Free Accompanying Mobile App!

A free anemia algorithm mobile app is available that covers concepts in this presentation

- The icon is included on slides where the app would be especially useful
- To download go to the Google Play store (Android phone/tablet users) or iTunes store (iPhone, iPad users)

Anemia Best Practices

- Anemia should not be considered a normal part of the aging process and should be evaluated further
  - A cause can often be determined, and treatment may alter outcomes and improve quality of life (QOL)
- Use mean cell volume (MCV) to narrow differential diagnosis of geriatric anemia and determine initial tests
  - Microcytosis, MCV <80 fL
  - Normocytosis, MCV 80-100 fL
  - Macrocytosis, MCV >100 fL
- Referral to hematologist for possible bone marrow examination should be carefully considered in patients with unexplained macrocytic anemia

Who Are We Talking About?

In 2016

- The life expectancy of a 65-year-old US male is: 17 years
- The life expectancy of a 65-year-old US female is: 19 years

US Census Bureau. Projections of the Population by Sex and Selected Age Groups for the United States: 2016 to 2060 (Table D)
http://www.census.gov/population/projections/data/natproj/2014/16 YEARS PROJECTIONS.html

Social Security Administration. Life Tables for the US Social Security Area 1900-2100.
http://www.ssa.gov/OACT/NOTES/as120/LifeTables_Body.html
Improving Outcomes in Geriatric Anemia: A Guide to the Differential Diagnosis of Treatable Causes

Who Are We Talking About?

According to US Census Bureau projections persons aged ≥85 years are the fastest growing segment of the population.

Prevalence of Anemia

26% for men

20% for women

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What is a “Normal” Hemoglobin?

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>White men</td>
<td>13</td>
<td>13.8</td>
<td>12.8</td>
<td>11.7</td>
<td>11.5</td>
</tr>
<tr>
<td>Black men</td>
<td>NRS</td>
<td>12.8</td>
<td>11.8</td>
<td>NRS</td>
<td>NRS</td>
</tr>
<tr>
<td>White women</td>
<td>12</td>
<td>12.3</td>
<td>12.0</td>
<td>12.2</td>
<td>12.0</td>
</tr>
<tr>
<td>Black women</td>
<td>NRS</td>
<td>11.3</td>
<td>11.3</td>
<td>11.5</td>
<td>NRS</td>
</tr>
</tbody>
</table>

*5% threshold in Gaussian distribution
NRS, not reported separately

Anemia Development is Predictive of Mortality in Older Persons
- During long-term follow-up (≥16 years) of the Cardiovascular Health Study (n=3,758), anemia development (HR 1.39, 95% CI 1.15, 1.69) and hemoglobin decline (HR 1.11, 95% CI 1.04, 1.18 per 1 g/dL decrease) over 3 years predicted subsequent mortality in men and women.
- Baseline increasing age, being African-American, and kidney disease predicted anemia development over 3 years.
- Numerous other studies show similar results.
- At-risk elderly individuals can be identified for early intervention to improve quality and quantity of life.

Key Takeaway

The cause of anemia in the elderly, even if mild, should be evaluated for treatment to improve quality and quantity of life.

Associations with a Low Hemoglobin Level in Older Persons

Increased
- Rates of recurrent falls
- Rates of major depression
- Frailty index
- Risk of hospitalization and longer duration in hospital

Decreased
- Mobility, bone density, skeletal muscle mass
- Cognitive function
- Outcomes in specific diseases (anemia as marker of disease severity – correlation ≠ causation)
  - Congestive heart failure (poor hemodynamics, more symptoms, higher mortality)
  - Cancer (decreased survival)
  - HIV infection, independent of viral load
Improving Outcomes in Geriatric Anemia: A Guide to the Differential Diagnosis of Treatable Causes

Anemia

- Anemia is a sign of disease, not a disease itself
- Dozens of causes, many common
- Organized approach essential
- A specific cause can be found in almost all cases

Causes of Anemia:
- Loss of RBCs
- Marrow failure
- Blasting hematopoiesis
- Nutritional deficiencies
- Hemolytic anemia
- Renal failure or denervation

Early iron, 
Vitamin B
or folate

Red Cell Distribution Width (RDW)

- RDW is the variation in RBC volume (reported as part of CBC)
- RDW = 3SD of MCV X 100
- Normal RDW: 11%–15%
- Elevated RDW (>15%) known as anisocytosis
- RDW useful in identifying anemia of mixed causes

