Anemia

Intensive Review in Internal Medicine
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Commercial/Faculty Disclosure
None

Anemia

• Hemoglobin or hematocrit below the normal range for age and gender

• Anemia can be due to:
  - ↓ red cell production (low retic count)
  - ↑ red cell destruction (high retic count)
  - Red cell (blood) loss (high retic count)

Morphological Classification of Anemias

<table>
<thead>
<tr>
<th>Anemias</th>
<th>Microcytic MCV&lt;80</th>
<th>Normocytic MCV 80-95</th>
<th>Macrocytic MCV&gt;95</th>
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<tbody>
<tr>
<td>Iron deficiency</td>
<td>Anemia of chronic Dx</td>
<td>Renal failure</td>
<td>Vit B12 def</td>
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<tr>
<td>Thalassemias</td>
<td>Aplastic anemia</td>
<td>Hypothyroidism</td>
<td>Folate def</td>
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<tr>
<td>Sideroblastic anemia</td>
<td>Aplastic anemia</td>
<td>Blood loss</td>
<td>Hypothyroidism</td>
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<tr>
<td></td>
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<td></td>
<td>Myelodysplasia</td>
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<td></td>
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<td>Alcoholic liver Dx</td>
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<td>Blood loss</td>
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</tbody>
</table>

Evaluating Anemias on & off the Medicine Boards

1. No. of retics
2. Size of cells
3. Blood smear
Evaluation of Anemia

Reticulocyte count

Corrected Reticulocyte Count/Reticulocyte Index

Reticulocyte Index = Retic count x Hematocrit

Normal Hct (45)

Reticulocyte Index in a normal healthy adult is between 1 and 2

Evaluation of Anemia

Reticulocyte Index and MCV

Low retic index

Low MCV

Iron deficiency
Sideroblastic anemia
Thalassemias
Renal failure
Aplastic anemia
Hypothyroidism
B12/folate deficiency
MDS
Alcohol liver disease

Normal MCV

High MCV

Hemolytic anemias
Blood loss

Case 1

58 y o woman w/ SLE, HTN and GERD presents with intermittent headaches and fatigue.

WBC 4.7, Hgb 9, Hct 27, MCV 74, platelets 544,000, retic count 1.5%, iron /TIBC : 45/520, ferritin 20.

Soluble transferrin receptor is 4.2 (0.8 – 3 mg/L).

She would benefit most from:

a) Erythropoietin therapy- 40,000U weekly
b) Better control of her SLE
c) 2 units of packed RBCs immediately
d) Intravenous iron
e) Proton pump inhibitor therapy

Iron Deficiency Anemia

Iron Cycle

Iron Absorption

Liver stores (stores iron in liver & heart)

Iron Regulatory Protein

Anemia

Iron Deficiency

http://www.cdc.gov/
**Iron Deficiency Anemia**

- Most common hematologic disorder seen in general practice
- Low reticulocyte index
- Ferritin < 20ng/dL is generally diagnostic
- Serum transferrin receptor level is high
- Gold standard for diagnosis — Bone Marrow Aspirate

- Look for and treat the cause

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**Iron Balance**

- Is primarily dependent on rate of Fe absorption
- Regulated by an iron regulatory hormone, Hepcidin

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**Peripheral smear**

- Microcytic hypochromic cells
- Platelets

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**Serum Transferrin Receptor**

- 129 adult patients
- Hb <12.8g/dL or <11.7g/dL
- BM Aspiration
- n=48
- n=64
- n=17

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**Anemia of Chronic Disease**

- Contributed to by - iron trapping in macrophages
- ↓ iron absorption from GI tract
- IL-6 induction of Hepcidin is central to etiology

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- Contributed to by - iron trapping in macrophages
- ↓ iron absorption from GI tract
- IL-6 induction of Hepcidin is central to etiology
Fe Deficiency Anemia vs Anemia of Chronic Dis.

<table>
<thead>
<tr>
<th></th>
<th>Fe deficiency</th>
<th>Anemia of Chronic Dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Fe</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>TIBC</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Very low</td>
<td>N/High</td>
</tr>
</tbody>
</table>

Management of Iron Deficiency Anemia

- Oral repletion - Ferrous sulfate/gluconate PO
  - Side effects – constipation, nausea and vomiting
- IV repletion – LMW dextran, ferric gluconate, Iron sucrose or Ferumoxytol
  - Side effects – rare. No anaphylactic rxns with IV formulations above.

Management of Iron Deficiency Anemia

- Expected Response to Fe Treatment
  - Reticulocytosis – 5-7 days
  - Increase in Hb – 2 weeks
  - Ferritin repletion – 6 months
  - If no response, re-evaluate

- If not, seek other cause.

