Approach to the Jaundiced Patient

- Educational Objectives:
  - To review bilirubin metabolism
  - To review diseases that affect the biliary tree
  - To become familiar with the clinical approach to the jaundiced patient
  - To be able to differentiate between the two major types of jaundice:
    - Obstructive
    - Hepatocellular jaundice
  - To understand the diagnostic studies used to diagnose the jaundiced patient
**Biliary System**

- Bile Canaliculus
- Terminal Ductules
- Interlobular Bile Ducts
- Left (or R) Hepatic Ducts
- Common Hepatic Ducts
- Cystic Duct
- Gallbladder
- Common Bile Duct

**Bile**

- Bile contains bile acids
- Critical for digestion and absorption of fats and fat-soluble vitamins in the small intestine
- Many waste products, including bilirubin, are eliminated from the body by secretion into bile and elimination in feces
- Adults produce 400-800 mL of bile daily
- Hepatocytes secrete bile into canaliculi
- Flows into bile ducts
- Contains large quantities of bile acids, cholesterol
- As bile flows, it is modified by addition of a watery, bicarbonate-rich secretion from ductal epithelial cells
Role of Bile Acids in Fat Digestion

- Bile acids are derivatives of cholesterol synthesized in the hepatocyte
- Cholesterol is converted into bile acids
  - Cholic Acid
  - Chenodeoxycholic Acid
- 500 mg of cholesterol are converted into bile acids and eliminated in bile every day
- Bile Acids are amphipathic
  - Contain both lipid soluble and hydrophilic faces
  - Emulsification of lipid aggregates
  - Solubilization and transport of lipids into an aqueous environment

Heme Metabolism / Bilirubin Synthesis and Excretion

- Bilirubin is a useless waste product of heme breakdown
- Heme released from red blood cells can act as an inhibitor of new heme synthesis unless old heme is removed from the system
- Converted to Bilirubin in phagocytic Cells
  - Heme → Biliverdin → Bilirubin
- Transported in blood tightly bound to serum albumin
- Delivered to the hepatocyte and stripped off albumin

Elimination of Bilirubin

- Conjugated bilirubin is secreted into the bile canaliculus as part of bile and then delivered to the small intestine
- Bacterial metabolizes bilirubin to either be eliminated in feces or after reabsorption, in urine
Bilirubin Metabolism

- 4 mg/dL of bilirubin is produced daily
- 80%-85% from catabolism of RBC’s
- Bilirubin is liberated into plasma, bound to albumin, transported to liver where uptake, conjugation and excretion (rate limiting step) into bile occurs.
- Conjugated fraction (water soluble) is excreted into aqueous bile.
- Unconjugated fraction remains in the blood.

Hepatocyte function includes all of the following except:

1. Drug detoxification
2. Protein synthesis
3. Gluconeogenesis
4. Urea formation by deamination of amino acids
5. Breakdown of hemoglobin
Approach to the Jaundiced Patient

- Jaundice

Introduction

- Jaundice (icterus) describes the yellow pigmentation of skin/ sclera/mucous membranes produced by increased serum bilirubin

- Hyperbilirubinemia can be classified into 2 major categories based on the predominant type of bile pigments in the plasma.
  - Unconjugated hyperbilirubinemia (water insoluble)
  - Conjugated hyperbilirubinemia (water soluble)

A 24 yo is referred for hyperbilirubinemia. He is asymptomatic, no drug or etoh use. Liver tests have previously been normal and he has given blood several times this year without being refused. He is on no medications, no family history of liver disease. Physical examination is normal. T. bilirubin 2.1 mg/dL, (0-1.5 mg/dL). Direct bilirubin is 0.2 mg/dL. Liver enzymes, albumin, and INR are normal. What should the next step in management be?

