Approaches to Anemia
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Disclosures

I have no disclosures

Objectives

- Approach to anemia in the pediatric patient
- Pertinent issues related to history and physical exam, laboratory work up, methods for classifying anemia
- Different ways of thinking of anemia
- Review of differential diagnosis

Outline

- Definition of Anemia
- Diagnosing Anemia
- Morphologies of Anemia
  - Microcytic anemia
  - Normocytic anemia
  - Macrocytic anemia

Anemia

- **Definition:**

Reduction in red cell mass OR hemoglobin concentration

Normal Values

Age	Hgb (g/dL) Mean	Hgb (g/dL) -2SD	Hct (%) Mean	Hct (%) -2SD	RBC (10^{12}/L) Mean	RBC (10^{12}/L) -2SD	MCV (fL) Mean	MCV (fL) -2SD	MCH (pg) Mean	MCH (pg) -2SD	MCHC (g/dL) Mean	MCHC (g/dL) -2SD
Birth (cord)	16.5	13.5	51	42	4.7	3.9	108	98	34	31	33	30
1-3 days	18.5	14.5	56	45	5.3	4.0	108	95	34	31	33	29
1 week	17.5	13.5	54	42	5.1	3.9	107	88	34	28	33	28
2 weeks	16.5	12.5	51	39	4.9	3.6	105	86	34	28	33	28
1 month	14.0	10.0	43	31	4.2	3.0	104	85	34	28	33	29
2 months	11.5	9.0	35	28	3.8	2.7	96	77	30	26	33	29
3-6 months	11.5	9.5	35	29	3.8	3.1	91	74	30	25	33	30
0.5-2 years	12.0	10.5	36	33	4.5	3.7	78	70	27	23	33	30
2-6 years	12.5	11.5	37	34	4.6	3.9	81	75	27	24	34	31
6-12 years	13.5	11.5	40	35	4.6	4.0	86	77	29	25	34	31
12-18 years												
Female	14.0	12.0	41	36	4.6	4.1	90	78	30	25	34	31
Male	14.5	13.0	43	37	4.9	4.5	88	78	30	25	34	31
18-49 years												
Female	14.0	12.0	41	36	4.6	4.0	90	80	30	26	34	31
Male	15.5	13.5	47	41	5.2	4.5	90	80	30	26	34	31

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Anemia

- How does one become anemic?
  - Increased hemoglobin loss (usually bleeding)
  - Decreased hemoglobin production
  - Increased destruction of RBC

Pathophysiology of Anemia

- Decreased production
  - Substrate deficiency
    - Iron deficiency, lead toxicity, vitamin deficiency
  - Mechanical interference
    - Leukemia, lymphoma, fibrosis, other oncology
  - Bone marrow failure
  - Ineffective erythropoiesis
    - Renal failure

Pathophysiology of Anemia

- Increased destruction
  - Intrinsic red cell factors
    - Membrane defects
    - Hemoglobinopathies
    - Enzyme defects
  - Extrinsic factors
    - Immune mediated
    - Non-immune
- Blood loss
  - Acute
  - Chronic

Diagnosing Anemia

-HISTORY HISTORY HISTORY!

-Physical & Laboratory Values

Use this information to focus on diagnosis and diagnostic considerations to guide further testing and confirm etiology

Evaluation

- Symptoms
- Past Medical History
- Gender, Race/Ethnicity
- Drug and toxin exposure
- Family History
- Dietary history
- Developmental history

Physical Exam

- Skin- jaundice, pale, uclers
- Facies-frontal bossing
- Mouth-glossitis
- Chest-shield chest
- Hands-triphalangeal thumbs, spoon nails,
- Spleen –enlargement

Laboratory

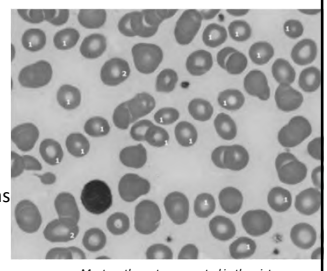
- CBC
- Reticulocyte count
- Iron studies
- Blood smear

Histology of Anemia

- Morphologic Classification of Anemias
  - Macrocytic
  - Normocytic, normochromic
  - Microcytic, hypochromic

Hypochromic Microcytic Anemia

- Iron deficiency (nutritional, chronic blood loss)
- Chronic lead poisoning
- Thalassemia syndromes
- Sideroblastic anemias
- Chronic inflammation
- Congenital hemolytic anemias with unstable hemoglobin



Most erythrocytes presented in the picture are microcytes (compare with the small lymphocyte).