Case 2

40 y o man who refurbishes old city buildings presents for a routine physical. He’s pale, discolored gum-tooth line & neuropathy.


Smear: RBCs cells with basophilic stippling.

Which would expect to see?
- a) BM aspirate with ringed sideroblasts
- b) Peripheral smear with teardrops
- c) Megaloblastic RBCs & elevated methylmalonic acid
- d) Elevated hepcidin level

Sideroblastic Anemia

- Heterogenous group of anemias
- Characterized by Ineffective erythropoiesis
- Hypoproliferative – low retic index
- Normocytic normochromic RBCs

Sideroblastic Anemias

<table>
<thead>
<tr>
<th>Common Causes</th>
<th>Clinical Associations</th>
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<tbody>
<tr>
<td>EtOH intoxication</td>
<td>Alcohol abuse history</td>
</tr>
<tr>
<td>Lead intoxication</td>
<td>Works producing batteries or removing paint from buildings</td>
</tr>
<tr>
<td>INH without vit B6</td>
<td>TB patient</td>
</tr>
<tr>
<td>Myelodysplastic Synd</td>
<td>Elderly person</td>
</tr>
</tbody>
</table>
**Sideroblastic Anemia**

RBCs containing Pappenheimer bodies

Ring sideroblasts in Bone Marrow

Courtesy Arthur Skarin, MD.

**Case 3**

- 70 y o woman with diabetes is brought to PCP by her family for progressive dementia. Labs are reported as normal. Aricept started.
  
  At six months f/u, no improvement. Gait is unsteady. Labs: WBC 2.9, hgb 8.3, hct 25%, plt ct 85,000, retic ct 0.9%.

**The Most Likely Diagnosis in Case 3**

- 70 y o woman with diabetes is brought to PCP by her family for progressive dementia. Labs are reported as normal. Aricept started.
  
  At six months f/u, no improvement. Gait is unsteady. Labs: WBC 2.9, hgb 8.3, hct 25%, plt ct 85,000, retic ct 0.9%.
  
  Most likely diagnosis –
  
  a) Vitamin B12 deficiency
  b) Myelodysplasia
  c) Alcohol abuse
  d) Folate deficiency

**Peripheral smear**

 hypersegmented neutrophil

macroovalocytic RBCs

**Megaloblastic Anemia**

- Caused by Vitamin B12 or Folate deficiency
- Hypoproliferative – low retic index
- Macro-ovalocytes
- Hypersegmented neutrophils (>5 lobes)
- Intrinsic factor (IF) Abs – Pernicious anemia
- Drugs – methotrexate, pentamidine, dilantin, triamterene, pyrimethamine

**We would expect other findings to include -**

a) ↑ folate, ↓ B12, normal MMA, ↓ homocysteine

b) normal folate, ↓ B12, ↑ MMA, ↓ homocysteine

c) normal folate, ↓ B12, normal MMA, ↑ homocysteine

d) ↑ folate, normal B12, ↑ MMA, ↓ homocysteine

e) ↑ folate, normal B12, ↓ MMA, ↑ homocysteine
Folic Acid vs Vitamin B12 Deficiency

<table>
<thead>
<tr>
<th>Diet history</th>
<th>Folic Acid def</th>
<th>Vitamin B12 def</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtOH, poor overall intake</td>
<td></td>
<td>Vegan</td>
</tr>
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</table>

Neurological deficits

Homocysteine

Methylmalonic acid

Other buzzwords

pregnancy, growing child

Fish tapeworm

Case 4

- 60 y o woman with Rheumatoid Arthritis presents with a 2 wk history of worsening weakness and dizziness.
- Labs: WBC 4.7, Hgb 7.3, Hct 25%, MCV 92, MCHC 39 platelet count 177,000. T bil 3.1, retic 23%, LDH 636, direct Coombs (+) for IgG and complement.

You would expect:
- a) Osmotic fragility to be abnormal
- b) Treatment with steroids to be beneficial
- c) Sputum culture positive for Mycoplasma pneumonia
- d) Schistocytes on her peripheral smear
- e) Splenomegaly on exam.