1. Liver imaging (MRI, U/S)
2. Liver biopsy
3. Genetic testing for a hepatic transport defect
4. Genetic testing for a hepatic metabolic defect
5. Reassurance, no further testing.
Diagnostic Approach

- Careful history and physical examination
- Screening laboratory evaluation
- Formulation of a differential diagnosis
- Further diagnostic studies to confirm diagnosis

Evaluation is usually not urgent except in the following instances:
- Massive hemolysis
- Ascending cholangitis
- Unconjugated hyperbilirubinemia in the neonatal period
- Acute Liver Failure

Clinical History – Patient with Jaundice

- Medications
- Drug and herbal medications
- ETOH
- Hepatitis risk factors
- History of abdominal operations/gallbladder surgery
- History of inherited disorders (liver/hemolytic disorders)
- HIV status
- Travel history
- Toxic substance exposure
- Fevers, anorexia, myalgias, malaise

Physical Examination

- Courvoisier sign (palpable gallbladder)
- Signs of portal hypertension or chronic liver disease
  - Ascites
  - Splenomegaly
  - Spider angiomata
  - Gynecomastia
- Skin hyperpigmentation (hemochromatosis)
- Kayser-Fleischer rings (Wilson’s)
- Xanthomas (primary biliary cirrhosis)
Laboratory Testing

- Initial screening laboratory studies
  - Determine if jaundice is hepatocellular cause or obstructive
  - Measurement of total bilirubin and indirect fraction
  - Serum transaminases (ALT/AST)
  - Alkaline phosphatase
  - Prothrombin time (INR)
  - Serum Albumin
  - Platelet Count

- Additional laboratory studies – if you suspect hepatocellular cause
  - Serologies for viral hepatitis
  - Anti-mitochondrial antibodies (PBC)
  - Anti-smooth muscle antibodies (autoimmune hepatitis)
  - Serum iron, transferrin, ferritin (hemochromatosis)
  - Serum ceruloplasmin/alpha-1 antitrypsin levels

Bilirubin Metabolism

- Unconjugated fraction (water insoluble) - indirect
  - Albumin-bound in serum
  - Never present in urine
  - Overproduction (hemolysis)
  - Impaired uptake by the liver
  - Abnormalities of bilirubin conjugation

- Conjugated (direct) and unconjugated fraction
  - Hepatocellular disease (viral hepatitis, cirrhosis)
  - Impaired canalicular excretion (drugs)
  - Biliary obstruction (gallstones)

Conjugated Hyperbilirubinemia

- Must determine intrahepatic vs extrahepatic etiology
- Intrahepatic cholestatic jaundice (impaired hepatic excretion)
- Drug induced cholestasis
- Primary Biliary Cirrhosis
- Sepsis
- Post-operative jaundice
- Primary hepatocellular disease
Common cause of Unconjugated Hyper-bilirubinemia

**Gilbert’s Syndrome**
- Isolated elevation of total and indirect bilirubin
- Usually an incidental finding
- All other transaminases normal (ALT, AST)
- Genetic defect in the UDP-glucuronyl transferase
- 7% population (male predominance)
- 2nd-3rd decade of life
- Exaggerated by fasting/viral illnesses
- Liver histology normal (no need to biopsy)
- No further follow-up needed

Laboratory Studies

- Hepatocellular disease vs. obstructive liver disease
- Hepatocellular disease
  - Transaminases elevated (any degree)
  - Alkaline phosphatase (may be elevated)
  - Prothrombin time (elevated)
  - Serum albumin (decreased)
  - Thrombocytopenia (low platelet count portal hypertension)
- Obstructive liver disease
  - Transaminases (elevated, varying degree)
  - Alkaline phosphatase (elevated, up to 5-10X normal)
  - Prothrombin time/serum albumin (+/- elevated)

Bilirubinuria

- Conjugated bilirubin is detected in the urine
- Unconjugated bilirubin is tightly bound to albumin, not filtered by the glomerulus and absent from urine
- Amount of conjugated bilirubin present in healthy subjects is small
- Elevated level, in serum or urine implies disease
- Most common cause is hepatocellular disease
- Rare causes
  - Dubin-Johnson and Rotor syndrome
  - Inability of hepatocytes to secrete conjugated bilirubin into bile
Imaging Studies

- Suspected obstruction of biliary tree
  - Transabdominal ultrasound*
  - Endoscopic ultrasound
  - Helical CT scan
  - Endoscopic retrograde cholangiopancreatography
  - Magnetic resonance cholangiopancreatography
  - Percutaneous transhepatic cholangiography
- *Screening procedure of choice

