Jaundice = Icterus

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Sources:
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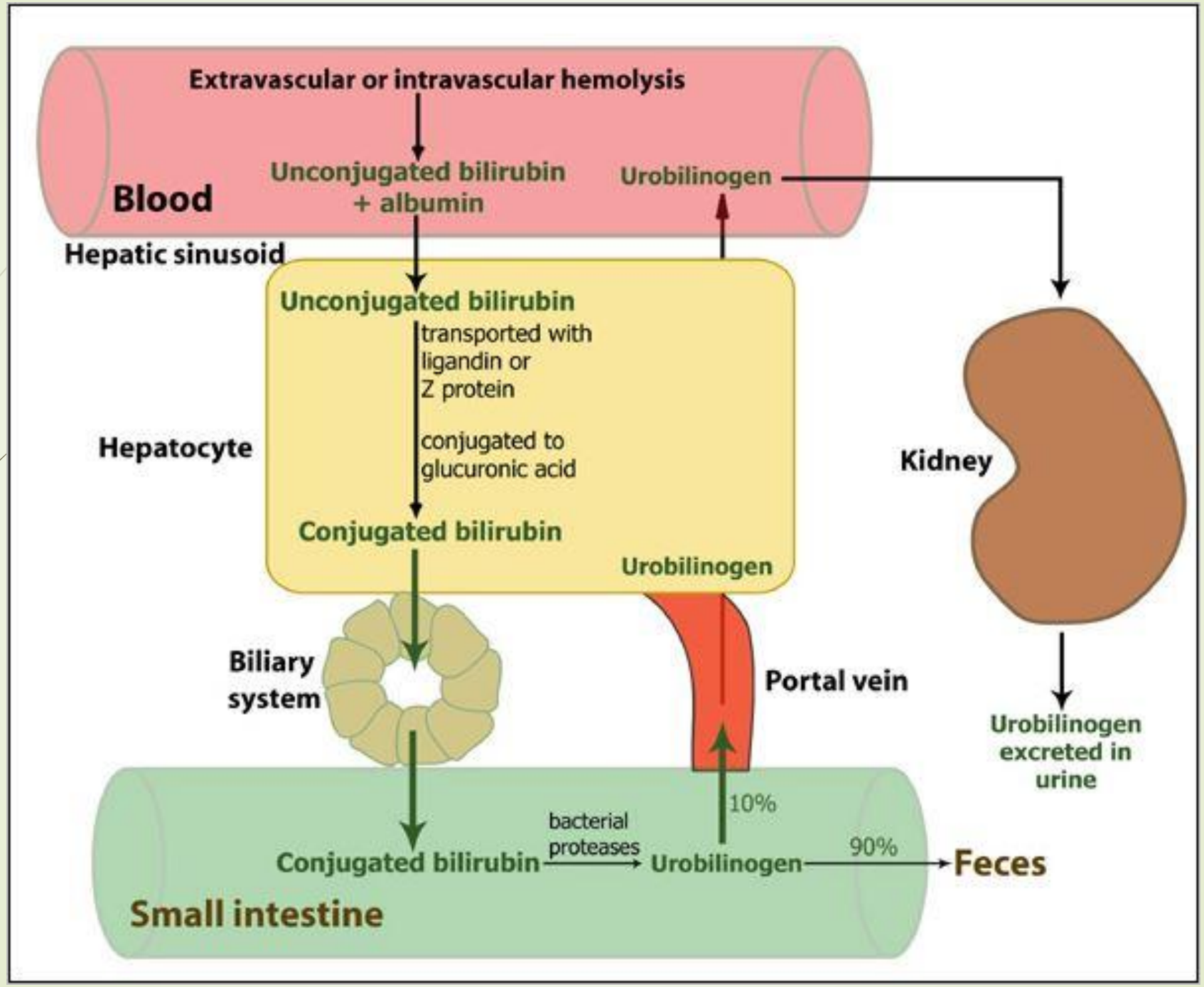
2. Anna Taylor Sally Stapley William Hamilton, *Family Practice*, Volume 29, Issue 4, 2012, 416–420,

What is the jaundice?