RDW, standard deviation

Anemia Differential Diagnosis by MCV

- Normal MCV
- Elevated MCV
- Low MCV

- Normal
- Elevated
- Normal

- Normal
- Elevated
- Normal

- Normal
- Elevated
- Normal

- Normal
- Elevated
- Normal

- Normal
- Elevated
- Normal

- Normal
- Elevated
- Normal

MCV, mean corpuscular volume

Reticulocytes

- Immature RBCs (typically ~1% of RBCs) containing ribosomal remnants that circulate in blood for about a day before fully developing into RBCs
- Serve as a marker of marrow red cell production activity
- Increase to compensate for severe loss of mature RBCs in conditions such as hemolytic anemia
- Reticulocytosis = elevated number of reticulocytes in the blood
- Abnormally low numbers indicate failure of erythropoiesis in marrow
- May indicate anemia of chronic inflammation, aplastic anemia, pernicious anemia, bone marrow malignancies, abnormal erythropoiesis, vitamin or iron deficiencies, or chemotherapy

62-year-old Business Owner

- Seen for routine follow up of type 2 diabetes, no complaints
- Early retinopathy, neuropathy, and diabetic kidney disease
- Laboratory studies:
  - Hemoglobin: 10.2 g/dL, MCV: 90 fl
  - Fasting blood sugar: 146 mg/dL; HbA1c: 7.8%
  - Urine microalbumin screen: 100 mg/g creatinine (normal, <30)
  - BUN 42 mg/dL; creatinine 1.9 mg/dL; Estimated GFR: 35 mL/min/1.73 m2
  - Vitamin B12 (510 ng/L) and RBC folate within normal range


62-year-old Business Owner

**CONTINUED**

- Iron studies
  - Serum ferritin: 58 ng/mL (normal range: 20-300 ng/mL)
  - Serum iron: 100 mcg/dL (normal range: 60-170 mcg/dL)
  - TIBC: 210 mcg/dL (normal range: 240-450 mcg/dL)
  - Transferrin saturation: 48% (normal range: 20%-50%)

**Anemia of CKD**

- Increased prevalence as disease progresses; anemia is a risk factor for progression of ESRD
- Typically normocytic, normochromic, and hypoproliferative (i.e., low reticulocytes)
- EPO deficiency is the predominant cause
- Relative EPO deficiency compared with similarly anemic patients with normal kidney function
- Associated with disordered iron homeostasis
  - Low serum transferrin saturation and normal to high serum ferritin with iron depletion in the bone marrow
  - Elevated hepcidin levels impair dietary iron absorption and iron mobilization from body stores
- Severity can be reduced by correcting the iron deficiency with iron supplementation
- ESA should be used after addressing all correctable causes of anemia

Iron Deficiency Anemia (IDA)

**59-year-old Fitness Instructor**

- Diagnosed with Crohn’s disease at age 27
- Symptoms have generally been mild to moderate and have responded to treatment with sulfasalazine, antibiotics, and budesonide in conjunction with nutritional therapy
- She now presents complaining of fatigue
- No bruising, bleeding, numbness, tingling or ataxia
- Other medications: NSAIDs for knee pain
- Surveillance colonoscopy performed 2 years ago was negative
- Physical examination:
  - Moderate palor, some abdominal discomfort; otherwise unremarkable

**59-year-old Fitness Instructor**

**CONTINUED**

- Complete blood count:
  - Hemoglobin: 9.8 g/dL
  - MCV: 77 fL
  - Hematocrit, RBC counts, and mean corpuscular hemoglobin all below normal ranges
  - Normal white blood count, differential and platelets
  - Ferritin 10 ng/mL (normal range, 10%-30%)
  - Transferrin saturation 9% (normal range, 20%-50%)
  - Erythrocyte sedimentation rate, albumin and C-reactive-protein levels within the normal ranges
  - A stool sample tested positive for occult blood

**Relationship Between Serum EPO Level and Hb Level**

- Adequate EPO production
- Inadequate EPO production in response to anemia

**Iron Deficiency Anemia (IDA)**

- Predominant cause of normocytic anemia in the US
  - 80% to 90% of patients with IDA iron normocytic
- Most common causes of IDA:
  - Abnormal uterine bleeding (20%-50%)
  - Gastrointestinal bleeding due to long-term use of aspirin or other NSAIDS (15%-30%)
  - Colorectal polyps or carcinoma (10%-20%)
- Dietary iron is rare in the US, but may be seen in vegetarians/vegans
- Plants contain non-heme iron, which is less well absorbed
- Diagnosis requires laboratory-confirmed evidence of anemia, as well as evidence of low iron stores (usually low serum ferritin, sometimes elevated soluble transferrin receptor)
- Once diagnosed, the cause of IDA should be evaluated

