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 N
- 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 ?

1

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 erythropoesis
- 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)

2

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

3

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

4

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 Glucuronosyl 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% δ bilirubin – Irreversibly bound

5

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

6

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.

7

Normal Values for LFT

Features	Healthy Normal
Total Bilirubin	Less than 1.00 mg
Conjugated Bilirubin	Less than 0.30 mg
AST (SGOT)	Less than 31 i.u/L
ALT (SGPT)	Less than 35 i.u/L
Alkaline phosphatase	Less than 112 i.u /L
GGT and 5' Nucleosidase, CDT	Significantly ↑ in ALD
Urine Bilirubin	Absent
Urine Urobilinogen	In trace quantity
Urine Bile Salts	Absent

8

First Step

Estimate Serum Bilirubin

Is it less than 1 mg % - Normal

Is it more than 1 mg % - Elevated

9

Second Step : If SB > 1.0 mg

Is unconjugated Bilirubin more? > 85%

Haemolytic Jaundice

Is Conjugated Bilirubin more ? (>30%)

Hepatocellular jaundice

Obstructive jaundice

10

Increased Unconjugated Bilirubin

Hemolytic Jaundice - Uncommon

1. Hemolytic Disorders + Anemia

Inherited – Sphero, SS, G6PD, PK

Acquired – MAHA, PNH

2. Ineffective Erythropoiesis–B_{12}, Fe, F

3. Drugs – Rifampicin, Probenecid

4. Inherited: Crigler Najjar, Gilbert's

11

Fourth Step : Hepatocellular

Hepatocellular – Features and D.D

Conjugated SB is increased

AST and ALT are increased

AKP, 5NS, GGT are normal

Hepatitis –A,B,C,D,E, CMV,EBV

Toxic Hepatitis – Drugs, Alcohol

Malignancy – Primary Ca

Cirrhosis – ALD, NAFLD

12

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%

13

The Three Primary Measures

	Measurement	Normal	Range
A.	RBC count (RCC)	5 million	4 to 5.7
B.	Hemoglobin (Hb%)	15 g%	12 to 17
C.	Hematocrit (PCV)	45	36 to 50

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.

14

The Three Derived Indicies

	Measurement	Normal	Range
A.	RCC	5 million	4 to 5.7
B.	Hemoglobin	15 g%	12 to 17
C.	Hematocrit	45 %	36 to 50

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

15

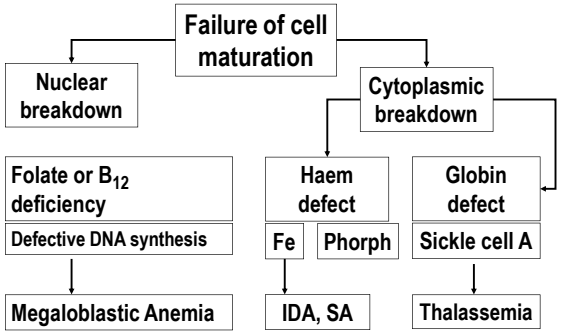
Causes of Anemia

1. Decreased <u>production</u> of Red Cells
   - Hypo proliferative, marrow failure
2. Increased destruction of Red Cells
   - Hemolysis (decreased <u>survival</u> of RBC)
3. Loss of Red Cells due to bleeding
   - Acute / chronic blood <u>loss</u> (hemorrhagic)

M = P x S (L)

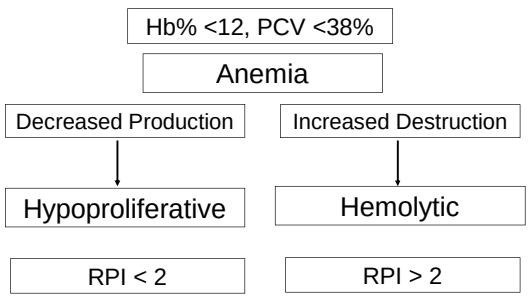
16

Hypoproliferative Anemias



17

Anemia



18

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)

19

Mean Cell Volume (MCV)

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

MCV		
Microcytic	Normocytic	Macrocytic
< 80 fl	80 -100 fl	> 100 fl
< 6.5 µ	6.5 - 9 µ	> 9 µ

20

Anemia Workup - MCV

MCV

Microcytic	Normocytic	Macrocytic
Iron Deficiency (IDA)	Chronic diseases, CKD	Megaloblastic anemia
Chronic Infections	Early IDA, Cytoskeleton	Liver disease/alcohol
Thalassemias	Hemoglobinopathies	Hemoglobinopathies
Hemoglobinopathies	Primary marrow disease	Metabolic disorders
Sideroblastic Anemia	Combined deficiencies	Marrow disorders
	Increased destruction	Increased destruction

21

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 ?

22

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

23

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

24

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

25

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)

26

Lab Diagnosis of Jaundice – D.D

Features	Pre hepatic (Haemolytic)	Intra hepatic (Hepatocellular)	Post hepatic (Obstructive)
Unconjugated	↑	**Normal**	**Normal**
Conjugated	**Normal**	↑ ↑	↑
AST or ALT	**Normal**	↑ ↑	**Normal**
Alkaline phos. and GGT	**Normal**	**Normal**	↑ ↑
Urine bilirubin	**Absent**	**Present**	**Increased**
Urobilinogen	**Increased**	**Present**	**Absent**

27

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)
  - Neonatal jaundice (NNJ: this is physiologic)
  - Hyperthyroidism; Estrogens, Wilson's, CLD

28

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

29

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

30