- Yellowish discoloration of the skin, sclera and mucous membranes because of hyperbilirubinemia, and deposition of bile pigments
  - Bilirubin has affinity to elastin (collagenous tissue),
  - scleral icterus is more sensitive
- Disequilibrium between bilirubin production and clearance
- Serum bilirubin level higher than 2 mg/dl
  - Normal range: total: 0.3-1 mg/dl, indirect:0,2-07, direct: 0,1-0,4 mg/dl) 1 mg/dl=17.1 µmol/l
  - Clinically obvious: 2- 2.5 mg/dl
- Jaundice is a sign (symptom) -not a disease - that can occur in many different diseases

What is bilirubin?

- Yellowish pigment found in bile; Bile = a fluid made by the liver
- The breakdown product of hemoglobin from injured red blood cells and other hem-containing proteins and ineffective erythropoiesis in the bone marrow
- Produced by cells of reticuloendothelial system
- Released to plasma mostly bound to albumin. A small portion of unconjugated bilirubin is unbound, that is neurotoxic (chronic form of the bilirubin encephalopathy= kernicterus)
- Under normal conditions, unconjugated bilirubin is rapidly taken up by hepatocytes, conjugated to water soluble bilirubin and is excreted through bile channels into small intestine


Extravascular or intravascular hemolysis
Blood
Unconjugated bilirubin
+ albumin
Urobilinogen
Hepatic sinusoid
Unconjugated bilirubin
transported with
ligandin or
Z protein
Hepatocyte
conjugated to
glucuronic acid
Conjugated bilirubin
Urobilinogen
Kidney
Biliary
system
Portal vein
Urobilinogen
excreted in
urine
10%
bacterial
proteases
Conjugated bilirubin
Urobilinogen
90%
Feces
Small intestine

The possible causes of hyperbilirubinemia

- Elevated production by reticuloendothelial system
- Failure of hepatic uptake
- Failure of conjugation or excretion
- Obstruction of biliary excretion to intestine

Types and causes of hyperbilirubinemia

Type of hyperbilirubinemia	Causes
Unconjugated hyperbilirubinemia (predominant indirect-reacting bilirubin)	**Increased bilirubin production** (hemolytic anemia, hematoma, pulmonary infarction, Impaired bilirubin uptake and storage (Gilbert syndrome, Crigler-Najjar syndrome, drug reaction)
Conjugated hyperbilirubinemia (**predominant direct reacting bilirubin)**	**Hereditary cholestatic syndromes**: Faulty excretion of bilirubin conjugates (Dubin-Johnson and Rotor syndrome, mutation in genes coding for bile salt transport proteins
	Hepatocellular dysfunction: biliary epithel and hepatocyte damage (cirrhosis, hepatitis), intrahepatic cholestasis (drugs, biliary cirrhosis, sepsis, postoperative jaundice), others: cholangitis, sarcoidosis, lymphomas, toxins, mononucleosis)
	Biliary obstruction: choledocholithiasis, atresia, sclerosing cholangitis, carcinoma of biliary tract, external pressure of biliary duct, pancreatitis, pancreatic neoplasm

Increased red blood cell turnover

- The major source of bilirubin are RBCs
  - Hemolytic anemia
  - Ineffective erythropoiesis (thalassemia, megaloblastic anemia)
- Laboratory result: increased unconjugated bilirubin
- In patients with chronic hemolytic anemia often develop bilirubinate gallstones