Total iron binding capacity (TIBC) = TIBC - Serum iron

- Iron’s bound to transferrin in the plasma
- TIBC is a direct measure of levels of transferrin (i.e., capacity to bind iron)
- Transferrin levels are increased in IDA and reduced in inflammation

Soluble transferrin receptor (sTfR)

- Cell surface transferrin receptor internalization resulting in increased receptor release or loss
- Expression of transferrin receptors in increased in the absence of adequate iron stores
- sTfR levels closely reflect iron stores and is not affected by the inflammatory process

Increased levels of sTfR are also found in conditions of increased red cell turnover

**Improving Outcomes in Geriatric Anemia: A Guide to the Differential Diagnosis of Treatable Causes**

[Image 61x357 to 88x377]
**Key Takeaway**

Ferritin level is **NOT** a reliable measure of iron storage in the body, because it is a positive acute-phase reactant.

---

**Intravenous Iron Therapy**

- Considered better tolerated and more effective than oral iron treatment in improving ferritin
- Can be used in patients who cannot tolerate/absorb oral iron, e.g., those who have undergone gastrectomy, gastrointestinal surgery, or other small bowel surgeries
- IMW iron dextran should be avoided (it is no longer marketed)
- Available as solutions for injection: dose based on weight and desirous change in Hb
- Iron deficient patients usually need 1000 mg to replete

<table>
<thead>
<tr>
<th>Form</th>
<th>Dose</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMW iron dextran (eg. Veldac®)</td>
<td>50 mg/mL</td>
<td>Up to 11%</td>
</tr>
<tr>
<td>Sodium ferric gluconate (Flucitron®)</td>
<td>25 mg/mL</td>
<td>30-40%</td>
</tr>
<tr>
<td>Ferric carboxymaltose (FeBC®)</td>
<td>62.5 or 125 mg</td>
<td>40-60%</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Ferinject®)</td>
<td>50 mg/mL</td>
<td>100%</td>
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</tbody>
</table>

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**Oral Iron Therapy**

- **Hb increase of ≥1 g/dL after one month of treatment** defines an adequate response to treatment and confirms the diagnosis
  - Red blood cells should increase after 1 week
  - Ferritin should increase because they are more readily absorbed than ferric (3+)
- Vitamin C and an acidic stomach increase iron absorption in some patients

**Microcytic-hypochromic Anemias**

**Common Causes**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical/Pathologic</th>
<th>Next test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Low ferritin</td>
<td>GI evaluation, unless bleeding obvious</td>
</tr>
<tr>
<td></td>
<td>Low TIBC</td>
<td>Hematocrit, MCV, SE Asian, chronic hemolysis</td>
</tr>
<tr>
<td></td>
<td>High iron</td>
<td>Considered malignant disease</td>
</tr>
<tr>
<td>Anemia of chronic disease/inflammation</td>
<td>Normal or low ferritin</td>
<td>ESR, CRP to confirm inflammation</td>
</tr>
<tr>
<td></td>
<td>Low TIBC</td>
<td>Specific immunological evaluation</td>
</tr>
<tr>
<td></td>
<td>Low transferrin</td>
<td>Serum C-reactive protein level</td>
</tr>
</tbody>
</table>

**Rarer Causes**

<table>
<thead>
<tr>
<th>Cause</th>
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</tr>
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<tbody>
<tr>
<td>Hemolytic anemia</td>
<td>Low Hb, low HCT, increased reticulocytes</td>
<td>Direct Coombs test, serum LDH</td>
</tr>
<tr>
<td></td>
<td>Increased LDH</td>
<td>Hemolysis tests</td>
</tr>
<tr>
<td></td>
<td>Increased bilirubin</td>
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---

**Microcytic-hypochromic Anemias**

**Thalassemia Syndromes/Sickle Cell Disease**

- Considered better tolerated and more effective than oral iron treatment in improving ferritin
- Can be used in patients who cannot tolerate/absorb oral iron, e.g., those who have undergone gastrectomy, gastrointestinal surgery, or other small bowel surgeries
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**Microcytic-hypochromic Anemias**

