Anemia 101, Too Low, No Go!

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Disclosure

• I have nothing to disclose except
  – I do work for food
  – I promote giving Blood
Blood Components

- Plasma 54%
- White cells and platelets 1%
- Red Cells 45%
White Blood Cells

- Fight infections
- Are increased in infections
- Move inside and outside of blood vessels
- Are made in the bone marrow
# White Blood Cells

**WBC - White Blood Cells**  4.5 - 11.0 K/uL  
**Low = Leukopenia  High = Leukocytosis**

**WBC Differential**

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils - Segs</td>
<td>54 - 62%</td>
</tr>
<tr>
<td>Neutrophils - Bands</td>
<td>3 - 5%</td>
</tr>
<tr>
<td>Lymphocytes - Lymphs</td>
<td>25 - 33%</td>
</tr>
<tr>
<td>Monocytes - Monos</td>
<td>3 - 7%</td>
</tr>
<tr>
<td>Eosinophils - Eos</td>
<td>1 - 3%</td>
</tr>
<tr>
<td>Basophils - Basos</td>
<td>0 - 0.75%</td>
</tr>
<tr>
<td>Atypical Lymphs</td>
<td>0</td>
</tr>
</tbody>
</table>
Platelets

- Plug holes in the body to stop bleeding
- Can help cause blood to clot
- Made in the bone marrow
Red Blood Cells

- Carry oxygen from the lungs
- Carry carbon dioxide back to the lungs
- Also carry CO and NO
- Normally live 120 days
- Contains the protein hemoglobin
- Made from iron, folic acid, vitamin B12
- Made in the bone marrow
Red Blood Cells - Hemoglobin

- Oxygen

Normal Hemoglobin A has 2 alpha and 2 beta globin chains with 4 iron binding sites
Hemoglobin FA – Biochemistry – Normal Newborn

Chromosome 16
- alpha
- alpha
- alpha
- alpha
- beta
- beta

Chromosome 11
- gamma
- gamma
- delta
- beta
- mom
- Dad

50 – 20 % Hemoglobin A

Hb F (newborn): 50% to 80%
(6 months): 8%
(over 6 months): 1% to 2%

2% Hemoglobin A2
Hemoglobin A – Biochemistry – Normal Adult

Chromosome 16

- alpha
- alpha
- alpha
- alpha

Chromosome 11

- gamma
- gamma
- delta
- beta

- gamma
- gamma
- delta
- beta

95 - 97% Hemoglobin A

1 – 2% Hemoglobin F or Fetal

2 - 3% Hemoglobin A2
Red Blood Cells - Retics

- Reticulocytes, or Retics are young red cells just released from the bone marrow. The Retic count is the best indicator about how the marrow factory is doing.
Red Blood Cells

Food with iron and vitamins is digested

Red cells are made in the bone marrow

Red cells live 120 days in the circulation
Red Blood Cells - Recycled

Red cells are recycled in the spleen and liver. The iron and protein are stored and bilirubin is released.
Hemoglobin Recycled

Bilirubin must be Directed through the Liver to be Conjugated

Liver

Indirect Bilirubin

Hemoglobin

Iron – Fe bound to Transferrin

LDH - Lactate Dehydrogenase

Kidney - Hemoglobinuria
Erythropoietin is made by the kidney as a signal to the bone marrow to make more red cells.
Hepcidin

Increased levels blocks absorption of Iron and cell release
- inflammation IL6

Hormone made in the liver

Decreased levels increase iron absorption and release from cells – Erythropoietin, low iron
The History

- Weakness
- Tiredness - Fatigue
- Dyspnea
- Dizzy – non vertigo
- Palpitations
- New angina
The History -2