Gilbert's syndrome

- Most common inherited cause of unconjugated hyperbilirubinemia
- Benign disease, autosomal recessive mode of inheritance
- Prevalence: 3-13% of general population
- Mild deficiency (10-50% of normal activity) of bilirubin glucoronosyltransferase attributed to mutation in the encoding gene
- It typically first presents as mild intermittent unconjugated hyperbilirubinemia in otherwise asymptomatic young adults
- Jaundice is mild and fluctuating, often related to stress, fasting or infection
- Mildly elevated serum unconjugated bilirubin level, the other liver function tests are normal
- Not associated with any morbidity
- Dg: Administration of iv. niacin or oral rifampin and monitoring the subsequent rise in bilirubin concentration

Crigler-Najjar syndromes

- Autosomal recessive disorder
- Type I : Serum bilirubin > 20 mg/dl
  - Complete absence of bilirubin UDP-glucuronosyltransferase 1-A1 expression in liver tissue
  - Fatal due to kernicterus – rapid death in neonate
- Type II: Serum bilirubin < 20 mg/dl
  - Reduced levels (< 10% of normal)of bilirubin UDP-glucuronosyltransferase 1-A1 expression in liver tissue
  - Bile is pigmented instead of pale or dark as normal
  - No risk of kernicterus
  - Dg: by gene analysis and sequencing the coding region for known mutations

Congenital hyperbilirubinemias

Dubin Johnson syndrome	Rotor syndrome
Autosomal recessive	Autosomal recessive
Mild conjugated hyperbilirubinemia	Mixed conjugated and unconjugated hyperbilirubinemia
Defect in the canalicular cationic transport protein (MRP2)	Defect of secretion of conjugated bilirubin into sinusoidal blood
Black pigmentation of the liver	No liver pigmentation
Normal total urinary coproporphyrin excretion, 80% coproporphyrin I	Increased total coproporphyrin excretion, 65% coproporphyrin I
CT: attenuation of the liver	
No clinical significance (occasional abdominal pain)	No clinical significance

Coproporphyrin I is a metabolic byproduct of hem synthesis and also an endogenous substrate of MRP2

Causes of hepatocellular jaundice

- **Infections**
  - Hepatitis viruses
  - Hemorrhagic viruses(e.g. Marburg, Ebola, Lassa, etc.)
  - Bacterial (leptospirosis, tuberculosis, brucellosis, etc.)
  - Protozoa, helminthiasis and fungal
- **Toxic, immunologic**
  - Medication
  - Alcohol
  - Toxins
  - Nonalcoholic steatohepatitis
  - Autoimmune hepatitis
  - PBC, PSC
- **Systemic**
  - Ischemia (heart failure)
  - Budd-Chiari syndrome (occlusion of the hepatic veins)
  - Sarcoidosis, amyloidosis
- **Neoplasms**
  - Hepatocellular carcinoma
  - Cholangiocarcinoma
  - Metastases
  - Lymphoma
- **Metabolic/hereditery**
  - Wilson's disease
  - Hemochromatosis
  - Porphyria's
  - Alpha-1 antitrypsin deficiency

Primary biliary cirrhosis

- Chronic liver disease of unknown origin, probably autoimmune characterized by inflammation and granulomatous destruction of intrahepatic bile ducts
- Male-female ratio 1:10, age: 30-65 years
- Middle aged women with obstructive jaundice, xanthomas, xantholesmas, increased serum cholesterol, fatigue, cirrhosis
- Increased conjugated bilirubin increased ALP, antimitochondrial antibody
- Other autoimmune diseases

Primary sclerosing cholangitis

- Chronic liver disease of unknown etiology characterized by segmental inflammation and fibrosing destruction of intra and extrahepatic bile ducts
- Male-female ratio 2:1, age: 20-40 years, most associated with ulcerative colitis
- Microscopy: periductal inflammation, concentric fibrosis around bile ducts, segmental stenosis of the bile ducts
- Beaded appearance of the bile ducts on cholangiogram
- ANCA positivity

Posthepatic obstructive jaundice

- Obstruction can be
  - Intraluminal (stone, cysts, worms)
  - Luminal: stricture (benign or cholangiocarcinoma, periampulary carcinoma
  - Klatskin tumor: hilar cholangiocarcinoma occurring at the confluence of the right and left hepatic bile ducts
  - Extra luminal: pancreatic cancer, lymph nodes, choledochal cyst

