Anemia of Chronic Disease
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Objectives
Identify causes of anemia
Discuss evaluation of anemia
Describe strategies to treat anemia

Disclosures
None
Anemia

Too few red blood cells or hemoglobin in the blood resulting in decreased capacity to carry oxygen.

Anemia is not normal.

Look for a cause.

Types of anemia

• Blood loss
  • Acute or chronic

• Destruction of blood cells
  • Hemolysis
  • Sickle cell, thalassemia
  • Toxins – venom, poison
  • Mechanical destruction

• Decreased or incorrect blood cell production
  • Iron deficiency
  • Nutrient deficits
  • Medications
  • Neoplasms
  • Malabsorption
  • Inflammation
  • Infection
  • Old age

50yo female

Normal creatinine
H/H normal, MCV/MCH low, RDW elevated
Hb falling

72yo male

CKD stage 4
SLE, RA, gout
Hb 7.2/24

45yo female

No CKD
Exhausted, ice pica
No bleeding source found
Hb 10 despite iron replacement

60yo female

SLE, TM, hypothyroid, CKD
Hb falls – 11.5 to 7.5

48yo male

Crohn’s dz, HBV, liver transplant, SBO

72yo male

CKD stage 4
SLE, RA, gout
Hb 7.2/24

48yo male

Normal creatinine
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Red blood cell evaluation

- **Hemoglobin (Hb)** – protein in RBCs that carries oxygen
- **Hematocrit (Hct)** – portion of RBCs in whole blood
- **Mean corpuscular volume (MCV)** – average RBC cell size
- **Mean corpuscular Hb (MCH)** – amount of Hb in average RBCs
- **Mean corpuscular Hb concentration (MCHC)** – concentration of Hb in RBCs
- **Reticulocyte count** – newly produced immature RBCs
- **Red cell width distribution (RDW)** – variability in size/width of RBCs

Koury, 2014; image: www.pathologystudent.com

Current knowledge

- Progenitor cells (derived from stem cells) may be the actual drivers of hematopoiesis rather than front line stem cells.
- Barcoding of DNA done in mice followed specific cell lines.
- **Current**: all RBC come from here
- **Research**: cells are generated by long lived progenitor clones

Sun et al., 2014; image: http://1.bp.blogspot.com/-k4bIJTZo9UY/TuTBCZ6hOAI/AAAAAAAAAbs/k_NaoxaYgLU/s1600/Bone_marrow_adult_Stems.png

Stem to progenitor cells research
Anemia of chronic disease – ACD
(anemia of inflammation)

2nd most common cause of anemia worldwide; iron deficiency is #1
• Infections
• Inflammation (30-60% of RA)
• Neoplasms (30-63%)
• Diabetes
• Old age (30% often due to inflammatory dz or CKD)
• Coexisting with other anemias e.g. iron deficiency

Schrier & Camaschella, 2015; Weiss, 2015

Acute ACD

• Inflammatory processes due to acute illness/injury
• Exacerbation of underlying chronic disease
• Trauma
• Surgery
• Sepsis
• Heart failure/MI

Schrier & Camaschella, 2015

Phases of inflammation

• Initiation
• Resolution
• Inflammation can persist for 10-15 yrs prior to complications e.g. DM, atherosclerosis, obesity, metabolic syndrome, RA, IBD, asthma
• Treatment can delay or reduce complications
• Current research suggests age 20-40 have more success with resolution
• Research focus on end product of omega 3 fatty acids – SPM (specialized pro-resolving mediators) which reduce/eliminate inflammation. Some people lack lipoxygenases to make the conversion.

Claria, 2017
Hypoxia driven cycle: Erythropoiesis stimulation

Normal cycle for RBC production

Reasons for ACD (acute and chronic)

Usually normochromic, normocytic, hypoproliferative, mild
- Shorter RBC life span especially with inflammation (cytokines)
- Decreased iron absorption — (hepcidin)
- Iron trapped in macrophages — (hepcidin)
- RBC precursor death — erythropoiesis can’t respond (cytokines)
- Inadequate response of erythroid cells to erythropoietin
- Decreased erythropoietin production
- Folate deficiency – folate competes with for binding sites for salicylates (used in treatment of RA), trimethoprim/sulfamethoxazole, & anticonvulsants. Folate excreted in urine.

