APPROACH TO ANEMIA

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Definition

- Males Hgb 14-17
- Females Hgb 12-16
Causes

• Blood loss
• Decreased production
• Increased destruction (hemolysis)
RBC FORMATION

- Production requires:
  - erythropoietin
  - iron (red meat, poultry, fish)
  - B 12
History

- Family hx of anemia
- Drugs, use or abuse
- Last Hgb?
Symptoms

- Asymptomatic
- Tachycardia
- DOE, chest pain
- Fatigue, malaise
- pallor
Exam

- Pallor
- Lymphadenopathy
- Petichiae
- Heme + stool
- Glossitis
- Stomatitis
Reticulocyte count

- Key to initial classification of anemia
- Residual RNA in newly made RBC
- Normal is 23,000 – 90,000
- > 110,000 suggests normal marrow response to anemia
- 2-3 x normal is expected within 10 days of onset of anemia.
Reticulocyte production Index

• Retic count x (measured Hgb/14)/2

Divided by 2 for maturation time correction, in the face of anemia, reticulocytes are released from the marrow prematurely, so this additional correction may be needed

• If polychromasia (normoblasts) are not seen on smear, this correction is not needed
Physiologic Classification of Anemia

High ------------------------- Retic count -------------------------Low or NL

Bleeding---yes---Blood loss
      no

Smear
      Macro

Schistocytes
Spherocytes
Folate

Sickle cells
Bite cells
Target cells
Inclusions

Micro          Normo
IDA            Aplasia      B12
Thal           Marrow infilt
sideroblast    Renal dx      MDS
Inflammation   Drug Tox      Etoh
Chronic dx     Chronic dx
MCV-BASED ALGORITHMIC APPROACH TO ANEMIA DIAGNOSIS
(DOES SIZE MATTER?)

Anemia

↓ RBC, ↓Hct, ↓Hb

<80 ft — Microcytic

Ferritin and iron status tests

Low — Iron deficiency anemia
Thalassemia, Hemoglobinopathy
Hemoglobin studies
Sideroblastic Anemia
Bone marrow ring sideroblasts

Normal — Thalassemia, Hemoglobinopathy
Anemia of chronic disease
Hemoglobin studies

High — Aplasia, Anemia of chronic disease
CRP and other cytokines

>>80-100 ft — Normocytic

Reticulocyte Count

Low — Aplasia, Anemia of chronic disease

High — Acute blood loss
Hemolysis, Chronic blood loss

>100 ft — Macrocytic

Blood Smear Morphology

No hypersegmented neutrophils
Hypersegmented neutrophils

Polychromasia
Target cells
Vit. B12 deficiency

Liver disease
Folate deficiency
B12 or folate levels
MMA
HYPOCHROMIC MICROCYTIC

- Iron Deficiency
- Thalassemia
- Chronic Disease, Inflammatory (usually normo, normo)
- Myelodysplastic syndrome (ringed sideroblasts seen on bone marrow)
Iron Deficiency

- Low Fe, high TIBC, low Ferritin. High RDW
- Reduced transferrin saturation (Fe/TIBC)
- If ferritin < 15, essentially no Fe stores
- Iron absorbed proximal small bowel: celiac dx, IBD, resection can affect
- May see accompanying thrombocytosis
Iron Deficiency

- Signs and symptoms
  - fatigue, malaise
  - headaches
  - pallor
  - pagophagia (ice chewing)
  - pica
  - glossitis
  - stomatitis
  - koilonychia (spooning of nails)
- chronic blood loss is always suspect in adults
Iron Deficiency Treatment

- Correct underlying problem if blood loss
- FeSO4 325 mg tid is least expensive, watch for nausea and constipation
- Slow Fe preparations not advised as absorption is markedly reduced
- Parenteral Fe therapy available for the rare patient who does not tolerate oral
- Duration: when Hgb normalizes, treat for additional 3-6 months to replenish the Fe stores
Thalassemia

- Hgb has 2 alpha chain globin and 2 B chain globin
- Ineffective erythrophoiesis, intravascular hemolysis and decreased Hgb production
- Microcytic, hypochromic RBC and target cells on smear
- Dx with Hgb electrophoresis
- RDW usually normal in Thal but elevated in IDA
Thalassemia

A single gene deletion is an asymptomatic carrier state that is normal clinically and hematologically

Alpha Thal Minor or Alpha Thal trait is a two gene deletion and is usually asymptomatic, mild anemia, microcytosis