Common signs and symptoms in patients with jaundice

- Yellow discoloration of the skin, mucous membranes and the withes of eyes
- Light-colored stools
- Dark colored urine
- Itching of the skin
- Nausea-vomiting
- Abdominal pain
- Fever
- Weakness
- Involuntary weight loss
- Bleeding
- Confusion
- Swelling of the legs and abdomen

Different color

Pale yellow: in hemolytic jaundice
Orange yellow: in hepatic and moderate cholestatic jaundice
Yellow green: in complete obstruction

Urobilinogen

- Conjugated bilirubin excreted into the duodenum through bile is converted by bacterial action to urobilinogen in the intestine
- The major part of urobilinogen is eliminated in the feces
- A part of urobilinogen is reabsorbed in blood, which undergoes recycling (enterohepatic circulation)
- A small amount, which is not taken up by liver, is excreted in urine
- Upon oxidation the urobilinogen (colorless) converted to urobilin, which is orange-yellow in color
- Normal daily excretion of urobilinogen in urine: 0.5-4 mg, therefore a small amount of urobilinogen is normally detectable
- A 2-hour post meal sample is preferred
- Urine urobilinogen
  - In hemolytic jaundice: elevated
  - In hepatocellular jaundice: elevated
  - In obstructive jaundice: absent

Bile pigments in urine

- The bile pigments are bilirubin and biliverdin
- Bilirubin converts to non-reactive biliverdin on exposure light and on standing at room temperature.
  - Biliverdin cannot be detected by tests that detect bilirubin, therefore fresh urine sample is needed that is kept protected from light
- Presence of bilirubin in urine indicates conjugated hyperbilirubinemia.
  - Unconjugated bilirubin is water-insoluble

Urine and stool color and presence or absence of pruritus according to the types of jaundice

Type	Prehepatic	Hepatic	Posthepatic
Urine color	normal	dark	dark
Stool color	normal	normal	acholic
Pruritus	no	no	yes

Taking medical history in patients with jaundice

Age	Possible backgrounds of jaundice
Age younger than year 20	Familial disorders of bilirubin metabolism: Gilbert, Crigler-Najjar, Dubin-Johnson and Rotor syndrome
Age between 20 and 40	Wilson's disease, Autoimmune hepatitis (mostly in women), Primary sclerosing cholangitis (especially in men)
Age older than 40 years	Primary biliary cirrhosis (in women), hemochromatosis, Pancreatic or bile duct cancer
Time course	
Was the onset abrupt?	Cholangitis, choledocholithiasis, Acute hepatitis, sepsis, Budd-Chiari syndrome,
Was the onset over weeks to months?	Pancreatic or biliary tract cancer, any cause of cirrhosis, infiltrative liver disease, heart failure
Are the jaundice episodes recurrent and self-limited?	Biliary colic or familiar disorders of bilirubin metabolism

Serious and benign causes of signs and associated symptoms in patients with jaundice

Sign/symptoms	Serious causes	Benign causes
Dark urine	Hemoglobinuria, any cause of conjugated hyperbilirubinemia	Medication (rifampicin), beets, myoglobinuria
Fever	Cholangitis, gallstone disease, acute hepatitis, sepsis	hematoma
Right upper quadrant pain	Cholangitis, gallstone disease, acute hepatitis, Budd-Chiari syndrome, right-sided heart failure	Varicella zoster
Confusion	Cholangitis, sepsis, hepatic encephalopathy, intracranial bleeding (coagulopathy), hypoglycemia	Any cause of delirium
Bleeding	Thrombocytopenia (hypersplenia, fulminant hepatic failure), DIC	Minor trauma to the affected site
Involuntary weight loss	Pancreatic or hepatobiliary cancer	