- History of melena, abdominal pain, Aspirin or non-steroidal anti-inflammatory agents (NSAIDs) use, past peptic ulcer disease, then consider GI bleeding, platelet dysfunction.
- In females the menstrual history quantifying the amount of bloodloss, or possible pregnancy should be obtained.
- History of pica or abnormal craving for ice, clay, starch...; dysphagia then consider iron deficiency.
- Poor diet, then consider iron or folate deficiency, and general malnutrition.
- History of gastric surgery, distal paresthesias, gait problems - consider B12 deficiency.
The History - 3

- History of alcohol abuse - consider folate deficiency or liver disease. If moonshine use or lead paint/pipe exposure, consider lead toxicity.
- Family history of blood cell or bleeding disorder: consider Sickle Cell disease, G6PD, Thalassemia, Hemophilia, von Willebrand
- History of jaundice, transfusion, new medication, infection - consider hemolytic process
- History of weight loss, Cancer, HIV, rheumatoid arthritis, thyroid disease, renal disease - then consider secondary cause
- History of fever and chills, cough, dyspnea, then consider Infection.
  - Medications – hemolysis, bone marrow toxicity, block nutrients (metformin – B12, Dilantin – Folate, PPIs) block EPO – (ACE inhibitors)
Physical Exam
Sclera
Spoon Nails – Fe Def.
Glossitis and Chelosis – Fe and B12
Physical Exam

- GENERAL INSPECTION- clubbing in TB or lung cancer
  - Skin- Hypothyroid, SLE, Bruises, lesions, petechiae or purpura.
  - Weight - Loss in Cancer, HIV, Chronic disease, gain in hypothyroid

- VITAL SIGNS- Pulse: Tachycardia from increased cardiac output
  - Respirations: Tachypnea from decreased oxygen transport
  - BP: Orthostatic if volume depleted
  - Temp: Fever in infections and drug or transfusion reactions,
  - HEENT- Eye: Jaundice if hemolysis, pallor in palpebral conjunctiva
  - Mouth: Glossitis and angular stomatitis in iron or B12 deficiency
Physical Exam - 2

- **NECK**- Thyroid enlargement or nodules, lymph nodes
- **HEART**- Increased output/murmur- JVD, LVH, S3, S4, consider high output failure
- **LUNG**- consider infection, lesion
- **ABDOMINAL**- Liver/spleen size, masses, tenderness, surgical scars
- **RECTAL**- Stool guaiac, prostate exam in men
- **PELVIC/BREAST**- Uterine abnormality, Pap smear, Breast nodule
- **LYMPHNODES**- consider lymphoma, leukemia, infection, connective tissue Disease
- **NEUROLOGIC**- Decreased vibratory and position sense in B12 deficiency
LAB- INITIAL SCREENING TESTS

- **Urinalysis**: Hematuria/proteinuria in renal disease, hemoglobinuria in hemolysis.
- **CBC**: red cell morphology and white blood cell differential, reticulocyte count
- **Chemistry profile**: (LDH, Bilirubin- Direct and Indirect, BUN, Creatinine, GPT),
- **Hemoglobin Electrophoresis**: if hereditary hemoglobinopathy is suspected
- **IF BLEEDING**: Platelet Count, PT, aPTT, PFA
<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>NORMAL ADULT</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>HB - Hemoglobin</td>
<td>Male= 15.5 +/- 2 mg/dl</td>
<td>Low = Anemia</td>
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<tr>
<td></td>
<td>Female = 13.5 +/- 2</td>
<td>High = polycythemia</td>
</tr>
<tr>
<td>HCT - Hematocrit</td>
<td>Male= 46.0 +/- 6%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female = 41.0 +/- 6%</td>
<td></td>
</tr>
<tr>
<td>RBC - Red Blood</td>
<td>Male = 4.3 - 5.9 Million/uL</td>
<td>High in Thalassemia</td>
</tr>
<tr>
<td>Cell Count</td>
<td>Female = 4.0 - 5.2</td>
<td></td>
</tr>
</tbody>
</table>
Red Cell Indices MCH, MCHC

