Jaundice

Definition:
- Jaundice: Yellowish colouration of sclera, mucous membrane & skin.
- It is a symptom, not a disease.
- Literally, means yellow.
- Caused by high Bilirubin.
- Normal range 0.3-1.2 mg/dL.
- Clinically obvious ≥ 2.0 mg/dL.

Bilirubin

- Bilirubin is formed by a breakdown product of heme rings.
- Approximately 80% of the heme moiety comes from catabolism of red blood cells.
- The remaining 20% resulting from ineffective erythropoiesis and breakdown of muscle myoglobin and cytochromes.

Jaundice - Classification

- Over production of Bilirubin (Hemolytic)
  - From hemolysis of RBC
  - Lysis of RBC precursors – Ineffective erythropoiesis
- Impaired hepatic function (Hepatitic)
  - Hepatocellular dysfunction in handling bilirubin
    - Uptake, Metabolism and Excretion of bilirubin
- Obstruction to bile flow (Obstructive)
  - Intrahepatic cholestasis
  - Extrahepatic Obstruction (Surgical Jaundice)

Introduction:
- Jaundice is not a common presenting complaint in adults.
- When present, it may indicate a serious problem.
- May present with no symptoms.
- They may present with a life-threatening condition.
- The wide range of possibilities is based.
- A systematic approach is warranted to clarify the cause quickly so that treatment can begin as soon as possible.

Hypercarotenemia or just carotenemia.

A yellow-to-orange color may be imparted to the skin by consuming too much beta carotene, the orange pigment seen in carrots. In this condition, the whites of the eyes remain white, while people with true jaundice often have a yellowish tinge to the eyes.

MedlinePlus Medical Encyclopedia.
Clinical Aspects of Jaundice

- Clinically detectable if SB is > 2.0 mg%
- With edema and dark skin – Jaundice is masked
- What is special about the sclera? – Rich Elastin
- Darkening of the urine – Differential Diagnosis
- Skin discoloration – Yellowish, - Carotinemia – Eyes N
- Mucosa – hard palate (in dark skinned)
- Greenish hue of skin and sclera - due Biliverdin – indicates long standing jaundice
- Generalized Pruritus – Obstructive Jaundice –

Coloured Urine – Differ. Diagnosis

- Bilirubin in urine due to Jaundice (CB)
- Concentrated urine in dehydration
- Fluid deprivation syndromes
- Sulfasalazine use – for Ulcerative colitis
- Rifampicin, Pyridium and Thiamine use
- Red urine – Porphyria,
- Hemoglobin & Myoglobinuria, Hematuria
- Dark black urine in Ochranosis - HGA
- Melanin excretion from Melanoma
- Red sweat in Clofazamine, Rifampicin

Clinical History – Imp clues

- Duration of jaundice – Acute / Chronic
- Abdominal pain v/s painless jaundice
- Fever – Viral / bacteria /sepsis
- Arthralgia, rash, glands; Pruritus - obstructive
- Appetite – Hepatocellular / Malignancy
- Weight loss – Malignancy – CAH
- Colour of stools – chalky white – obstructive
- Family history – Hemolytic – Inherited dis.
- H/o transfusion, promiscuity, IDU
- Alcohol abuse, Medications – INH, EM, Largactil

Fate of Senescent RBC

- RBC life span in blood stream is 90-120 days
- Old RBCs are phagocytosed and/or lysed
- Lysis occurs extravascularly in the RE system subsequent to RBC phagocytosis
- Intravascular Hemolysis of young RBC
- This is due to hemolytic diseases of RBC

The Hepatobiliary & Portal System

- Hepatobiliary Tree
- Portal Circulation

E V Pathway for RBC Scavanging

Liver, Spleen & Bone marrow → Phagocytosis & Lysis

Hemoglobin

Globin → Heme → Bilirubin

Amino acids → Fe²⁺ Through Liver

Amino acid pool → Excreted
Bilirubin Handling

Bilirubin Metabolism - Summary

Bilirubin – And its nature

<table>
<thead>
<tr>
<th>Properties</th>
<th>Unconjugated</th>
<th>Conjugated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal serum fraction</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>Water solubility (polarity)</td>
<td>0 (non polar)</td>
<td>+ (polar)</td>
</tr>
<tr>
<td>Affinity to lipids (Kernicterus)</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Renal excretion</td>
<td>Nil</td>
<td>+</td>
</tr>
<tr>
<td>Vanden Berg Reaction</td>
<td>Indirect</td>
<td>Direct</td>
</tr>
<tr>
<td>Temporary Albumin Binding</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>Irreversible Delta Bilirubin</td>
<td>0</td>
<td>++</td>
</tr>
</tbody>
</table>