Taking medical history in patients with jaundice

Open-ended questions	
How you were feeling when you first noticed the color change?	Non-judgmental attitude. The patients has to feel safe revealing details of high-risk behaviors (e.g.. Alcohol intake, illicit drug use, suicide attempt)
What other symptoms have accompanied the color change?	Differential diagnosis
Closed-ended question	**Possible backgrounds of jaundice**
Do you drink alcohol?	Acute alcoholic hepatitis, cirrhosis, liver injury at therapeutic doses of acetaminophen
Have you ever used injection drugs?	Hepatitis C: 65% prevalence among injection drug users
Have you been recently exposed to anyone with hepatitis	Hepatitis A is a common cause of food-borne outbreaks of hepatitis Hepatitis B: transmission through sexual activity

Taking medical history in patients with jaundice

Closed-ended question	Possible backgrounds of jaundice
Have you received blood transfusion?	The risk of the transmission of hepatitis B and C is low today, but transfusions prior 1990 were not routinely tested for hepatitis C
Does anyone in your family have hepatitis or history of jaundice?	Familial causes: hemochromatosis, Wilson's disease, Gilbert's syndrome etc.
Have you become jaundiced with prior illnesses?	Gilbert's syndrome often coincides with viral illness
Do you have a history of heart failure?	Right heart failure or constrictive pericarditis
Do you have a history of ulcerative colitis?	Primary sclerosing cholangitis develops in 1-4% of patients with ulcerative colitis.
Are you diabetic?	Diabetes and obesity are risk factors for NAFLD. Diabetes is a manifestation of hemochromatosis
Have you recently ingested any acetaminophen, new medications, herbal supplements or wild mushrooms	Fulminant hepatic failure from numerous medications or Amanita mushrooms

Diagnostic steps in patients with jaundice

- Physical examination – may be hepatomegaly
- Bilirubin blood test – increased
- Urine analysis – urobilinogen and bilirubin
- Other tests:
  - Liver function tests
  - Hepatitis virus panel
  - Complete blood count
  - Abdominal ultrasound
  - Abdominal CT scan
  - Endoscopic retrograde cholangio-pancreatography
  - Percutan transhepatic cholangiogram (PTCA)
  - Liver biopsy
  - Cholesterol level, prothrombin time, autoimmune panel

Serum aminotransferases

- AST/ALT are the sensitive markers of acute hepatocellular injury
- AST (SGOT) is both cytosolic and mitochondrial, but extrahepatic sources: heart/muscle/kidney/brain – less specific
- ALT (SGPT) is a cytosolic enzyme, primarily found in liver – more specific
- Normal ALT-AST ratio is 0.7 to 1.4
- In case of necrosis of the cells containing these enzymes, aminotransferases are released into the blood, the concentration in blood correlates with the extent of tissue damage
  - Most marked elevation (> 15 times normal) in acute viral hepatitis, toxin induced hepatocellular damage, and centrolobular necrosis due to ischemia (congestive heart failure)
  - Moderate elevation (5-15 times): in chronic hepatitis, autoimmune hepatitis, alcoholic hepatitis, drug-induced hepatitis, acute biliary tract obstruction
  - Mild elevation (1-3 times): in cirrhosis, nonalcoholic steatosis, cholestasis
- ALT and AST are elevated in acute viral hepatitis even before the appearance of icterus
- Mitochondrial AST is released primarily in alcoholic hepatitis
- Persistence of elevated AST and ALT indicates of development of chronic hepatitis

Serum gamma-glutamyl transferase (GGT)

- High levels of GGT are present in liver, pancreas, kidney and prostate
- GGT is found primarily on the canalicular surface of hepatocytes. Bile acids accumulate in cholestasis and dissolve membrane fragments, releasing bound enzymes into the plasma
- Measurement of this enzyme is useful in following liver diseases:
  - Alcoholism: increased enzyme activity, and is a helpful clue in suspected cases of occult alcoholism
  - Cholestasis: elevation of GGT parallels that of ALP and 5'-NT in liver diseases like primary biliary cirrhosis or sclerosing cholangitis
  - Recovery in acute hepatitis: GGT is the last enzyme that returns to normal following acute hepatitis and its normalization is indicative of a favorable outcome

The use of liver function tests in the differential diagnosis of jaundice

Liver function test profile in hepatocellular disease

- Marked elevation of ALT and AST (> 500 IU)
- Mild, moderate increase of alkaline phosphatase activity (less than 3x to normal)
- Hyperbilirubinemia – if present is mixed, conjugated and unconjugated type

Liver function test profile in cholestatic disease

- Marked elevation of ALP
- Elevation of GGT
- Mildly increased or normal aminotransferase
- Elevation of conjugated bilirubin

Treatment of jaundice

- Depends on the cause of the underlying condition leading to jaundice and any potential complications related to it
- Watchful waiting
- Causal therapy
- Supportive therapy
- Discontinuation of drug/toxin
- In certain cases of newborn jaundice special colored lights or/and exchange transfusions
- Surgical treatment

Case report

- Male patient, 68 years
- **Chief complaints**:
  - Abdominal pain 20 days
  - Generalized itching 20 days
  - Fever 3 days
- Past history
  - No history of similar complaint previous surgery, previous jaundice or drug intake in the past
- Family history
  - No history of similar complaints in the family was noted
- Personal history
  - Appetite reduced, 6 kg weight loss
  - Pale stool
  - Sleep disturbed due to itching
  - Smoker since 20 years
  - Not an alcoholic

Evaluation of data of medical history

- Past history
  - No history of similar symptoms in the past : relapsing hepatitis, choledocholithiasis
  - No surgery in the past: biliary stricture, recurrent or retained stones, anesthesia exposure
- Family history
  - Wilson disease
  - Dubin-Johnson or Rotor syndrome
  - Antitrypsin deficiency
- Alcohol
  - Alcoholic hepatitis can lead to cholestasis

Physical examination

- RR: 130/80 mmHg, p:62/min, respiratory rate:16/min,
- Scratch marks over the abdomen and peripheries
- Normal S1 and S2 without murmur
- Normal vesicular breathing, no added sound
- Nervous system: normal
- Abdomen: normal size and shape, no dilated veins
  - Tenderness in right hypochondrium and epigastrium
  - Palpable hard mass of about 5x3 cms in epigastrium with an irregular border
  - hepatomegaly, 3 cm below the costal margin
  - No splenomegaly, no free abdominal fluid

First impression ?