Koury, 2014; Schrier & Camaschella, 2015; Calabrese, Spivak, & Kay
ACD: evolutionary defense against infection

• “Nutritional Immunity” - assisting innate immune defenses
• Microbes require iron for development and reproduction
• Sequestering iron reduces its availability
• Malignant cell growth may be hindered if iron is less available
• Anemia may be “collateral damage” from noninfectious chronic inflammation

Weiss, 2015

Pathways for ACD development

• Inflammatory mediators on iron regulation
• Suppression of erythropoietin
• Cytokine inhibition of erythroid progenitor cells

Weiss, 2015

Evaluation of anemia

• History & physical including onset, diet, medical history, meds
• CBC with diff and retic count and peripheral blood smear
• Renal function
• Iron studies – if suspected
• Folate/B-12 – if suspected
• Erythrocyte sedimentation rate and C-reactive protein – if indicated
• Explore other abnormalities e.g. leukopenia, thrombocytopenia as source of other disease

Koury, 2014; Price & Schrier, 2015
Peripheral blood smears

- Normal RBC – central pallor is 1/3 RBC diameter
- Normochromic normocytic anemia; need CBC to diagnose anemia

Ingredients for an erythrocyte

- **Iron (heme)** – main element of RBC
- **Protein (globin)** – protein portion of RBC
- **Vitamin B12 (cobalamin)** – needed for DNA synthesis in erythroblast nucleus to produce proteins. A cofactor for converting folate to active form.
- **Folate** – works with B12 for RBC synthesis
- **Pyridoxine (B6)** – transports B12; works with folic acid to lower homocysteine levels
- **Vitamin C** – glucose transporters carry C to the RBC; needed for pliability of RBC
- **Nicotinic acid (B3)** – needed for cellular energy metabolism; protects against ischemia
- **Copper** – 2 enzymes; converts ferrous to ferric for use in transferrin; aids iron uptake into RBC
- **Cobalt** – part of B12 for cell synthesis; interacts with hypoxia-inducible factors (HIF) to increase erythropoietin production

Hypoxia-inducible factors: HIFs

- Stimulated by hypoxia which
- Increases erythropoietin production
- Suppresses hepcidin which
- Increases absorption of duodenal iron
- Further research on the specifics of these pathways is continued
Hypothyroid

- Thyroxine increases cell metabolism and O2 consumption.
- Probably causes tissue anoxia which stimulates erythropoiesis.
- Hypothyroidism leads to a mild degree of anemia.
- Slightly increased MCV (macrocytosis) possible even with normal B-12; thyroid hormone T3 reduces erythroblast size.
- Anemia can be corrected by thyroxine e.g. levothyroxine.

Mekoto, 2014; Kaury, 2014

Iron deficiency: does your patient have this?

- Pagophagia: craving for ice.
  - Anemia may not be present yet.
  - Responds almost immediately to iron therapy.
- Beeturia: bright red urine after eating beets.
  - Occurs normally in ~12% of the population.
  - 50-80% in iron deficiency.
  - Betalaine (betanin) red pigment in beets is decolorized by ferric ions.
  - No iron – red urine. Disappears with iron repletion.
- Restless legs: one of the most common causes of RLS.
  - May have favorable response to oral iron even if the ferritin is not low.

Schrier & Mentzer, 2014

Normal iron cycle – 3-4 gms normal content

- 2gms in hemoglobin
- 400mg in proteins e.g. myoglobin
- 3-7mg plasma Fe on transferrin
- Remainder storage as ferritin or hemosiderin in liver, spleen, bone marrow
  - Males: 10mg/kg
  - Females: may be 50-70% less
- >4ml/day iron loss leads to iron deficit

Schrier & Mentzer, 2014; Kaury, 2014
Cell types

- **monocytes**
  - come from stem cells in the marrow
  - circulate in the blood for about 20-40 hours
  - migrate to the tissues to become...
- **macrophages**
  - function in phagocytosis
  - storage site for iron
  - can live for months to years

Makama, 2014; macrophage image: fineartamerica.com; monocyte image: histologyworld.com

Cytokines

- Inflammatory markers e.g. interleukins IL-1 and IL-6, tumor necrosis factor TNF from activated monocytes
- Bone marrow less responsive to erythropoietin
- RBC precursors destroyed
- May down regulate erythropoietin in renal cells
- May down regulate ferritin and transferrin receptors