MCH - Mean Corpuscular 27 - 32 pg
Low = Hypochromic
High = Hyperchromic

Hemoglobin

MCHC - Mean Corpuscular 30 - 36 gm/dl
Low = R/O Fe def.
High = Spherocytosis

Hemoglobin Concentration
Red Cell Indices MCV - RDW

MCV - Mean Corpuscular Volume  80 - 94 fl
   Low = Microcytosis    High = Macrocytosis

RDW - Red Cell Distribution Width  11.5 - 14.5
   Variation in RBC size
## RBC Morphology

<table>
<thead>
<tr>
<th>Red Cell Morphology</th>
<th>SIGNIFICANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burr Cells</td>
<td>Uremia, Low K, artifact, Ca stomach, PUD</td>
</tr>
<tr>
<td>Spur Cell</td>
<td>Post-splenectomy, Alcoholic liver disease</td>
</tr>
<tr>
<td>Stomatocyte</td>
<td>Hereditary, Alcoholic liver disease,</td>
</tr>
<tr>
<td>Spherocyte</td>
<td>Hereditary, Immune hemolytic anemia, water dilution, post-transfusion</td>
</tr>
<tr>
<td>Shistocyte - helmet</td>
<td>TTP, DIC, vasculitis, glomerulonephritis, heart valve, burns</td>
</tr>
<tr>
<td>Eliptocyte - Ovalocyte</td>
<td>Hereditary, Thalassemia, Fe Def., Myelophthistic, megaloblastic anemias</td>
</tr>
<tr>
<td>Sickle Cells</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Target Cells</td>
<td>Thalassemias, hemoglobinopathies</td>
</tr>
<tr>
<td>Microcytes</td>
<td>Thalassemia, Iron Def., Lead Toxic, B12 of Folate Def.</td>
</tr>
<tr>
<td>Macrocytes</td>
<td>Malaria, Babesiosis, Bartonellosis</td>
</tr>
</tbody>
</table>
Platelets

- Platelet Count  150 - 400 K cell/uL
  Low = Thrombocytopenia
  High = Thrombocytosis
Retics or Reticulocyte count

- Retic - Reticulocyte Count 0.5 - 1.5%
  Low in anemia = low marrow output
  High = RBC loss
Correcting the Retic

- absolute reticulocyte count (measured)
- reticulocyte (%) = absolute number of reticulocytes ÷ number of RBC × 100
- reticulocyte index = % reticulocytes × actual hematocrit ÷ normal hematocrit
- corrected reticulocyte index (corrects for appropriate bone marrow release of reticulocytes) = reticulocyte index ÷ maturation factor
- maturation factor = 3.25 – (actual hematocrit ÷ 20)
  - if hematocrit 45, maturation factor = 1
  - if hematocrit 35, maturation factor = 1.5
  - if hematocrit 25, maturation factor = 2
  - if hematocrit 15, maturation factor = 2.5
Anemia Diagnosis

• Loosing red cells (high retic count)
  – Bleeding
  – Hemolysis (High indirect Bili and LDH)
• Not making enough – (low retic count)
  – Low materials – Fe, B12, Folate
  – Low epo (Kidney disease)
  – Marrow problem (replaced, toxin....)
Diagnostic Pathway

Reticulocyte Production Index

- Decreased Production
  - <2
- Increased Loss
  - >2

Red Cell Indices

- MCV
- Hemolysis
- Bleeding

- >94
- 80-94
- <80

- Macro
- Normo
- Micro

Extrinsic
- Coombs Positive
  - Drug
  - Warm Antibody
  - Cold Antibody

Intrinsic
- Coombs Negative
- Membrane
- Hb
- Enzy
Anemia – low Hb/Hct Lab work-up
BPH = Bleeding/Production/Hemolysis

Anemic- Lab – CBC, Retic, RBC morphology, Metabolic Profile, UA

Retic Production index < 2 – Marrow Production Problem
Check MCV

MCV < 80 – Microcytic
Order Iron studies, HbELP, Lead Level

MCV 80 – 100 Normocytic
Order West Sed Rate, TSH, Renal Hepatic, Preg Test

MCV > 100 Macrocytic
Order B12, RBC and serum Folate

Increased Indirect Bilirubin and LDH = Hemolysis
Order Coombs, Hinze Body stain, HbELP

Retic Production Index >2 RBC Loss
Bleeding or Hemolysis

Bleeding
Microcytic

- MICROCYTIC = "TICS"
- T-Thalassemias
- I-Iron Deficiency
- C-Chronic Inflammation
- S-Sideroblastic - lead, drug, or hereditary
Microcytic Tests

TESTS TO ORDER:
• Serum Iron

• TIBC = Transferrin binding sites

• % Saturation = Transferrin saturation with Iron

• Ferritin = Storage Iron

• HBELP = Hemoglobin Electrophoresis

• Lead level if exposed
Microcytic workup
TICS – Thalassemia, Iron Deficiency, Chronic inflammation, Sideroblastic (Lead)

Iron studies (Ferritin) Low

- Yes = Iron Deficiency
  - Work up for Chronic Blood loss – GI, Menses

- No, West Sed rate CRP elevated - Inflammatory Block
  - Diet

- No, Lead Level elevated – Chelation therapy

- No, Abnormal HbELP?
  - Yes = Thalassemia – Refer to hematologist if severe
  - Refer to Hematologist for Bone Marrow Bx
Thalassemia Syndromes.

- Hereditary – Alpha or Beta chain
- Decrease Hemoglobin A
- Hemoglobin ELP abnormal and normal Ferritin are diagnostic
- Hemolysis (increased indirect Bili and LDH)
- Target Cells
- Supportive therapy or BMT
Iron deficiency

- Low Serum iron, **Low Ferritin**, High TIBC
- Find out why – GI bleed, menses, diet, H pylori, celiac disease
- Treat FeSO4 300mg tid
- Add vitamin C/meat to increase absorption
- Follow up Retic increase 1 week, Ferritin 1 month
Chronic Inflammation

• Block of normal iron stores transport to bone marrow factory
• Normal Ferritin, serum iron and TIBC are low with a low saturation
• 30% Microcytic, 70% Normocytic
• High Sed rate or c-reactive protein
• Treat inflammation – RA, SLE, HIV....
Sideroblastic

- Ring sideroblasts in bone marrow
- Serum iron is increased and TIBC normal resulting in a high saturation. Serum ferritin is increased
- RBC Basophilic stippling
- Lead toxicity is suspect
Normocytic Anemia

- NORMOCYTIC = "NORMAL SIZE"
- N-Normal Pregnancy
- O-Over hydration, Drowning
- R-Renal Disease
- M-Myelophthistic – Marrow replaced
- A-Acute Blood Loss
- L-Liver Disease

- SI-Systemic Infection/Inflammation
- Z-Zero Production- Aplastic anemia
- E-Endocrine: Hypothyroid, hypoadrenal, decreased androgen
Normocytic Tests

• Blood Urea Nitrogen (BUN), Creatinine, SGOT, Alkaline Phosphatase, Bilirubin, Erythrocyte Sedimentation Rate (ESR), Urinalysis, and Thyroid profile

• Renal Function tests

• Pregnancy Test

• Bone Marrow Biopsy
Normocytic workup

“NORMAL SIZE”

Check BUN/Creat/Liver, UA, West Sed Rate, Preg Test

- BUN/Creat elevated or abnormal UA
  - Work up for Renal Disease and Low EPO

- TSH elevated = Hypothyroid

- AST/ALT/AlkP – Liver disease

- West Sed rate elevated - Inflammatory Block

- Pregnancy test + Prenatal care
  - Pancytopenia
    - No - Repeat CBC, Retic in 2 week
    - Refer to Hematologist for Bone Marrow Bx
Normocytic - Renal Failure