Autoimmune Hemolytic Anemia

- Due to formation of ‘auto’antibodies that attach to own RBC antigens
- Mechanism – macrophage stimulation in spleen (RES) or activation of the complement system.
- Reticulocyte count is high
- Diagnosis: Coomb’s test is positive
- Antibody is IgG or IgM

Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th>Warm AIHA</th>
<th>Cold AIHA</th>
</tr>
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<tbody>
<tr>
<td>Direct Coombs</td>
<td>IgG or IgG &amp; C3</td>
</tr>
<tr>
<td>Antibody</td>
<td>IgG</td>
</tr>
<tr>
<td>Etiology</td>
<td>Methylidopa, Penicillin, Procainamide, leukemia, lymphoma</td>
</tr>
<tr>
<td>Treatment</td>
<td>Steroids, Rituxan, splenectomy</td>
</tr>
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</table>

Case 5

- 45 y o accountant presents to his PCP with fatigue, and dyspnea on exertion.
- Physical exam: Marked pallor and petechiae on his ankles.
- Labs: WBC 1.1, hgb 6, hct 19%, retic count 0.2%, platelets 17,000.

Bone Marrow Biopsy

Normal bone marrow

Patient’s bone marrow
**What is Case 5 most consistent with?**

- 45 y o accountant presents to his PCP with fatigue, and dyspnea on exertion.
- Physical exam: Marked pallor and petechiae on his ankles.
- Labs: WBC 1.1, hb 6g/dL, hct 19%, retic count 0.2%, platelets 17,000.

*This is most consistent with a preceding:*

a) Viral hepatitis
b) Pneumonitis
c) Viral gastroenteritis
d) G6PD deficiency
e) None of the above

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**Aplastic Anemia**

- Due to a defect in the pluripotent stem cell
- Causes - Idiopathic
  - Drugs: sulphonamide, chloramphenicol
  - Viral: parvovirus, CMV, EBV, Hep B,C
  - Radiation
  - severe vitamin B12 deficiency
- Treatment:
  - Young pt– Bone marrow transplant
  - Older pt– Immunosuppression (ATG) & cyclosporine

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**Case 6**

32 y o woman presents with 3 day history of colicky abdominal pain and fatigue.

Labs: Hgb 2.9, Hct 22% MCV 78, platelets 60,000, retic count 9%, direct and indirect Coombs (-), ferritin 10. Abdominal USS shows portal vein thrombosis.

U/A – hemosiderin (+).

*The most likely diagnosis is:*

A) Factor V Leidin mutation
B) Paroxysmal cold hemoglobinuria
C) Warm autoimmune hemolytic anemia
D) Aplastic anemia
E) Paroxysmal nocturnal hemoglobinuria

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**Paroxysmal Nocturnal Hemoglobinuria**

- Acquired mutations of PiG-A gene → loss of Glycosyolphosphatidylinositol (GPI) anchor on RBCs, WBC & platelets
- GPI-anchored proteins include: Membrane inhib of reactive lysis (MIRF, CD59) & Decay Accelerating Factor (DAF, CD55)
- MIRF & DAF protect against c’-mediated lysis
- Resultant unrestricted c’-mediated lysis of RBCs

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**Eculizumab**

- Recombinant humanized monoclonal Ab binds to complement protein C5 inhibiting its cleavage into C5a and C5b, which prevents the generation of the terminal complement complex C5b-9.
- Inhibits formation of Membrane Attack Complex responsible for intravascular hemolysis in PNH.

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**Paroxysmal Nocturnal Hemoglobinuria**

Features:
- Chronic hemolysis → urine hemosiderin → Fe def.
- Thrombocytopenia
- Thrombosis in unusual sites – hepatic, mesenteric, cerebral veins.

Diagnosis: flow cytometry for CD55 & CD59.

Treatment: Eculizumab
  - Steroids
  - Allogeneic BM transplant
Case 7

34 yr old Hispanic woman is 20 weeks pregnant. Presents to office with generalized aches and fatigue. She’s jaundiced and tachycardic. Hct 22, WBC 14, plt ct 420. LDH 374, T. bil 5.4.

What diagnostic test is most appropriate?

34 yr old Hispanic woman is 20 weeks pregnant. Presents to office with generalized aches and fatigue. She’s jaundiced and tachycardic. Hct 22, WBC 14, plt ct 420. LDH 574, T. bil 5.4.

A) Full liver function tests.
B) Hemoglobin electrophoresis
C) Bone marrow biopsy
D) Rapid strep test
E) Osmotic fragility

What is the most appropriate treatment?

The 34 yr old Hispanic woman, 20 weeks pregnant. Admitted to hospital, given fluids, pain medication. On re-eval: tachycardic, diaphoretic, O2 sat on room air 83%. Hct 20, WBC 12, plt ct 420. Peripheral smear – sickle cells, targets and multiple nRBCs.