Bilirubin in the Liver Cell

1. Hepatocyte (HC) uptake of UGB
   - Alb+UCB dissociates and UCB enters HC
   - By passive diffusion into HC – Ligandin bound
   - Insoluble UCB is to be made soluble in HC

2. Conjugation in ER of Hepatocyte (HC)
   - Formation of mono and di glucuronides BMG, BDG
   - UDP Glucuronosyl transferase is energy depend.
   - Insoluble UCB made water soluble for excretion

3. Excretion into biliary canaliculi
   - Rate limiting step in metabolism
   - CB 95% is not protein bound – no loss of albumin
   - Remaining 50% δ bilirubin – Irreversibly bound

Bilirubin in Liver Cell - Schematic

Blood

Bile
Bilirubin in the Intestine

1. CB in bile is excreted into Duodenum
   - CB 10% diffuses in to blood
   - CB excreted is not reabsorbed

2. Conversion of CB into uro & sterocobilinogen
   - Urobilinogen excreted in stool
   - Part of the UBG enters EHC

3. From gut, UBG but not CB enters EHC
   - Kidney excretes absorbed UBG
   - In biliary obst, UBG absent in urine

An Approach to Jaundice

- Is it isolated elevation of serum bilirubin?
- If so, is the unconjugated or conjugated fraction?
- Is it accompanied by other liver test abnormalities?
- Is the disorder hepatocellular or cholestatic?
- If cholestatic, is it intra- or extrahepatic?
- These can be answered with a thoughtful
  - History and physical examination
  - Interpretation of laboratory tests and
  - Radiological tests and procedures.

Bilirubin handling in Kidney

- Conjugated Bilirubin
  - Bound (20 days)
  - Bilirubin in urine is conjugated

- Unconjugated Bilirubin
  - Not filtered or secreted
  - Nil in urine

- Urobilinogen in urine
  - Normally traces
  - ↑ in Cholestaiss

Bilirubin testing

- Van den Berg Reaction
- SB + SAA ⇒ Diaz compound formed
- Diaz is chromogenic – Colourimetry
- Reaction in H₂O medium – Direct – CB
- Reaction in ethanol medium – Indirect
- Indirect includes CB and UCB = Total B
- Time is the essence of the direct test
- Foam test, Ictotest for urine – CB only

Normal values for LFT

<table>
<thead>
<tr>
<th>Features</th>
<th>Healthy Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Bilirubin</td>
<td>Less than 1.00 mg</td>
</tr>
<tr>
<td>Conjugated Bilirubin</td>
<td>Less than 0.15 mg</td>
</tr>
<tr>
<td>AST (SGOT)</td>
<td>Less than 31 i.u/L</td>
</tr>
<tr>
<td>ALT (SGPT)</td>
<td>Less than 35 i.u/L</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>Less than 112 i.u/L</td>
</tr>
<tr>
<td>GGT and 5’ Nucleosidase, CDT</td>
<td>Significantly ↑ in ALD</td>
</tr>
<tr>
<td>Urine Bilirubin</td>
<td>Absent</td>
</tr>
<tr>
<td>Urine Urobilinogen</td>
<td>In trace quantity</td>
</tr>
<tr>
<td>Urine Bile Salts</td>
<td>Absent</td>
</tr>
</tbody>
</table>
### Lab Diagnosis of Jaundice – D.D

<table>
<thead>
<tr>
<th>Features</th>
<th>Prehepatic (Haemolytic)</th>
<th>Intrahepatic (Hepatocellular)</th>
<th>Posthepatic (Obstructive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unconjugated</td>
<td>↑</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Conjugated</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>AST or ALT</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Alkaline phos. and GGT</td>
<td>Normal</td>
<td>Normal</td>
<td>↑</td>
</tr>
<tr>
<td>Urine bilirubin</td>
<td>Absent</td>
<td>Present</td>
<td>Increased</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>Increased</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