**Thalassemia Syndromes**

- **β-thalassemia major (HbSS)**: Transfusion-dependent hypochromic anemia; HbA² < 2%
- **β-thalassemia intermedia (HbSC)**: Variable anemia (HbA² > 2%), splenomegaly, and chronic transfusion requirement
- **β-thalassemia minor (HbAS)**: No clinical symptoms

**Sickle Cell Disease**

- **Homozygous (HbSS)**: Severe anemia, hypochromic, and microcytic
- **Compound heterozygous (HbSC)**: Intermediate symptoms
- **HbAS**: No symptoms

**Hemoglobinopathies**

- **Hemoglobin E**: More common in Southeast Asia
- **Hemoglobin C**: More common in Africa
- **Hemoglobin E/C**: More common in Mediterranean countries
- **Hemoglobin D**: More common in Southeast Asia
- **Hemoglobin F**: More common in the fetus and newborn
- **Hemoglobin S**: More common in African Americans
- **Hemoglobin D-Punjab**: More common in the Punjab region of India

**Other Hemoglobinopathies**

- **Hemoglobin Lepore**: More common in the Mediterranean region
- **Hemoglobin Bart’s**: More common in fetuses

---

**Microcytic-hypochromic Anemias**

**Sideroblastic Anemia**

- **Microcytic, hypochromic anemia**
- **Increased serum iron**
- **Reduced total iron binding capacity (TIBC)**
- **Normal or low ferritin**
- **Normal or low transferrin**
- **Increased sTfR**
- **Increased hepcidin**

**Megaloblastic Anemia**

- **Macrocytic, hypochromic anemia**
- **Increased serum iron**
- **Increased total iron binding capacity (TIBC)**
- **Normal or low ferritin**
- **Normal or low transferrin**
- **Decreased sTfR**
- **Decreased hepcidin**

**Other Anemias**

- **Anemia of chronic disease**
- **Anemia of inflammation**
- **Anemia of gastrointestinal bleeding**
- **Anemia of chronic renal failure**
- **Anemia of iron deficiency**
- **Anemia of blood loss**
- **Anemia of folate deficiency**
- **Anemia of vitamin B12 deficiency**
- **Anemia of myelodysplastic syndrome**
- **Anemia of rare genetic disorders**

---

**Key Takeaway**

Ferritin level is **NOT** a reliable measure of iron storage in the body, because it is a positive acute-phase reactant.
68-year-old Retired Teacher

- Complains of reduced stamina and new dyspnea upon exertion, no chest pain
- Past medical history: breast cancer 6 years ago, treated with lumpectomy and adjuvant chemotherapy and radiotherapy, follow up exams all negative
- No significant alcohol use or smoking history
- Physical examination: lungs clear, mild sinus tachycardia (heart rate ~102/min.); exam otherwise unrevealing

Key Takeaway

- Once gastrointestinal bleeding, nutritional cause, and renal failure have been ruled out, evaluation of anemia should continue
- A bone marrow examination may be indicated even if anemia is the only cytopenia

68-year-old Retired Teacher

- Laboratory studies:
  - Hemoglobin 9.6 g/dL, MCV 102 fL; rest of CBC within normal range
  - Folate, B12, thyroid stimulating hormone (TSH), serum ferritin, serum iron, % iron saturation all within normal range
  - Fecal occult blood negative x 2
  - 2 years ago, screening colonoscopy was negative

Algorithm for Laboratory Workup of Macrocytic Anemias

Vitamin B₁₂ / Folate Deficiency

- Low intake of animal source foods; may be seen in vegetarians/vegans
- Severe vitamin B₁₂ deficiency most commonly caused by autoimmune gastritis (pernicious anemia)
- Methodological problems may compromise the sensitivity and specificity of current vitamin B₁₂ assays
  - Vitamin B₁₂ deficiency may be confirmed by measurement of methylmalonic acid, homocysteine, or both
  - An elevated level of methylmalonic acid is more sensitive and specific for the diagnosis
  - Folinic acid levels are elevated, then a folic deficiency may exist
- High-dose oral vitamin B₁₂ tablets (1000 to 2000 μg) taken daily are as effective as intramuscular monthly injections in correcting blood and neurologic abnormalities
- Pernicious anemia / malabsorption require lifelong vitamin B₁₂ therapy

Classification of Hematologic Malignancies

- Neoplasms
  - Leukemia
    - Chronic Myeloid Leukemia
    - Acute Myeloid Leukemia
  - Myeloproliferative Neoplasms
    - Essential Thrombocythemia
    - Polycythemia Vera
    - Thrombocythemia
  - