvis; ERCP: endoscopic retrograde cholangiopancreatography; LKM-1: liver-kidney microsomal antibody type 1; MRCP: magnetic resonance cholangiopancreatography

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10. First Aid Q&A for the USMLE Step 1 3rd Edition Gastrointestinal Question 1 & 50

Quiz time!

Question 1

A 50-year-old man presents to his physician because of a 6.8-kg weight loss over the past month, epigastric pain radiating to the back, and jaundice. He also complains of redness, swelling, and tenderness of his left lower extremity.

Laboratory studies show

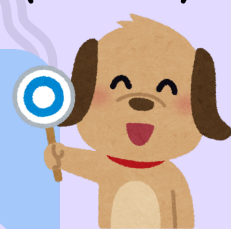
- Amylase level 500 U/L
- Lipase level of 300 U/L
- Alkaline phosphatase level 500 U/L



Which **tumor markers** are most likely to be **elevated** in this patient?

- (A) a-Fetoprotein and b-human chorionic gonadotropin
- (B) a-Fetoprotein and CA 19-9
- (C) a-Fetoprotein and carcinoembryonic antigen (CEA)
- (D) b-Human chorionic gonadotropin and carcinoembryonic antigen (CEA)
- (E) CA 19-9 and carcinoembryonic antigen (CEA)

Find the answer in the comment section!



Quiz time!

Question 2



A 35-year-old woman who is HIV positive presents with jaundice and right upper quadrant abdominal pain. She reports having had multiple episodes of jaundice over the past 10 years. Physical examination is remarkable for scleral icterus, marked ascites, and splenomegaly.

A hepatitis panel is positive for HBsAg and anti-HBc IgM, but negative for HBsAb and anti-HAV IgM.

Which of the following would most likely be **lower than the normal reference range** in this patient?

- (A) Alkaline phosphatase
- (B) Bilirubin
- (C) Platelet count
- (D) Prothrombin time
- (E) Transaminases

Find the answer in the comment section!

