Clinical Aspects of Jaundice

- It is clinically detectable only 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 – DD – see next slide
- Skin discoloration – Yellowish, - Carotinemia – Eyes
- Mucosa – hard palate (in dark skinned), under tongue
- Greenish hue of skin and sclera - due to Biliverdin – indicates long standing jaundice
- Generalized Pruritus – Obstructive Jaundice – Why?

Jaundice – Classification

- Normal Serum Bilirubin (SB) is 0.3 to 1.0 mg%
- Jaundice is increased levels of SB > 1.0 mg%
- Over production of Bilirubin (Hemolytic)
  - From Hemolysis of RBC
  - Lysis of RBC precursors – Ineffective erythropoiesis
- Impaired hepatic function (Hepatocellular)
  - Hepatocellular dysfunction in handling bilirubin
    - Uptake, Metabolism and Excretion of bilirubin
  - Obstruction to bile flow (Obstructive)
    - Intrahepatic cholestasis
    - Extrahepatic Obstruction (Surgical Jaundice)

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 diseases
- 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 (EV) in the RE system subsequent to RBC phagocytosis
- Intravascular (IV) Hemolysis of young RBC
- This is due to hemolytic diseases of RBC
- 80% Bilirubin originates from senescent RBCs
- 1-2 x 10^8 RBCs destroyed per hour
- 6 g Hb is produced in the body per day
- 250-300 mg Bilirubin produced per day

Bilirubin in the Liver Cell

1. Hepatocyte (HC) uptake of UCB
   - 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 Glucuronyl transferase is energy depend.
   - Insoluble UCB made water soluble for excretion

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

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 & stercobilinogen
   - 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 it ↑ unconjugated or conjugated fraction?
- Is it accompanied by other liver test abnormalities?
- Is the disorder Hepatocellular or Cholestatic?
- If cholestatic, is it intra- or extra hepatic?
- These can be answered with a thoughtful history and physical examination
- Interpretation of laboratory tests and
- Radiological tests and procedures.

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 0.30 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>

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 unconjugated Bilirubin more? > 85%
  - Haemolytic Jaundice
- Is Conjugated Bilirubin more? (>30%)
  - Hepatocellular jaundice
  - Obstructive jaundice

Increased Unconjugated Bilirubin

- Hemolytic Jaundice - Uncommon
  1. Hemolytic Disorders + Anemia
     - Inherited – Sphero, SS, G6PD, PK
     - Acquired – MAHA, PNH
  2. Ineffective Erythropoiesis–B, Fe, F
  3. Drugs – Rifampicin, Probenecid
  4. Inherited: Crigler Najjar, Gilbert’s

Fourth Step: Hepatocellular

- Hepatocellular – Features and D.D
  - Conjugated SB is increased
  - AST and ALT are increased
  - AKP, SNS, GGT are normal
  - Hepatitis – A, B, C, D, E, CMV, EBV
  - Toxic Hepatitis – Drugs, Alcohol
  - Malignancy – Primary Ca
  - Cirrhosis – ALD, NAFLD

Dr RVSN Sarma, MD., FIMSA
Screening Tests – Anemia

- Clinical Signs and symptoms of Anemia
- Look for bleeding – all possible sites
- Look for the causes for anemia
- Routine Hemoglobin examination
- Cut off marks for Hb –
  - US < 13.5 g
  - WHO < 12.5 g
  - India (ICMR) Less than 12 g%

The Three Primary Measures

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. RBC count (RCC)</td>
<td>5 million</td>
<td>4 to 5.7</td>
</tr>
<tr>
<td>B. Hemoglobin (Hb%)</td>
<td>15 g%</td>
<td>12 to 17</td>
</tr>
<tr>
<td>C. Hematocrit (PCV)</td>
<td>45 %</td>
<td>36 to 50</td>
</tr>
</tbody>
</table>

A x 3 = B x 3 = C - This is the rule of thumb
Check whether this holds good in a given result
If not - indicates micro or macrocytosis or hypochro.

The Three Derived Indicies

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normal</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. RCC 5 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B. Hemoglobin 15 g%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. Hematocrit 45 %</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

MCV C ÷ A x 10 = 90 fl
MCH B ÷ A x 10 = 30 pg
MCHC(%) B ÷ C x 100 = 33%

Causes of Anemia

1. Decreased production of Red Cells
   - Hypo proliferative, marrow failure
2. Increased destruction of Red Cells
   - Hemolysis (decreased survival of RBC)
3. Loss of Red Cells due to bleeding
   - Acute / chronic blood loss (hemorrhagic)
      \[ M = P \times S \times L \]

Hypoproliferative Anemias

- Failure of cell maturation
- Cytoplasmic breakdown
- Folate or B\textsubscript{12} deficiency
- Defective DNA synthesis
- Megaloblastic Anemia
- Haem defect
- Fe Phorph
- IDA, SA
- Globin defect
- Sickle cell A
- Thalassemia

Anemia

- Hb% <12, PCV <38%
- Anemia
  - Decreased Production
  - Increased Destruction

- RPI < 2
  - Hypoproliferative

- RPI > 2
  - Hemolytic
**Workup – Third Test**
- The next step is *What is the size of RBC*?
- MCV indicates the Red cell volume (size)
- Both the MCH & MCHC tell Hb content of RBC
- If the RPI is 2 or less
- We are dealing with either
  - Hypoproliferative Anemia (lack of raw material)
  - Maturation defect with less production
  - Bone marrow suppression (primary/ secondary)