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Substrate Deficiency

- Most common nutritional deficiency in children – **Iron Deficiency- Microcytic Anemia**
- #1 cause is inadequate intake
  - Most common in <2 years old
  - Associated with history of excessive milk intake

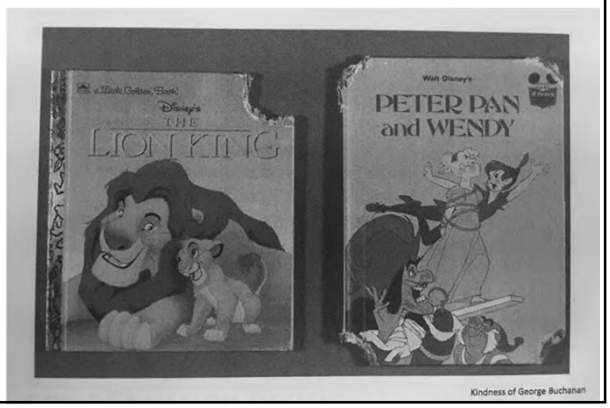
PICA

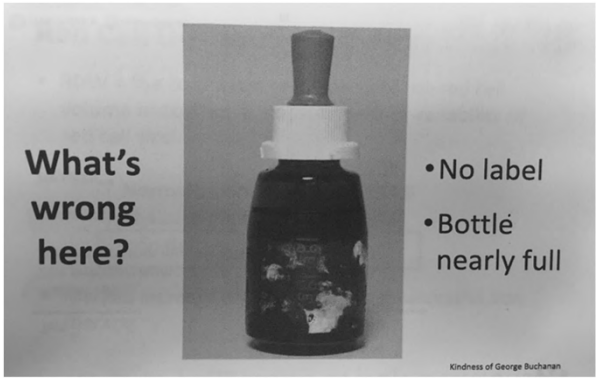
When what you crave is not fit for human consumption

PICA

Rocks
Dirt
Paint Chips
Ice Chips
Cardboard
Insects
Hair
Clay Starch
Carrots
Ice
Celery
Clothing

PICA vs waiting room books





Iron Deficiency Anemia

- Blood loss
  - GI
  - Mucosal (nosebleeds)
  - Lungs
  - Menstrual
  - Renal
- Impaired absorption
  - Inflammation
  - Infection/H Pylori
  - Receptor defects

Iron Deficiency Labs

- ↓ MCV
- ↓ MCH
- ↓ MCHC
- ↑ RDW
- ↓ Hgb A2 (normal ~2.5%)
- ↓-to-normal retic count
- ↓ serum Fe
- ↓ transferrin
- ↓ Fe saturation
- ↑ TIBC
- ↓ ferritin

Oral supplementation

- Iron salts:
- Ferrous sulfate ~20%
  - Lots of different preparations
- Ferrous gluconate ~12% elemental iron
- Ferrous fumarate ~33% elemental iron

Oral supplementation

- Dose:
  - 3-6 mg/kg of elemental iron daily
    - Depending on severity
- Results:
  - Peak reticulocytosis 5-10 days
  - Hgb increases by 0.25-0.4 g/dL/day = 1g/dL in 4wk
  - (or Hct by 1% per day)
- Cons:
  - lengthy course (3+ months),
  - troublesome dosing, multiple Rx refills forgetting, refusing
  - adverse effects (real or perceived)
  - the "well" patient taking daily meds for prolonged period

Parenteral/IV supplementation

- Indications:
  - Poorly tolerated oral iron
  - GI absorption of oral iron is compromised
  - Rapid replacement of iron stores needed
  - EPO therapy