### Liver Function Tests (LFT)

<table>
<thead>
<tr>
<th>Liver function test</th>
<th>Normal Range</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilirubin Total</td>
<td>0.1 to 1.0 mg</td>
<td>Dx. Of Jaundice, Severity</td>
</tr>
<tr>
<td>Bilirubin Conjugated</td>
<td>&lt; 0.2 mg</td>
<td>Dx of Obstructive Jaundice</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>25-112 iu/L</td>
<td>Dx of Obstructive Jaundice</td>
</tr>
<tr>
<td>Aspartate transaminase (AST/SGOT)</td>
<td>8-31 iu/L</td>
<td>Early Dx and follow up</td>
</tr>
<tr>
<td>Alanine transaminase (ALT/SGPT)</td>
<td>5-35 iu/L</td>
<td>AST/ALT &gt; 1 in ALD</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.5-5.5 g/dL</td>
<td>Assess severity of disease</td>
</tr>
</tbody>
</table>

### Utility of Liver Function Tests

<table>
<thead>
<tr>
<th>LFT</th>
<th>Utility of the test</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT/SGPT</td>
<td>ALT, than AST in alcoholism</td>
</tr>
<tr>
<td>Albumin</td>
<td>Assess severity / chronicity</td>
</tr>
<tr>
<td>AKP</td>
<td>Cholestasis, hepatic infiltrations</td>
</tr>
<tr>
<td>AST/SGOT</td>
<td>Early Dx of Liver disease, Flap</td>
</tr>
<tr>
<td>Bilirubin (Total), Conjug.</td>
<td>Diagnose jaundice</td>
</tr>
<tr>
<td>Gamma-glubulin</td>
<td>Dx. Flap Chronic hepatitis &amp; cirrhosis</td>
</tr>
<tr>
<td>GGT</td>
<td>Dx alcohol abuse, Dilantin toxicity</td>
</tr>
</tbody>
</table>

### Non Hepatic causes of abnormal LFT

<table>
<thead>
<tr>
<th>Abnormal LFT</th>
<th>Non hepatic causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>Nephrotic syndrome, Malnutrition, CNI, CHF</td>
</tr>
<tr>
<td>AKP</td>
<td>Bone disease, Pregnancy, Malignancy, Adv age</td>
</tr>
<tr>
<td>AST</td>
<td>MI, Myositis, I.M. injections</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>Hemolysis, Sepsis, Ineffective erythropoiesis</td>
</tr>
<tr>
<td>PTT</td>
<td>Antibiotics, Anticoagulant, Steatorrhea, Dietary</td>
</tr>
</tbody>
</table>

### Algorithmic approach for Jaundice

- How to clinically evaluate the patient?
- What tests will help us in D.D? 
- What imaging modalities will be useful?
- How to monitor the progress?

### First Step

- **Estimate Serum Bilirubin**
  - Is it less than 1 mg % - Normal
  - Is it more than 1 mg % - Elevated
Second Step: If SB > 1.0 mg

- Is it unconjugated bilirubin?
  - Haemolytic Jaundice
- Is it Conjugated Bilirubin? (> 20%)
  - Hepatocellular jaundice
  - Obstructive jaundice

Third Step: If CSB is increased

- Do - AST and ALT (SGOT and SGPT)
  - Elevated AST and ALT
  - Hepatocellular jaundice
  - AKP, 5N, GGT will be normal
- Do - Alkaline Phosphatase and GGT
  - AKP, GGT ↑ in Obstructive Jaundice
  - AST and ALT will be normal

Fourth Step: Hepatocellular

- Hepatocellular – Features and D.D
  - Conjugated SB is increased
  - AST and ALT are increased
  - AKP, 5NS, GGT are normal
- Do - Alkaline Phosphatase and GGT
  - AKP, GGT ↑↑ in Obstructive Jaundice
  - AST and ALT will be normal

What imaging we need

- Ultrasonography - 98% Sp, 90% Sen.
- For GB stones USG better than CT
- For duct stones -only 40% seen in USG
- PTC - Extrahepatic obstr. - drainage
- ERCP - Distal biliary obstruction Dx.Rx.
- MRCP - Most useful for duct stones

Liver Biopsy

- Conditions in which needle biopsy is useful include:
  - cirrhosis.
  - chronic hepatitis.
  - granulomatous hepatitis
  - tumors, undiagnosed hepatomegaly.
  - cholestasis of unknown cause, infiltrative processes and miliary tuberculosis

↑ in Unconjugated Bilirubin

- Hemolytic Jaundice - Uncommon
  - 1. Hemolytic Disorders + Anemia
    - Inherited – Spher, SS, G6PD, PK
    - Acquired – MAHA, PNH
  - 2. Ineffective Erythropoiesis –B₁₂, F₂, F
  - 3. Drugs – Rifampicin, Probendic
  - 4. Inherited –Crigler Najjar, Gillets
Neonatal Jaundice

- Neonatal jaundice is common
- 50% healthy term infants
- Re-emergence of kernicterus
- In utero bilirubin is handled by placenta and mother’s liver
- After birth, neonate to has cope with increase in bilirubin production and the immature liver cannot handle for a few days

Treatment options for neonatal jaundice

- 1. Phototherapy
- 2. Exchange Transfusions
- 3. HD Inhibitors

Basis of photo therapy?

- UCB is not water soluble in its form
- Blue light confrontational change in UBG
- Its Photo Isomers are water soluble
- Blue light converts the UCG into its photo isomers
- The soluble photo isomers pass through the Glomerular filter and get excreted
- Thus conjugation in liver is by passed.

New Onset Jaundice

- Viral hepatitis
- Alcoholic liver disease
- Autoimmune hepatitis
- Medication-induced liver disease
- Common bile duct stones
- Pancreatic cancer
- Primary Biliary Cirrhosis (PBC)
- Primary Sclerosing Cholangitis (PSC)
**HBV Serology**

<table>
<thead>
<tr>
<th></th>
<th>HBSAg</th>
<th>HBcAb</th>
<th>HBcAb IgM</th>
<th>HBcAb IgG</th>
<th>HBSAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute HBV</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Resolved HBV</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Chronic HBV</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>HBV vaccinated</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

**Acute Hepatitis C**

Plateau phase = 57 days

**Alcoholic Liver disease**

- The history is the key – 60 grams/day
- Gynecomastia, parotids, Dupuytren’s
- Lab clues: AST/ALT > 2, MCV > 94
  - AST < 300
- Alcoholic hepatitis:
  - Anorexia, fever, jaundice, hepatomegaly
- Treatment:
  - Abstinence
  - Nutrition
  - Consider prednisolone or pentoxifylline

**Alcoholic Liver Disease**

**Discriminant Function Formula**:

\[ DF = [4.6 \times (PT - \text{control})] + \text{bilirubin} \]

Consider treatment for DF > 32

- Prednisolone 40 mg/day x 28 days
  - contraindications: infection, renal failure, GIB
- Pentoxifylline 400 mg tid x 28 days
**Autoimmune Hepatitis**

- Widely variable clinical presentations
  - Asymptomatic LFT abnormality (ALT and AST)
  - Severe hepatitis with jaundice
  - Cirrhosis and complications of portal HTN
- Often associated with other autoimmune dz
- Diagnosis:
  - Compatible clinical presentation
  - ANA or ASMA with titer 1:80 or greater
  - IgG > 1.5 upper limits of normal
  - Liver biopsy: portal lymphocytes + plasma cells

**Drug-induced Liver Disease**

- Hepatocellular
  - acetaminophen, INH, methyldopa, MTX
- Cholestatic
  - chlorpromazine, estradiol, antibiotics
- Chronic Hepatitis
  - methyldopa, phenytoin, macrodantin, PTU
- Hypersensitivity Reaction
  - Phenytoin, Augmentin, allopurinol
- Microvesicular Steatosis
  - amiodarone, IV tetracycline, AZT, ddI, stavudine

**Acetaminophen Toxicity**

- Day 1:
  - Nausea, vomiting, malaise, or asymptomatic
- Day 2 – 3:
  - Initial symptoms resolve
  - AST and ALT begin to rise by 36 hours
  - RUQ pain, tender enlarged liver on exam
- Day 4
  - AST and ALT peak > 3000
  - Liver dysfunction: PT, encephalopathy, jaundice
  - Acute renal failure (ATN)