**Mean Cell Volume (MCV)**
- RBC size is measured indirectly by
  - The Mean Cell Volume (MCV) and RDW

<table>
<thead>
<tr>
<th>MCV</th>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 80 fl</td>
<td>&lt; 6.5 µ</td>
<td>6.5 - 9 µ</td>
<td>&gt; 9 µ</td>
</tr>
<tr>
<td>&gt; 100 fl</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Anemia Workup - MCV**

<table>
<thead>
<tr>
<th>MCV</th>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron Deficiency (IDA)</td>
<td>Chronic diseases, CKD</td>
<td>Megaloblastic anemia</td>
<td></td>
</tr>
<tr>
<td>Chronic Infections</td>
<td>Early IDA, Cytoskeleton</td>
<td>Liver disease/alcohol</td>
<td></td>
</tr>
<tr>
<td>Thalassemias</td>
<td>Hemoglobinopathies</td>
<td>Hemoglobinopathies</td>
<td></td>
</tr>
<tr>
<td>Hemoglobinopathies</td>
<td>Primary marrow disease</td>
<td>Metabolic disorders</td>
<td></td>
</tr>
<tr>
<td>Sideroblastic Anemia</td>
<td>Combined deficiencies</td>
<td>Marrow disorders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased destruction</td>
<td>Increased destruction</td>
<td></td>
</tr>
</tbody>
</table>

**Anemia Workup - 5th Test**
- Peripheral Smear Study

- Are all RBC of the same size?
- Are all RBC of the same normal discoid shape?
- How is the colour (Hb content) saturation?
- Are all the RBC of same colour/ multi coloured?
- Are there any RBC inclusions?
- Are there any hemo-parasites in the RBC?
- Are leucocytes normal in number and D.C.?
- Is platelet distribution adequate?

**Hemolytic Anemia**

Anemia of increased RBC destruction
- Normochromic, normocytic anemia
- Shortened RBC survival
- Reticulocytosis – due to ↑ RBC destruction
Will not be symptomatic until the RBC life span is reduced to 20 days – as the BM compensates 6 times

**Tests Used to Diagnose Hemolysis**

1. Reticulocyte count
2. Combined with serial Hb levels
3. Hemoglobin electrophoresis
4. Serum LDH, Isopropanol Stability
5. Serum Bilirubin Fractionation
6. Osmotic Fragility test in NaCl
7. Haptoglobin, Acid Hemolysis test
8. Urine Hemosiderin, Hemoglobinuria
Findings in Hemolytic Anemia

- Reticulocyte count and RPI: Increased
- Serum Unconjugated Bilirubin: Increased
- Serum LDH 1: LDH 2: Increased
- Serum Haptoglobin: Decreased
- Urine Hemoglobin: Present
- Urine Hemosiderin: Present
- Urine Urobilinogen: Increased
- Cr 51 labeled RBC life span: Decreased

Tests to Define the cause of Hemolysis

1. Hemoglobin electrophoresis
2. Hemoglobin A 2 (βeta-Thalassemia trait)
3. RBC enzymes (G6PD, PK, etc)
4. Direct & indirect antiglobulin tests (immune)
5. Cold agglutinins
6. Osmotic fragility (Spherocytosis)
7. Acid Hemolysis test (PNH)
8. Clotting profile (DIC)

Lab Diagnosis of Jaundice – D.D

<table>
<thead>
<tr>
<th>Features</th>
<th>Pre hepatic (Haemolytic)</th>
<th>Intra hepatic (Hepatocellular)</th>
<th>Post hepatic (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>Normal</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>

DD of ↑ Unconjugated Bilirubin
- Increased Bilirubin Production
- Extravascular or intravascular hemolysis
- Extravasation of blood into tissues
- Errors in production of red blood cells (ineffective erythropoiesis)
- Impaired Hepatic Bilirubin Uptake
  - CHF, Portosystemic shunts
  - Drug inhibition: rifampin, probenecid, Flava beans
  - Impaired Bilirubin Conjugation
    - Gilbert's Syndrome
    - Crigler-Najjar syndrome (Type 1 and 2)
  - Impaired Bilirubin Conjugation
    - Neonatal jaundice (NNJ: this is physiologic)
    - Hyperthyroidism; Estrogens, Wilson's, CLD

Hemolytic Anemia - Classification

- Intracorpuscular
- Hereditary
  - Hemoglobinopathies (SS, Thalass, HbC)
  - Cytoskeleton defects (HS, Stomato, ellipto)
  - Enzymopathies (G6PD, PKD)
- Acquired
  - PNH

- Extracorpuscular
- Hereditary
  - Familial HUS
  - Acquired
  - MAHA (Mechanical)
  - Toxic Agents
  - Infectious
  - Autoimmune
  - Drugs

Hereditary Spherocytosis

- Relatively common – 1 in 5000, Familial
- AD Inheritance, Screen blood relatives
- Defect in the RBC membrane cytoskeleton
- Spherocytes in peripheral blood
- Increased osmotic fragility at 0.7 NaCl
- Spectrum is from mild to severe cases
- Jaundice, ISB ↑, Splenomegaly, Hypersplenism
- Gall stones due to excess pigment
- Normocytic Anemia; ↑ MCHC (unique)
- Positive family history, de novo mutation
- Splenectomy, watch for infections, GB stones
- Pneumococcal and meningococcal vaccines