Hepcidin

- Peptide from the liver
- Controls iron absorption from the intestines via the iron transport protein ferroportin
- High hepcidin = low iron absorption (acute phase reactant in response to IL-6)
- Blocks iron release from storage in the macrophages
- Kidney is main route of hepcidin excretion
- Hepcidin levels are not available for clinical use

Hepcidin blockage of iron transfer

Functional iron deficiency

- Iron stores are adequate but not available
- High ferritin suggests iron trapped in macrophages and low iron and low transferrin suggests a deficiency in ability to recycle iron.
- Low ferritin (<30ng) indicates absolute iron deficiency; look for blood loss.
- ACD may actually suppress erythropoietin production.
- Reticulocyte hemoglobin gives an indication of available functional iron in the past 3–4 days. It may be a more sensitive indicator of functional iron deficiency in ACD. Can be ordered as part of hematology panel.

Zinc

- If insufficient iron is available, zinc substitutes in the heme and forms zinc protoporphyrin (ZPP).
- ZPP can be measured.
- Its presence indicates a lack of iron but not a reason for the lack.
- ZPP is also present in elevated lead levels and can be useful in monitoring response to lead treatment. Not a good screening test for mild lead toxicity.
- Copper and zinc are absorbed at the same intestinal site.
- Consider Cu deficit with anemia e.g. bypass surgery, poor absorption.
- Poor iron utilization with Cu deficit.
- Zn takes precedence in absorption if doses are >50mg/day.
- Levels can be measured.
ACD & Inflammatory Bowel Disease

- Primary defect: iron deficiency
- IL-6 is prime inflammatory marker
- Hepcidin blocks ferroportin which transfers iron across endocyte membrane into the circulation
- This blocks absorption of iron from food or storage RES or macrophages
- Be alert for folate and B-12 deficits too due to malabsorption

Goldberg, 2013; Basseri et al., 2013

Case study: Crohn disease w/ additional risks

- 48 yo male
- PMH: Crohn’s disease, hepatitis B, ETOH abuse, liver transplant
- Recent hospitalization for small bowel obstruction
- Meds include tacrolimus
- Allergies: infliximab and numerous others
- Labs: Hemoglobin 10, iron 21, ferritin 14
- Considerations for treatment-
  - B12/Folate ok?
  - Crohn’s disease monitored and controlled?
  - Iron replacement ok? What form is best – oral or IV?

Case study: Acute ACD - vasculitis

- 53 yo male
- HTN, DM, microscopic polyangiitis
- Baseline creatinine 1.3-1.5 for 7 years; AKI with vasculitis
- Baseline Hb 11-12 w/ chronic low indices and elevated RDW; 7-8 with AKI
- Folate/B12/TSH normal
- Tired – no illnesses, no bleeding
- Medications hx – rituximab, dapsone, omeprazole, azathioprine
Risks and treatment

- Underlying microcytic anemia with low indices
  - Diabetes
- Acute illness with vasculitis and AKI
  - Cytokine production
  - Blood loss
  - Erythropoietin suppression
- Required blood transfusions, apheresis, acute HD, immunosuppressive therapy, iron supplementation and erythropoiesis therapy

ACD and SLE/transverse myelitis

- 60 yo female
- PMH: transverse myelitis, SLE, CKD sCr 2, hypothyroidism
- Hospitalized with dehydration and recurrent pneumonia; developed acute kidney injury sCr 4
- Hemoglobin dropped from 11.5 baseline to 7.5
- Rehydrated, transfused, diuretic readjusted
- ACD risks
  - SLE flare or TM exacerbation? Cellcept continued
  - Pneumonia symptomatic of underlying immunoglobulin deficiency? No
  - Bleeding? No source – transfused 2 units
- Successful return to baseline kidney function.

ACD and rheumatoid arthritis

- IL-6 causes elevated hepcidin levels and blocks iron availability
- IL-6 increases plasma volume (diluted Hb)
- Inhibition of IL-6 (e.g. tocilizumab or infliximab) increases iron availability
- Divide ferritin by 3; if < 20 iron deficiency is probably present
- ~1/3 have sCr >2 with CKD so ESA therapy is helpful
- Anemia often occurs later in the disease and is more common in women

Calabrese, Spald, & Kogilrud et al., 2014; Schrier & Mentzer, 2014
Case study: contributing factors

- 50yo female
- Diabetes
- HTN
- Lumbar radiculopathy
- Rheumatoid arthritis – nonerosive
- GERD
- Iron deficiency
- Polysubstance abuse (cig, crack, marijuana)

### Laboratory Results

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<th>Parameter</th>
<th>Normal Range</th>
<th>Value</th>
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<tr>
<td>Pts</td>
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<td>MCV</td>
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<td>MCH</td>
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<tr>
<td>RDW</td>
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<td>21.5</td>
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<tr>
<td>Iron</td>
<td>11-18</td>
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<tr>
<td>Sat%</td>
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<tr>
<td>eGFR</td>
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<td>HbA1C</td>
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<tr>
<td>Rheum factor</td>
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</table>

Treatment plan:
- Replace iron – PO not tolerated; insurance requested preauthorization; nausea HR 2.5
- Minimize pill burden
- Combine appointments
- Substance abuse therapy (current is smoking cessation)

Case study: lupus nephritis

- 72 yo male
- PMH: CKD stage 4, lupus nephritis per biopsy, rheumatoid arthritis, gout, hypothyroid
- Several RBC transfusions and IV iron infusions
- Medications – mycophenolate, hydroxychloroquine, levethoxine, losartan, colchicine
- Darbepoetin 150mcg every 2-4 weeks
- Considerations: B12/folate deficiency; thyroid function

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<thead>
<tr>
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<th>Value</th>
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<tr>
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<td>MCV</td>
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<td>MCH</td>
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<td>RDW</td>
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<td>Ferritin</td>
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<td>Iron</td>
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<tr>
<td>Creatinine</td>
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<tr>
<td>eGFR</td>
<td>&gt;60</td>
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</tbody>
</table>

Overcoming ACD: research areas

- Hepcidin lowering agents
- Mouse and monkey models
- Early clinical trials with healthy human volunteers
- Activation of hypoxia-mediated pathways to reduce hepcidin
- Erythropoietin therapy research to inhibit cytokine formation
- Monoclonal antibodies e.g. tocilizumab binds to IL-6 receptors and reduces inflammation
- Vitamin D

Poggiali et al. 2014; Weisz, 2015
Vitamin D and Hepcidin suppression

- Vitamin D is an inducer of antimicrobial proteins (e.g., cathelicidin CAMP)
- Hepcidin is an iron-regulatory protein in monocytes and hepatocytes
- Vitamin D (25D) seen to suppress hepcidin by 34% for 72 hr in study
- Hepcidin suppression increases iron availability

Iron overload: research

- Hereditary hemochromatosis and B-thalassemia both have iron overload from hepcidin deficiency
- Hepcidin agonists – too expensive to reproduce hepcidin
- Hepcidin has short ½ life
- Mini-hepcidin in the animal lab have decreased iron load in serum & liver
- Synthetic hepcidin antagonist research options
- Anti hepcidin antibodies are being investigated

Peripheral blood smears
Thalassemia

• Inherited blood disorder; either the alpha (α) or beta (β) globin are missing or mutated and cause a hemoglobin abnormality
  • Heterozygous are silent carrier w/ low normal Hb or slightly low Hb and MCV
  • Homozygous have mild microcytic anemia
• Thalassemia trait found in 30% African Americans
  • This ethnic group has slightly lower Hb even without thalassemia, iron deficiency, sickle cell traits/disease
• Thalassemia trait also found in persons from Mediterranean, Africa, Middle East, China, and Southeast Asia
• Alert - B12/folate macrocytosis may be masked
• Iron stores and RBC count usually normal

Case study: multifactorial causes of anemia

• 45yo African American female
• Symptoms: Significant fatigue, ice pica (pagophagia)
• PMH: anemia during pregnancy, DM2, hypertension, hyperlipidemia, sleep apnea
• Pertinent negatives: no overt blood loss, normal colonoscopy, no menorrhagia, no kidney disease
• Oral iron had not repleted her and caused GI upset
• Given several IV iron infusions over 2 years with return of symptoms

Case study (cont)

• Hematology evaluation
• Pertinent lab findings:
  • Decreased - Hb 10.2, MCV 74, MCH 24, ferritin 10.
  • Elevated - RDW 16, soluble transferrin receptor > (1.9-4.4 n/l)
• Soluble transferrin receptor (sTfR) – elevates with iron deficiency and is not an acute phase reactor (from bone marrow erythroid precursors – indicates erythropoietic activity so not specific for iron deficiency)
• Alpha-globin gene analysis – one alpha globin gene is deleted; patient is a silent alpha thalassemia carrier. Mild microcytosis is common.
• Additional diagnoses: iron deficiency and ACD/inflammation