A) Exchange RBC transfusion
B) Aggressive hydration and IV pain medication
C) Intubation for respiratory protection
D) ASA, beta blocker and heparin

Hemoglobinopathies

• Abnormalities in hemoglobin that cause clinical consequences.
  ➢ Sickle cell syndromes (qualitative defects)
    β6 glu → val
  ➢ Thalassemias
    (quantitative defects)
  ➢ Unstable hemoglobin

Sickle Cell Syndromes (Qualitative Defect)

• Due to a point mutation in β-globin chain causing Glu→Val

Sickle Cell Anemia

• Due to homozygous inheritance of S β-globin
  • HbS -75-95%, HbF 2-20%, HbA2<4%
  • Functional asplenia, Vaso-occlusive crises

Common Complications:
  • Acute chest syndrome – major cause of mortality
  • Aseptic necrosis of bone
  • Priapism
Treatment of Sickle Cell Disease

Rx of Bone pain crisis – Fluid repletion and liberal pain medication as needed

Rx to prevent frequent crises – Hydroxyurea

Indications for Exchange Blood Transfusion
- Impending Acute Chest Syndrome
- Stroke-in-evolution/TIA
- Severe unrelenting bone pain crisis with end organ deterioration

Sickle Cell Trait
- Not considered a disease state
- Heterozygous inheritance of HbS:
  - <50% HbS, >50% HbA
- Vast majority are asymptomatic
- Rarely patients may have renal papillary necrosis, painless hematuria, isothenuria, splenic infarcts

Other Sickle Cell Syndromes
- Heterozygous inheritance of sickle gene and other abnormal gene
- HbSC disease - 50% HbS and 50% HbC
  - Clinically less severe phenotype than HbSS
  - Propensity for avascular necrosis of femur, retinal infarcts

α-thalassemia (Quantitative Defect)
- Absent or ↓ production of α chains of hemoglobin

<table>
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<tr>
<th>Locus Defect</th>
<th>Nomenclature</th>
<th>Clinical manifestation</th>
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<tr>
<td>αα/α-</td>
<td>α-thal trait</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>α-α- or αα/-</td>
<td>α-thal minor</td>
<td>little to no anemia</td>
</tr>
<tr>
<td>α-/- -</td>
<td>α-thal HbH</td>
<td>moderate hemolysis,</td>
</tr>
<tr>
<td>-/- -</td>
<td>α-hydrops fetalis</td>
<td>death in utero</td>
</tr>
</tbody>
</table>

β-thalassemia (Quantitative Defect)
- ↓ or absent production of β chains of hemoglobin
- Have low MCV and ↑HbA2

<table>
<thead>
<tr>
<th>Clinical Nomenclature</th>
<th>Clinical manifestations</th>
</tr>
</thead>
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<tr>
<td>β- thal major (Cooley’s Anemia)</td>
<td>severe anemia, ↑↑↑HbF, ‘chipmunk facies’ transfusion dependent for life.</td>
</tr>
<tr>
<td>β- thal intermedia</td>
<td>mod. anemia, non-transfusion dependent</td>
</tr>
<tr>
<td>β- thal minor</td>
<td>mild or no anemia, ↑RBC count</td>
</tr>
</tbody>
</table>

Diagnosis of Thalassemias
- α-thal. – Hemoglobin electrophoresis is NORMAL
  - Usually requires molecular restriction analysis
- β-thal. – Hemoglobin electrophoresis for diagnosis

Management of Thalassemias
- β-thalassemia major – RBC transfusions & Fe chelation
  - Bone marrow transplant is curative
- Other thalassemias – Supportive management
Hereditary Spherocytosis

- Due to abnormality of the integral proteins underlying the RBC membrane
- Loss of RBC membrane in the spleen → spherocytes
- Chronic premature hemolysis → early gall stones
- >65% are autosomal dominant – (+) family hx
- MCHC ≥ 39

Diagnosis: Increased osmotic fragility

Treatment: Folic acid, Splenectomy - limits hemolysis

Summary on Anemias

Summary on Anemias

- Diagnosis and Treatment of Iron Deficiency
  - Differentiating Fe Deficiency – High TIBC, low ferritin
    - from Anemia of Chronic Dx – Low TIBC, high ferritin
  - Soluble transferrin receptor – normal in ACD
  - Bone marrow iron – normal in ACD
  - Differentiating folate vs B12 deficiency
    - ↑ Methylmalonic acid & neurological deficits in B12 def.
    - Intrinsic factor Ab - – 99% specificity for pernicious anemia

Summary on Anemias

- Hemolytic anemias - ↑LDH, ↑ retic count
  - Spherocytes – AIHA or hereditary spherocytosis
  - Schistocytes – microangiopathic hemolytic anemia

- Indications for exchange blood transfusion in SCD
  - Stroke or Acute chest syndrome

- Diagnosis and Treatment of PNH
  - Gold standard for diagnosis: Flow cytometry for CD55 & CD59
  - Treatment: with monoclonal Ab Eculizumab

References