CONS: weekly infusions, weekly PIV placements, time off from work/school, underlying problem not addressed

Parenteral supplementation

- Results:
  - Peak reticulocytosis in 10 days
  - Complete correction 4-6 weeks
  - Hct rises enough in 1-2 weeks for symptom relief

Altered Mental and Motor Development

- Lower mental and/or psychometric test scores and altered affect/behavior in anemic infants and school age children
- Correlation of iron status with IQ
- Reversal of anemia with oral iron does not always normalized mental and motor development, either immediately or years later

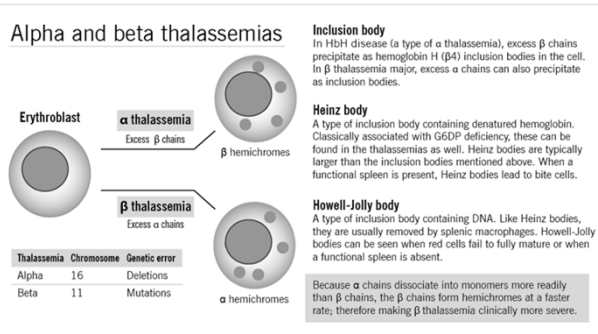
Doom JR et al, Curr Pediatr Rep (2014) 2:291-298

Mentzer Index

- Useful for deciphering iron deficiency anemia from beta-thalassemia
- MI = MCV/RBC count
- MI <13 = Thalassemia
- MI >13 = Iron deficiency

Thalassemia

- Normal Adult hemoglobin is a tetramer made up of 2 alpha and 2 beta subunits
- Alpha globin gene is on chromosome 16 and found in 2 pairs = 4 genes total
- Beta globin gene is a single copy gene on chromosome 11= 2 genes total
- More genes missing = more severe clinical course

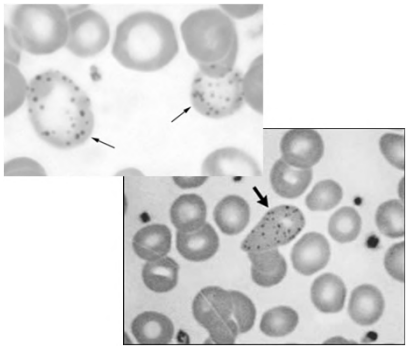


http://www.pathophys.org/thalassemia/

Compare: Lead poisoning

- Basophilic stippling
- Serum iron elevated
- Elevated serum lead level

Basophilic Stippling



Basophilic stippling represents aggregates of ribonucleoprotein (RNA).

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Lead Poisoning

- Blocks placement of iron into heme
- May cause neurological damage and anemia
- Usually related to lead-based paints and industrial exposures
- Test for a SERUM LEAD LEVEL
- Treatment – chelation

Iron Deficiency and Lead Poisoning

- Dietary Iron Deficiency → PICA
- PICA→ lead ingestion
- Iron deficiency → increased lead absorption from intestine (10x in animal studies)

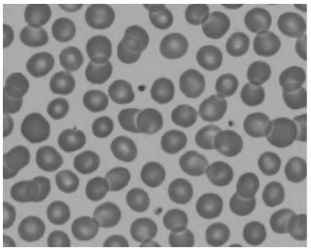
- Causes basophillic stippling
- Does NOT cause microcytic anemia (secondary to iron deficiency)

Microcytic Anemia Take Home

- Past medical history and family history
- CBC, retic, ferritin, Hemoglobin Fractionation
- Mentzer Index
- Iron deficiency Anemia
  - Supplement 3-6mg/kg/day BID or TID
  - Treat underlying cause!

Normocytic Anemia

- Congenital hemolytic anemias
  - Hemoglobin mutants
    - Hgb SS or Hg SC
  - Red cell enzyme defects
    - Hereditary spherocytosis
    - Hereditary eliptocytosis
  - Disorders of RBC membrane
    - G6PD deficiency
    - Pyruvate kinase deficiency



The picture shows normal erythrocytes seen at the correct site of the blood film. Only a few erythrocytes overlap, but in other cells there are distinct central halos.