**Fulminant Hepatic Failure**

- Definition:
  - Rapid development of hepatic dysfunction
  - Hepatic encephalopathy
  - No prior history of liver disease
- Most common causes:
  - Acetaminophen
  - Unknown
  - Idiosyncratic drug reaction
  - Acute HAV or HBV (or HDV or HEV)

**5,6741 Liver Transplants in 2003**

Indications:

- Hepatitis C 29%
- Alcoholic Liver Disease 15%
- Cirrhosis of unknown etiology 8%
- Hepatocellular Carcinoma 7%
- Fulminant Hepatic Failure 6%
- Primary Sclerosing Cholangitis 5%
- Primary Biliary Cirrhosis 4%
- Metabolic Liver Disease 4%
- Autoimmune Hepatitis 3%
- Hepatitis B 3%
Liver Transplantation: Contraindications

- **ABSOLUTE**
  - active alcohol or drug abuse
  - HIV positivity
  - extrahepatic malignancy
  - uncontrolled extrahepatic infection
  - advanced cardiopulmonary disease

- **RELATIVE**
  - Age over 65
  - poor social support
  - poorly controlled mental illness

Obstructive Jaundice

**CBD stones (choledocholithiasis) vs. tumor**

- Clinical features favoring CBD stones:
  - Age < 45
  - Biliary colic
  - Fever
  - Transient spike in AST or amylase

- Clinical features favoring cancer:
  - Painless Jaundice
  - Weight loss
  - Palpable gallbladder
  - Bilirubin > 10

Ascending Cholangitis

- Pus under pressure
- Charcot's triad: fever, jaundice, RUQ pain
  - All 3 present in 70% of patients, but fever > 95%
  - May also present as confusion or hypotension
- Most frequent causative organisms:
  - E. Coli, Klebsiella, Enterobacter, Enterococcus
  - anaerobes are rare and usually post-surgical
- Treatment:
  - Antibiotics: Levaquin, Zosyn, meropenem
  - ERCP with biliary drainage

Post hepatic Obstructive Jaundice

- Painful v/s painless
- Obstruction can be
  - Luminal (stone)
  - Stricture (benign v/s cholangiocarcinoma)
  - Extra luminal pancreatic cancer, Sec. lymph nodes
- Investigate & treat with
  - Radiology (US, CT, MRCP)
  - ERCP / PTC

Ascending Cholangitis

Indications for Urgent ERCP

- Persistent abdominal pain
- Hypotension despite adequate IVF
- Fever > 102
- Mental confusion
- Failure to improve after 12 hours of antibiotics and supportive care

---

Table 55-1 | Gallstone Prevalence by Age in Women and Men from Defined Populations*

<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>POPULATION</th>
<th>AGE (YR)</th>
<th>20-29</th>
<th>30-39</th>
<th>40-49</th>
<th>50-59</th>
<th>&gt;60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil</td>
<td></td>
<td></td>
<td>3.0 (1.8)</td>
<td>11 (2.9)</td>
<td>13 (6.3)</td>
<td>23 (7.8)</td>
<td>30 (16)</td>
</tr>
<tr>
<td>Cuban</td>
<td></td>
<td></td>
<td>11 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Americans</td>
<td></td>
<td></td>
<td>5 (2)</td>
<td>6 (2)</td>
<td>14 (7)</td>
<td>20 (13)</td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td></td>
<td></td>
<td>1.9 (1.4)</td>
<td>5.6 (4.3)</td>
<td>9.5 (10.5)</td>
<td>14 (10)</td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td></td>
<td></td>
<td>3 (2)</td>
<td>9 (2)</td>
<td>17 (8)</td>
<td>22 (12)</td>
<td>28 (17)</td>
</tr>
<tr>
<td>Mexico</td>
<td></td>
<td></td>
<td>11 (1)</td>
<td>13 (5)</td>
<td>20 (7)</td>
<td>22 (10)</td>
<td>27 (14)</td>
</tr>
<tr>
<td>Mexican</td>
<td></td>
<td></td>
<td>14 (3)</td>
<td></td>
<td>26 (10)</td>
<td>(16)</td>
<td></td>
</tr>
<tr>
<td>Americans</td>
<td></td>
<td></td>
<td>6 (5)</td>
<td>15 (1.3)</td>
<td>25 (10)</td>
<td>29 (25)</td>
<td>41 (37)</td>
</tr>
<tr>
<td>Norway</td>
<td></td>
<td></td>
<td>6.5</td>
<td>9.2</td>
<td>14</td>
<td>21 (21)</td>
<td>(12)</td>
</tr>
<tr>
<td>Nova Scotia</td>
<td></td>
<td></td>
<td>5.3</td>
<td>9.2</td>
<td>14</td>
<td>21 (21)</td>
<td>(12)</td>
</tr>
<tr>
<td>Puerto Rico</td>
<td></td>
<td></td>
<td>4.3</td>
<td>7.2 (1.1)</td>
<td>8.2 (5.6)</td>
<td>12 (7.3)</td>
<td>16 (17)</td>
</tr>
</tbody>
</table>

*Prevalence expressed as percentage of population of each defined age group.
Obstructive Jaundice
Malignant Causes

- Cancer of the Pancreas
- Cancer of the Bile Ducts (Cholangiocarcinoma)
- Ampullary Tumors
- Portal Lymphadenopathy

Primary Biliary Cirrhosis

- Cholestatic liver disease (ALP)
  - Most common symptoms: pruritus and fatigue
  - Many patients asx, and dx by abnormal LFT
- Female: male ratio 9:1
- Diagnosis:
  - Compatible clinical presentation
  - AMA titer 1:80 or greater (95% sens/spec)
  - IgM > 1.5 upper limits of normal
  - Liver biopsy: bile duct destruction
- Treatment: Ursodeoxycholic acid 15 mg/kg

Primary Sclerosing cholangitis

- Cholestatic liver disease (ALP)
- Inflammation of large bile ducts
- 90% associated with IBD
  - but only 5% of IBD patients get PSC
- Diagnosis: ERCP (now MRCP)
  - No autoantibodies, no elevated globulins
  - Biopsy: concentric fibrosis around bile ducts
  - Cholangiocarcinoma: 10-15% lifetime risk
- Treatment: Liver Transplantation

Diagnosis of Immune-Mediated Liver Disease

<table>
<thead>
<tr>
<th></th>
<th>LFT</th>
<th>Serology</th>
<th>Quantitative Immunoglobulins</th>
<th>Biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIH</td>
<td>↑ALT</td>
<td>ANA</td>
<td>↑IgG</td>
<td>Portal inflammation, Plasma cells, necrosis</td>
</tr>
<tr>
<td>PBC</td>
<td>↑ALP</td>
<td>AMA</td>
<td>↑IgM</td>
<td>Bile duct destruction, granulomas</td>
</tr>
<tr>
<td>PSC</td>
<td>↑ALP</td>
<td>none</td>
<td>normal</td>
<td>Periductal concentric fibrosis</td>
</tr>
</tbody>
</table>

Unusual Causes of Jaundice

- Ischemic hepatitis
- Congestive hepatopathy
- Wilson’s disease
- AIDS cholangiopathy
- Amanita phalloides (mushrooms)
- Jamaican bush tea
- Infiltrative diseases of the liver
  - Amyloidosis
  - Sarcoidosis
  - Malignancy: lymphoma, metastatic dz
Wilson’s Disease
- Autosomal recessive – copper metabolism
- Chronic hepatitis or fulminant hepatitis
- Associated clinical features:
  - Neuropsychiatric disease
  - Hemolytic anemia
- Physical exam: Kayser-Fleischer rings
- Diagnosis: ceruloplasmin, urinary Cu
- Treatment: d-penicillamine