Price & Schrier, 2015; Schrier, 2014

Schrier & Ventrac, 2014
α-thalassemia

Older adults: those >65 years

- WHO Hb criteria: <13-14g/dL for men; <12.3g/dL for women
- Older person proposed: 12.7-13.2g/dL men; 11.5-12.2g/dL women
- ~10-25% older adults are anemic
- Lower level needs evaluation – may have underlying process & ↑ morbidity/mortality (more frailty, depression)
- Ferritin levels increase with age; “normal” may mask deficiency.
- Decreased ferritin with normal/low anemia can have gi blood loss.
- Thalassemia trait; what is their anemia history
- Estimated world population – by 2030 8.4 billion people, 216 million >80 with 49 million being anemic

Case study: 86 yo female

- HTN, GERD, OA, CKD 3b
- Depressed, confused
- Hb 9 – falls to 7
- Iron stores normal
- Labs: n’l MCV, MCH, MCHC
- Hb falls to 6, requires blood
- N’l iron stores, neg hemocult
- Declines further w/u
- B-12/folate obtained: B12 low; given cyanocobalamin replacement.
- One month later B-12 n’l, Hb 10.5, confusion cleared.
Risk factors for B-12 or folate deficiency

Age >65 year old
Medications e.g. proton pump inhibitors, H2 blockers, metformin
Lack of intrinsic factor (IF) – underdiagnosed and more common in > age
Gastritis, gastrectomy, ileal disease, IBD
Inadequate diet – vegans/vegetarians (B-12 is only in animal products)
HIV – nutrition, diarrhea, ileal dysfunction (B12 <125pmol/L poorer survival)
Megablastic changes (> MCV/MCH) may not be present especially if GI
blood loss is present

B-12 vs. folate

<table>
<thead>
<tr>
<th>B-12</th>
<th>folate</th>
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<tbody>
<tr>
<td>• Huge stores so it takes years for</td>
<td>• Small stores so deficiency occurs</td>
</tr>
<tr>
<td>deficiency to appear</td>
<td>in 4-5 months</td>
</tr>
<tr>
<td>• Can cause permanent neurologic</td>
<td>• Most common cause is diet or</td>
</tr>
<tr>
<td>damage (&lt;vibratory sense, + Romberg –</td>
<td>ETOH (animal products/leafy veg)</td>
</tr>
<tr>
<td>can’t stand with feet together)</td>
<td>• Symptoms are r/t anemia not</td>
</tr>
<tr>
<td></td>
<td>neurological</td>
</tr>
</tbody>
</table>

Case study: age & risks

81 yo male
PMH: CKD, CAD, aortic valve replacement, HTN, peptic ulcer disease, DM, hypothyroid, gout, stasis leg ulcer, melanoma 50 years ago
Multiple meds
Had IV iron 6 months ago; c/o tired and cold. Labs unchanged

Elevated kappa and lambda light chains can be found in severe kidney disease, monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma, and amyloidosis.
Case study: is it EPO deficiency?

- 62 yo female
- PMH: SLE, lupus nephritis per biopsy, hypothyroid, gout
- Meds: allopurinol, mycophenolate, hydroxychloroquine, losartan, spironolactone, levothyroxine, etc
- Hospitalized with AKI (diarrhea, dehydration)
- Anemia contributors
  - Decline in kidney function (3b to 4)
  - SLE & gout – no active flares
  - Action plan is to start Epo
  - Monitor labs and check thyroid function
- If Hb doesn’t respond repeat iron studies and retic Hb

Erythropoietin levels

- Normal is 4-24 mlU/ml with 8-10 the usual range (follow your lab guide)
- If Hb <10.5 begin to observe elevated EPO levels
- Levels increase in iron deficiency
- EPO regulated by cytokine production, oxygen in tissues, & iron availability
- In older patients EPO levels may rise with age
  - possibly r/t need to maintain erythropoiesis
  - response to hypoxia
  - hypoplastic bone marrow

Summary

- Anemia always needs to be investigated
- Anemia is often multifactorial
- Anemia not responding to therapy - look for additional cause
- New onset anemia – assess for health changes and cause
- Approach is global but treatment needs to be individualized
References