- Anemia caused by decrease erythropoietin production causing decreased bone marrow production
- Can monitor erythropoietin levels
- Treat with epoetin alfa injections weekly or darbepoetin alpha every other week or monthly
- Check for Iron deficiency (altered metabolism) – May need to supplement
Macrocytic Anemia

- MACROCYTIC = "BIG FAT RED CELLS"
  Or my "BF"

- **B-B12 Malabsorption**
- **I-** Inherited
- **G-** Gastrointestinal disease or surgery
- **F-Folic Acid Deficiency**
- **A-** Alcoholism
- **T-** Thiamine responsive
- **R-** Reticulocytes miscounted as large RBCs
- **E-** Endocrine - hypothyroid
- **D-** Dietary

- **C-** Chemotherapeutic Drugs
- **E-** Erythro Leukemia
- **L-** Liver Disease
- **L-** Lesch-Nyhan Syndrome
- **S-** Splenectomy
Macrocytic Tests

- The peripheral blood changes include:
  - Anemia with decreased reticulocyte count, Increased MCV
  - Neutropenia with hypersegmented Neutrophils
  - Thrombocytopenia with large platelets.

- LABS to order:
  - B12, Serum Folate, RBC Folate
  - if all normal, consider Metylmalonic Acid and Homocytene levels, TSH, and a Bone Marrow Bx.
Macrocytic Work-up

Serum B12
RBC/Serum Folate

B12 normal/Folate normal - Order Metymalonic Acid and Homocytleine levels

Metylnalonic Acid Elevated in early B12 Deficiency

Consider Liver disease, hypothyroid, Drugs, Toxins – Refer for BM Bx

B12 low/Folate low = B12 Deficiency or both

Replace with oral, nasal or IM B12 and Folate
B12 Cobalamin Deficiency

Physical signs include edema, pallor, jaundice, smooth tongue, dementia, decreased vibratory and position sensation,

Hypersegmented polys
Elevated LDH, Indirect Bili
Low serum B12 level
Metformin, Gastric bypass, H2 or PPI as cause?
Methylmalonic acid (B12) and homocysteine levels elevated
Pernicious anemia - anti- intrinsic factor antibodies Schilling's test

• Rx - cobalamin 1000 mg I.M., oral, or Nasal Spray
Folate Deficiency

- **Causes** - liver disease, diet vitamin B12 deficiency (needed as co-factor), and drugs such as methotrexate, ethanol, and dilantin.
- **Lab** – low serum and RBC Folate
- **Rx** – Folate 1mg po qD
Hemolysis (HIT)

• **Hereditary** (HEM)
  – Hemoglobin (sickle cell, thalassemia)
  – Enzyme (G6PD deficiency)
  – Membrane (Spherocytosis, Eliptocytosis)

• **Immune attack** – Coombs positive (transfusion, IgM – cold antibody-infections, IgG warm antibody – Drug induced, PNH)

• **Trauma** – Microangiopathic (TTP, ITP, HUS, DIC, HIT, HELLP- Eclampsia, Malaria, Splenomegaly)
Hemolytic Anemia

- HEMOLYTIC = "HEMATOLOGIST"

- H-Hemoglobinopathy: sickle cell disease
  - Hemoglobinuria: Paroxysmal Nocturnal Hemoglobinuria

- E-Enzyme Deficiency

- M-Medication - drug induced: aldomet, INH

- A-Antibodies - Immune attack

- T-Trauma to the red cells: D.I.C, artificial heart valves

- O-Ovalocytosis

- L-Liver disease

- O-Osmotic fragility in Hereditary spherocytosis
  - and in Hereditary Elliptocytosis