- African, Mediterranean, SE Asia, Middle Eastern descent
- No treatment is needed
Thalassemia

• Hemoglobin H disease is caused by deletion of 3 alpha genes
• Severe anemia with CHF and hypoxia
• Hydrops fetalis or Hemoglobin Bart is caused by 4 gene deletion of the alpha chain and usually causes intrauterine demise
Thalassemia

- B Thal more prevalent in Mediterranean, SE Asian, Indian and Pakistan descent
- B Thal trait: mild anemia, microcytosis, hypochromia, target cells, increase A2 Hgb and sometimes also Hgb F
- No tx needed

- B Thal Intermedia: hemolytic anemia moderate to severe, can have massive extramedullary erythro in liver and spleen and in children in the facial bones causing chipmunk facies and frontal bossing
- Often develop Fe overload
- Increased Hgb A2, F or both
Thalassemia

• B Thal major: Cooley’s anemia, almost complete absence of B globin
• Unbalanced alpha and B chains causes accumulation of insoluble alpha chains in the marrow which kills developing erythroblasts
• Severe anemia
• Growth retardation
• Iron overload
• Tx with transfusions and chelation therapy
<table>
<thead>
<tr>
<th>Macrocytic Anemia</th>
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<tr>
<td><strong>No Hypersegmented neutrophils</strong></td>
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B 12 (cobalamin) Deficiency

- B12 sources: calf liver, sardine, shrimp, scallop
- Effective enterohepatic uptake, deficiency takes years to develop, stores generally good for 3-4 years
B 12 deficiency

• Decreased absorption:
• Pernicious anemia (antibody directed destruction directed at parietal cells)
• Aging with achlorhydria
• Celiac disease
• Pancreatic insufficiency
• Bacterial overgrowth
B12 deficiency exam

- Glossitis
- Pallor
- Jaundice possible due to ineffective erythropoiesis
- Neuropathy
- Spastic ataxia
- Dementia
- Psychosis
B 12 Smear

- Hyperchromic macrocytic RBC’s
- Oval macrocytes with basophilic stippling
- Hypersegmented neutrophils with > 5 lobes
- Decreased platelets
- Decreased WBC
B 12 Diagnosis

- B12 level
- Methylmalonic acid level is more sensitive than measuring the B 12 level and will be high with B 12 deficiency (expensive test)
- Homocysteine level should be high
- Haptoglobin level may be decreased
- LDH may be high
- Indirect Bili may be high
B 12 Treatment

• B12 1000 mcg IM per month, 6 injections spaced every 3-7 days should replenish stores
• Oral replacement has been shown to be as effective and less costly at 1000-2000Mcg/day
• Hemoglobin levels may take several months to normalize, if they do not, consider alternative diagnosis such as MDS
• Neuropsychiatric disorders take longer to resolve and ultimately may not
Folate Deficiency

- **Sources:** green leafy vegs., melons, lemons, bananas, fortified grains
- **Dietary deficiency** is unusual
- **Stores** are only 3-4 months
- Triamterene, Phenytoin accelerate folate metabolism
- **Alcohol** decreases folate absorption
- It is best to measure erythrocyte folate levels, serum folate may go up quickly with a meal
Folate Deficiency Diagnosis

- Folic acid levels
- Homocysteine level increased but are not used for diagnosis
- Methymalonic acid level is NOT increased contrasting with B 12 deficiency
Folate Deficiency treatment

• Folic acid 5-15 mg daily
• Will take about 4 months to treat
• Always check B 12 level before giving the Folic acid, if this is low and not corrected, the anemia will improve but not the Neuropsych symptoms
• Long term therapy may be needed for patients with a degree of hemolysis or those on dialysis
INFLAMMATORY ANEMIA

- Inflammation
- Infection
- Tissue injury
- Other conditions (cancer for one) causing release of inflammatory cytokines such as TNF alpha, IL 6, IL 1, and interferon
INFLAMMATORY ANEMIA
DIAGNOSIS

- Normochromic normocytic or microcytic, hypochromic
- Fe is normal or decreased
- TIBC is decreased
- Ferritin is normal or increased
INFLAMMATORY ANEMIA

TREATMENT

• No treatment needed in general
• Use Epo carefully as this may cause Htn and increase risk of thrombosis
ANEMIA WITH NORMOCHROMIC NORMOCYCTIC INDICES

• Renal disease: level of anemia correlates with degree of renal failure
• Normo, normo
• Fe levels, TIBC, ferritin all normal
• Those on dialysis may also develop Fe deficiency
• Epo levels low
ANEMIA WITH NORMOCHROMIC NORMOCYTIC INDICES