Obstructive jaundice owing to carcinoma of the head of pancreas

Periampullary carcinoma: heterogenous group of neoplasm arising from the

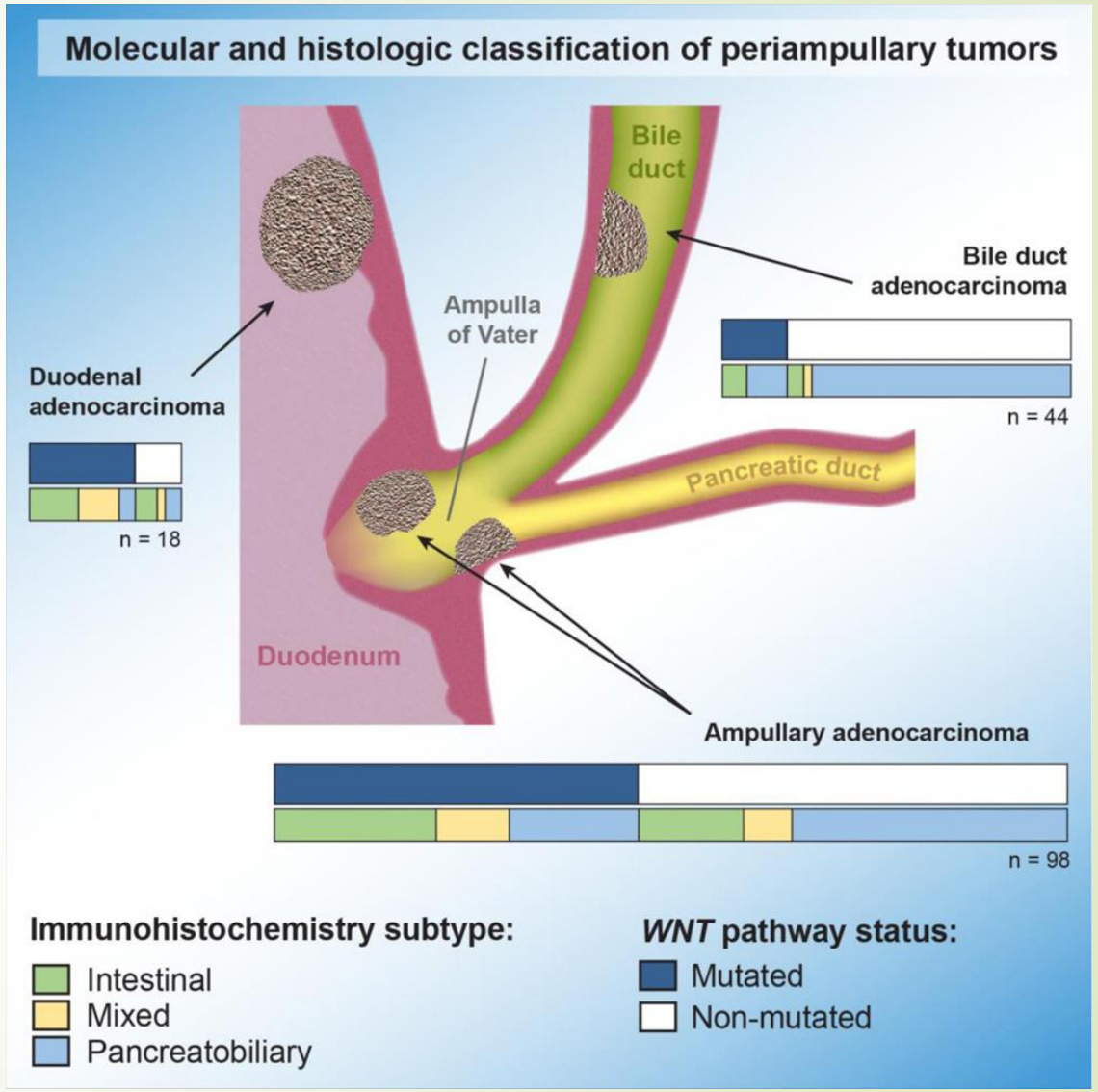
Periampullary region: within 2 cm of ampulla Vateri in the duodenum

Head of pancreas

Ampulla of papilla Vateri itself

Distal common bile duct

The second part of duodenum



Clinical presentations of periampullar pancreas carcinoma

- Jaundice – 75%
- Weight loss – 51%
- Abdominal pain – 39%
- Nausea, vomiting – 13%
- Pruritus – 11%
- Palpable mass in the epigastrium or in the right upper quadrant – 9-15%
- Fever – 3 %
- Gastrointestinal bleeding – 1%

Causes of obstructive jaundice

Intrahepatic causes

- Familial/hereditary disorders
- Acquired
  - Cholestatic drugs
  - Biliary cirrhosis
  - Sclerosing cholangitis
  - Viral and alcoholic hepatitis
  - Pregnancy induced cholestasis

Extrahepatic causes

- Benign
  - Gallstone (most common cause)
    - Intermittent pyrexia, rigors, pain, jaundice
    - Murphy's sign
  - Chronic pancreatitis
  - Parasitic infection
  - Choledochal cysts
- Malignant
- Carcinoma of pancreas, periampulla/bile duct/gallbladder
  - Painless, progressive deep jaundice, weight loss, Courvoisier's sign