Manifestations of Wilson’s Disease

<table>
<thead>
<tr>
<th>Hepatic</th>
<th>Psychiatric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirrhosis, Fulminant</td>
<td>Behavioral, organic dementia,</td>
</tr>
<tr>
<td>Disease</td>
<td>Early Neurological</td>
</tr>
<tr>
<td></td>
<td>Psychoneurosis, manic-depressive</td>
</tr>
<tr>
<td>Incoordination, dysarthria</td>
<td>Schizophrenic psychosis</td>
</tr>
<tr>
<td>Resting and intention</td>
<td>Ophthalmic</td>
</tr>
<tr>
<td>tremors</td>
<td>Mask-like facies, ataxia</td>
</tr>
<tr>
<td></td>
<td>Hematologic and others</td>
</tr>
<tr>
<td>Excessive salivation,</td>
<td>Tinger, sunflower cataract</td>
</tr>
<tr>
<td>dysphagia</td>
<td></td>
</tr>
<tr>
<td>KF ring, Keratin rings,</td>
<td></td>
</tr>
<tr>
<td>Sunflower cataract</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dysoria, spasticity, Rigidity, TCS</td>
</tr>
<tr>
<td></td>
<td>Distal RTA, Osteomalacia, OS</td>
</tr>
</tbody>
</table>

Critical Questions in the Evaluation of the Jaundiced Patient

- Acute vs. Chronic Liver Disease
- Hepatocellular vs. Cholestatic
  - Biliary Obstruction vs. Intrahepatic Cholestasis
- Fever
  - Could the patient have ascending cholangitis?
- Encephalopathy
  - Could the patient have fulminant hepatic failure?

Chronic Liver Disease (CLD)
- Alcoholic Liver (ALD)
  - Hepatitis B
  - Hepatitis C
- Chronic viral hepatitis
- Autoimmune liver disease:
  - Autoimmune hepatitis
  - Primary Biliary Cirrhosis (PBC)
- Inherited conditions
  - Haemochromatosis
  - Wilson’s Disease
  - Alpha1-Antitrypsin Deficiency (AATD)
- Non-alcoholic steato-hepatitis (NASH)
- Budd-Chiari syndrome
- Cryptogenic

Hepato toxic drugs

<table>
<thead>
<tr>
<th>Conventional Drugs</th>
<th>Natural Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen, Alpha-methyldopa</td>
<td>Vitamins, Hypervitaminosis A</td>
</tr>
<tr>
<td>Amiodarone, Dantrolene, Diclofenac</td>
<td>Niacin, Cocaine, Mushrooms</td>
</tr>
<tr>
<td>Diazepam, Fluconazole, Glipizide</td>
<td>Ataxine, Herbal remedies</td>
</tr>
<tr>
<td>Glyburide, Isoniazid, Ketoconazole</td>
<td>Senecio, croatilia</td>
</tr>
<tr>
<td>Labetalol, Lovastatin, Nitrofurantoin</td>
<td>Pennyroyal oil, Chappedar,</td>
</tr>
<tr>
<td>Thioracil, Trogilitone, Trazadone</td>
<td>Germander, Senna, Herbal mix</td>
</tr>
</tbody>
</table>

KF Ring of Periphery of Iris

Courtesy of Robert L. Carithers, Jr., M.D.
Acute Cholecystitis

GB wall is thickened and striated.
Courtesy of Udo Schmiedl, M.D.

Causes of Cholestatic Jaundice

<table>
<thead>
<tr>
<th>Intrahepatic</th>
<th>Extrahepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute liver injury, Viral hepatitis</td>
<td>Cholecystolithiasis</td>
</tr>
<tr>
<td>Alcohol hepatitis, Drugs</td>
<td>Stone obstructing CBD, CD</td>
</tr>
<tr>
<td>Chronic liver injury, PSC, PSC</td>
<td>Biliary strictures</td>
</tr>
<tr>
<td>Autoimmune cholangiopathy</td>
<td>Cholangiocarcinoma</td>
</tr>
<tr>
<td>Drugs, Total parenteral nutrition</td>
<td>Pancreatic carcinoma</td>
</tr>
<tr>
<td>Systemic infection, Postoperative</td>
<td>Pancreatitis, Periampullary Ca</td>
</tr>
<tr>
<td>Benign causes, Amyloid, lymphoma</td>
<td>PSC, Biliary stress, duct cysts</td>
</tr>
</tbody>
</table>

Drugs causing Cholestasis

- Anabolic steroids (testosterone, norethandrolone)
- Antithyroid agents (methimazole)
- Azathioprine (Immunosuppressive drug)
- Chlorpromazine HCl
- Clofibrate, Erythromycin estolate
- Oral contraceptives (containing estrogens)
- Oral hypoglycemics (especially chlorpropamide)

Complications of CLD

- Portal hypertension
  - Varices
  - Ascites
  - Hypersplenism
- Synthetic dysfunction
  - Coagulopathy
  - Encephalopathy
- Immunodeficiency
- Malnutrition
- Hepato-cellular carcinoma

Magnetic Resonance Cholangio-Pancreatography (MRCP)

Two stones in the common bile duct
Courtesy of Udo Schmiedl, M.D.