Table 1. Causes of Cholestasis

<table>
<thead>
<tr>
<th>Causes of Cholestasis</th>
</tr>
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<tbody>
<tr>
<td>Hepatobiliary disorders</td>
</tr>
<tr>
<td>Primary liver disorders</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
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<tr>
<td>Drugs and toxins</td>
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<tr>
<td>Tumors</td>
</tr>
<tr>
<td>Malignancy</td>
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<td>Congenital hepatic fibrosis</td>
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<tr>
<td>bile duct obstruction</td>
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<tr>
<td>Intrahepatic cholestasis</td>
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<tr>
<td>Pregnant (first and second trimesters)</td>
</tr>
<tr>
<td>Genetic disorders</td>
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<tr>
<td>Cholestasis of pregnancy</td>
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<tr>
<td>Acute liver failure</td>
</tr>
<tr>
<td>Portal hypertension</td>
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<tr>
<td>Neonatal jaundice</td>
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<tr>
<td>Obstructive jaundice</td>
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<tr>
<td>Cirrhosis</td>
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<tr>
<td>Alcoholic cirrhosis</td>
</tr>
<tr>
<td>Nonalcoholic fatty liver disease</td>
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<tr>
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</tr>
<tr>
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<tr>
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Neonatal Jaundice

- Yellowing of the skin in a newborn
- Bilirubin level > 5mg/dL
- 1. Breakdown of fetal hemoglobin as it is replaced with adult hemoglobin in a liver with immature metabolic pathways
- 2. Childhood Liver disease
  - Biliary Atresia
  - Progressive Familial intrahepatic cholestasis
  - Alagille syndrome
  - Alpha-1 Antitrypsin Deficiency

Diseases that Affect the Biliary Tree

- Primary Biliary Cirrhosis
- Primary Sclerosing Cholangitis
- Other
  - Drug injury
  - Viral hepatitis
  - Biliary Obstruction
  - Cholecystolithiasis
  - Malignancy
  - Graft vs Host disease

Clinical Question

- An icteric patient with sickle cell disease might be expected to have
  - Bilirubinuria
  - Absence of urinary uribilinogen
  - Cholesterol Stones
  - Unconjugated hyperbilirubinemia
PRIMARY BILIARY CIRRHOSIS (PBC)

- Destruction of intrahepatic bile ducts
- Progressive cholestatic liver disease
- Considered to be of autoimmune etiology
  - Positive Anti-mitochondrial (AMA) antibody
- Most common in middle-aged women
- Elevated Alkaline Phosphatase
  - Elevated total bilirubin is a sign of advanced disease

Insidious onset of fatigue and pruritis. Jaundice is late in course

FLORRID DUCT LESION

Periductal inflammation with granuloma formation and duct destruction
Primary Biliary Cirrhosis

- Cholestatic symptoms
  - Pruritis
  - Fatigue
  - Xanthomas (cholesterol deposits)
  - Jaundice
- Elevated alkaline phosphatase, cholesterol and bilirubin (late)
- Rule out obstruction
- Positive AMA (90-95%) + anti-mitochondrial antibody
- Liver biopsy: intrahepatic bile duct destruction with granulomas
- Treatment: first medically, then liver transplantation
  - Ursodeoxycholic Acid (Ursodiol)

Primary Sclerosing Cholangitis

- Obliterative fibrosis of intrahepatic and extrahepatic bile ducts with inflammation and dilation of preserved segments.
- ERCP shows "beading" (stricturing/dilation of intrahepatic ducts)
- Associated with Inflammatory Bowel Disease
  - Ulcerative Colitis and Crohn’s Disease
- Cholestatic Symptoms (pruritis)
- Progresses to End Stage Liver Disease
- No medical treatment available
- Liver Transplantation
- Risk of Cholangiocarcinoma (7%)
- 20-40’s; males > females 2:1
Bile duct undergoing degeneration and is surrounded by dense fibrosis with a “onion skin” pattern.
Choledocholithiasis

Choledocholithiasis

Cholelithiasis

Ultrasound Exam of the Gallbladder
You are a lab technician working in a liver disease clinic. The labs have come off of the blood samples drawn that day. You must match the LFT's to the specific diseases:

- **Carcinoma of the head of the pancreas**
  - Bili = 1.2, Alk Phos = 117
  - AST = 42, ALT 45

- **Acute Hepatitis B**
  - Bili = 13.1, Alk Phos = 133
  - AST = 445, ALT 532

- **Chronic Hepatitis C**
  - Bili = 6.5, Alk Phos = 453
  - AST = 64, ALT 89

- **Primary Biliary Cirrhosis**
  - Bili = 1.8, Alk Phos = 221
  - AST = 42, ALT = 44