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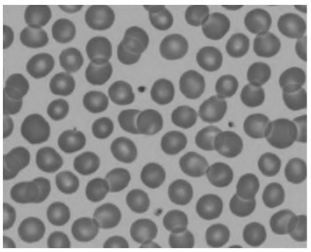
Normocytic Anemia

- Acquired hemolytic anemias
  - Antibody-mediated
  - Microangiopathic
  - Secondary to acute infections
- Acute blood loss
- Splenic sequestration
- Chronic renal disease
- Hyper or hypothyroid



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Red Cell Membrane disorders

- Hereditary Spherocytosis
- Many others with cell membrane or cytoskeleton defects
- Osmotic Fragility for testing
- Clinical Presentation (hemolytic anemia): pallor, jaundice, fatigue, splenomegaly, dark urine, gallstones

RBC Enzyme Disorders

- Enzymes essentially protect from oxidative damage
- G6PD deficiency
  - X linked
  - Decreased production of NADPH
  - Hemolysis in response to oxidative stress
  - Avoid fava beans, napthalene
  - G6PD.org website

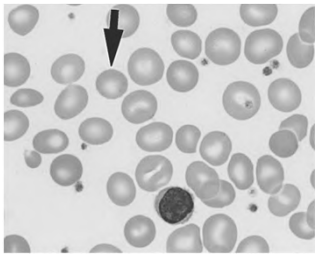
Normocytic Anemia Take Home

- Birth history, family history, past medical history
- Enzyme and membrane defects will have jaundice at birth, gallstones in family members
- CBC, retic, Osmotic Fragility
- Hemoglobin Fractionation for sickle cell

Macrocytic and Megaloblastic Anemia

Macrocytic: generally MCV < 105fl
- Hemolysis/reticulocytosis
- Marrow hypoplasia/aplasia
- Liver disease
- Drugs/Toxins

Megaloblastic: generally MCV>110fl
- Folate deficiency
- Vitamin B_{12} deficiency
- Inherited Metabolic disorders
- Drugs/Toxins



The arrow indicates normocyte. Most erythrocytes are macrocytes (compare with the lymphocyte). Five ovalocytes are seen.

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Folate and B12 Deficiency

- Lab findings:
  - Macrocytosis, low retic count
  - Mild thrombocytopenia/neutropenia
  - Hypersegmented neutrophils
  - Megaloblastic changes in bone marrow
- Clinical Findings:
  - Jaundice (ineffective erythropoiesis)
  - Smooth tongue
  - Neurological findings (B12 only): motor deficits, ataxia, seizures, depression, psychosis→ due to degeneration of posterior columns of spinal cord

Folate Deficiency

- Decreased intake
  - Malnutriotion, unpasteurized goat milk, sick premie
- Intestinal Malabsorption
- Increased requirements
  - Pregnancy, chronic hemolytic anemia (rare)
- Hereditary

Folate Facts

- Absorption in proximal ileum
- Dietary sources
  - Fresh fruits and leafy veggies
  - Meat
  - Cow and human milk
  - Fortified cereals and bread

B12 (Cobalamine) deficiency

- Reduced Intake
  - Vegan, breast feeding infant of B12 def mother
- Decreased absorption
  - Reduced intrinsic factor (IF) (pernicious anemia)
- Malabsorption despite normal IF
  - Ileal resection, IBD
- Increased intestinal utilization
  - Blind loop/statis→ bacterial overgrowth
  - Fish tapeworm infection

Macrocytic/Megaloblastic Anemia Take Home

- History is important: dietary, surgical, inflammatory etc
- Have suspicion for B12 and folate deficiency in malnourished patients, GI surgery patients, IBD patients
- Labs: CBC, retic, folate level, B12 level, hemoglobin fractionation (r/o Diamond Blackfan Anemia)

Summary

- History
- Physical exam
- Use your CBC to help guide your thinking!
- Consider hemoglobin fractionation in appropriate settings
- Iron deficiency is the most common form of pediatric anemia→ encourage compliance, fix underlying cause

THANK YOU!
Any questions??