Retrograde Cholangiogram - ERCP

Bile leak from the cystic duct after cholecystectomy
Courtesy of Michael Kimmey, M.D.
Primary sclerosing cholangitis (PSC) with stricture due to cholangiocarcinoma. Courtesy of Robert L. Carithers, Jr., M.D.

Irregular dilation of intrahepatic and extrahepatic ducts. Courtesy of Charles Rohrmann, M.D.

Primary Sclerosing Cholangitis

Normal Extra hepatic BD

Narrowed abnormal intra-heptic bile ducts.

Alcoholic Cirrhosis of Liver

The cut surface of a autopsy liver of a patient with alcoholic cirrhosis - multiple small nodules and diffuse scarring. Courtesy of Robert L. Carithers, Jr., M.D.

Causes of Jaundice - Frequency

<table>
<thead>
<tr>
<th>Type</th>
<th>Cause</th>
<th>Clinical example</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatic</td>
<td>hepatitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>alcoholism</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cholangitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cholestasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>biliary tract obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cholangiocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cystic fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hemolytic anemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrahepatic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>biliary tract obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cholangiocarcinoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>cystic fibrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>hemolytic anemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
When to refer to GE Specialist

- Unexplained jaundice
- Suspected biliary obstruction
- Acute hepatitis - severe or fulminant
- Unexplained abnormal LFTs persisting (for 6 months or greater)
- Unexplained cholestatic liver disease
- Cirrhosis (non-alcoholic) for consideration of liver transplant
- Suspected hereditary hemochromatosis
- Suspected Wilson's disease
- Suspected autoimmune hepatitis
- Chronic hepatitis C for consideration of antiviral therapy

Conclusions

- Jaundice and liver injury are very common
- Careful history and physical examination are a must
- Acute hepatocellular diseases with jaundice
- Chronic hepatocellular jaundice (CLD)
- Cholestasis and obstructive jaundice
- LFT – SB, CB, — AST, ALT, AKP, 5’ NS, GGT, Alb, PT
- Ultrasoundography, MRCP, ERCP, PTC
- Laparoscopy and liver biopsy
- Treatment as per the cause

Unknown Case #1

- 59 year old male lawyer
  - Nausea, vomiting, lethargy, chronic back pain
  - Drinks 3-4 scotch and water/day
  - PMH: HTN, hypercholesterolemia
  - Meds: Prinivil, Lipitor, Vicodin
  - VSS afebrile, jaundice, no stigmata cirrhosis
  - A/O, no asterixis no edema, no ascites
  - sl RUQ tender, liver span 18 cm, no palp spleen
  - AST 3246, ALT 4620, ALP 105, bili 5.2

Unknown Case #2

- 38 year old female manager of Mi Pueblo
  - 3 days of episodic severe RUQ pain
  - 2 days of fever/chills/rigors
  - Daughter noticed yellow eyes today
  - PMH: DM, HTN
  - Meds: glipizide, HCTZ
  - BP 110/64 HR 112, temp 101.8
  - Jaundice, no stigmata of cirrhosis
  - RUQ tender to palp, no spleen, no ascites
  - AST 602, ALT 654, ALP 256, bili 5.2

Unknown Case #3

- 64 year old female bartender
  - 1 month history of fatigue, anorexia, arthralgias
  - 1 week history of jaundice
  - No abdominal pain, no fever, 5 lb wt. loss
  - Denies ETOH “I never liked the stuff”
  - PMH: none PSH: none meds: rare Motrin
  - AST 256, ALT 302, ALP 162, bili 8.6
  - alb 3.2 INR 1.3 TP 8.4 plt 256