- G-G6PD Glucose-6-Phosphate Dehydrogenase Deficiency

- I-Infection: malaria, babesiosis

- S-Splenic destruction in hypersplenism

- T-Transfusion

- Thalassemias
Hemolytic Signs

- 1. Elevated reticulocyte count, with stable or falling hemoglobin.
- 2. Elevated indirect bilirubin -
- 3. Elevated serum lactate dehydrogenase (LDH)-
- 4. Decreased Haptoglobin levels - Haptoglobin binds hemoglobin released in the plasma from red cell breakdown.
- 5. Hemoglobinemia and hemoglobinuria
- 6. Erythroid hyperplasia in bone marrow in chronic hereditary causes
- 7 Abnormal Hemoglobin Electrophoresis
Hemolytic Tests

• 1. The direct antiglobulin (Coombs') test  Direct Coombs test looks for antibody on the red cells. The Indirect Coombs looks for antibody in the serum.

• 2. Hemoglobin electrophoresis

• 3. Heinz body stain

• 4. Osmotic fragility

• 5. Blood smear
Hemolysis
Retic Production Index > 2, high LDH High indirect Bilirubin

- Coombs or DAT
  - No – Heinz body +
    - Yes = G6PD Deficiency
  - No – HbELP abnormal+
    - Hemoglobinopathy – SS, SC, SD S beta Thal Thalassemia
  - Yes
    - Warm Antibody
  - No – RBC Morphology+
    - Shistocytes and Low Platelets in DIC, HIT, TTP, HELLP
    - Cold Antibody
Genetic Hemoglobin Issues

- Thalassemia – Normal DNA sequence, Reduction in globin production
- Alpha – Not enough alpha globin production - Southeast Asian, Indian, southern Chinese, Middle Eastern and African ancestry
- Beta – Not enough Beta globin production Greek, Italian, Middle Eastern, Southeast Asian, southern Chinese and African descent
Hemoglobinopathy

Sickle Cell Disease – SS, SC, SD, SE, SOarab, S beta Thal

Newborn Screening or HbELP

Daily Penicillin –birth -6yo

Hydroxyurea prolongs life, prevents complications

Hydration, Oxygen, Temperature, and Folate
Enzyme - G6PD - Glucose - 6 - Phosphate Dehydrogenase Deficiency

X linked genetic
Precipitated by oxidant drugs
Heinz body stain show denatured Hb

Avoid medications such as antimalarials, aspirin, sulfa drugs, and avoid eating fava beans.
Membrane problems Spherocytosis and Ovalocytosis
Immune Attack

- Coombs Test: IgG and Compliment +/-
- Transfusion reaction: immediate or delayed
- IgM – (IgG Neg Comp +) cold antibody-infections like mycoplasma, EBV, HIV
- IgG warm antibody – Drug induced – Antibiotics, Ibuprofen, Autoimmune diseases
- PNH Paroxysmal Nocturnal Hemoglobinuria – Red cells attacked by complement Lack of CD55 or CD59 on RBC surface
Trauma To Red Cells

- Microangiopathic - Coagulation gone wild, fibrin shredding red cells - TTP, ITP, HUS, DIC, HELLP - Eclampsia
- Splenomegaly
- Infections within the red cell
  - Malaria – Mosquito parasite - Tropics
  - Babesiosis – Tick parasite - New England area
  - Bartonellosis – Bacteria - Cat Scratch
Parasites – Malaria, Babesiosis, Bartonellosis
Take Home Points

• The cause of Iron deficiency confirmed by a low serum ferritin should be pursued.
• Neuropathy, dementia, and anemia should prompt a search for vitamin B12 deficiency.
• A low corrected reticulocyte count is your best indicator of marrow decreased production vs red cell loss
• The MCV is the best guide to diagnose decreased marrow production anemias (Micro, Normo and Macrocytic)
• Microcytic anemia should prompt a TICS work up (Thalassemia, Iron deficiency, Chronic Inflammation and Sideroblastic/lead)