• Liver disease
• Smear: spur cells, stomatocytes
• If Alcoholic, may have also Folate deficit and may have blood loss so check the Iron levels also
HEMOLYTIC ANEMIA

• Signs: DOE, pallor, jaundice, gallstones, splenomegalgy
• Labs: LDH increased
  Indirect Bili increased
  Haptoglobin decreased
HEMOLYTIC ANEMIA

CONGENITAL

• Erythrocyte membrane – spherocytosis
• Erythrocyte enzyme – G6PD
• Defective Hgb structure – Sickle, Thalassemias
HEMOLOYTIC ANEMIA
CONGENITAL

• G6PD deficiency – Male > Female, AA most common
• Episodic hemolysis in response to stressors (infection, TMP-SMX, Nitrofurantoin), fava beans
• Heterozygotes protected to some degree against P. falciparum
• Smear : Bite cells
• Tx: supportive, withdraw offending agent
HEMOLYTIC ANEMIA
ACQUIRED

Autoimmune: Warm – IgG 80%
  mild splenomegaly
  Direct Coombs + 90%, weakly + C3
  spherocytes may be seen

Treatment: Prednisone 1 mg/kg
  splenectomy
  Rituximab
  Cytoxan
HEMOLYTIC ANEMIA ACQUIRED

- Autoimmune: Cold agglutinin– IgM 20%
  Direct Coombs neg, positive C3
  clumped RBC
  may develop weeks after EBV or mycoplasma infection

Treatment: Warm clothes
  Chlorambucil, Cytoxan, Rituxan
  Steroids and splenectomy not effective
  Plasmapheresis for acute
HEMOLYTIC ANEMIA ACQUIRED

- Microangiopathic smear shows helmet cells or schistocytes
- TTP, DIC, HUS, aged mechanical heart valve
- Plasma exchange may be lifesaving for TTP and HUS
HEMOLYTIC ANEMIA ACQUIRED

PNH

• stem cell disorder with hemolytic anemia, pancytopenia and atypical thrombosis (mesenteric, cerebral).

• Dx based on flow cytometry

• Tx with anticoagulants, Eculizimab helpful, steroids may help occasionally but ultimately require immunosuppressants or allogeneic BMT

• Median survival 10-15 years
HEMOLYTIC ANEMIA ACQUIRED

• Exposures – Malaria, Arsine gas, Babesiosis (Nantucket, Cape Cod, NC), Clostridial sepsis
• Venoms – brown recluse spider bite, snakes, massive wasp or bee stings
• Drugs – Cyclosporine, Tacrolimus, Clopidogrel, Ticlopidine
• Copper toxicity – Wilson’s disease
• Severe burns, Radiation
SMEARS

- Microcytosis: Fe def, Inflammatory, Thal
- Macrocytes: B12, Folate, MDS
- Spherocytes: Hereditary Spherocytosis
- Target cells: Hemoglobinopathy, Liver disease, splenectomy
- Burr cells: Kidney dx
- Bite cells: G6PD
- Spur cells: severe liver dx
- Sickle cells: SCD
- Nucleated RBC: marrow stress (hemolysis, hypoxia)
- Teardrop cells: Fibrosis, infiltrative marrow dx, marrow granuloma

(from Harrison’s Principles of Internal Medicine)
HEMATOLOGIC CAUSES OF SPLENOMEGALY

• Hemolytic anemia
• Spherocytosis
• Thalassemia
• SCD (early)
• Myelofibrosis
• Leukemia
HEMATOLOGIC CAUSES OF MASSIVE SPLENOMEGALY

>1000 grams

Thalassemia
CML
CLL
Lymphoma
Hairy Cell Leukemia
P. Vera
Myelofibrosis
Autoimmune Hemolytic Anemia
QUESTIONS

• 1. In B12 Deficiency, the Haptoglobin level may be decreased
  • A. True
  • B. False
QUESTIONS

2. In Fe deficiency anemia:
   • A. it will take 3-6 months after the Hgb is normalized to replace Fe stores
   • B. Slow Fe is preferred replacement
   • C. Thrombocytosis is often present
   • D. RDW is usually normal

3. In Inflammatory Anemia

- A. cells are Normo/normo or micro/hypo
- B. Fe is normal or decreased
- C. TIBC is decreased
- D. Ferritin is low

- 1. A, B, and C
- 2. A and C
- 3. B and D
- 4. All of the above.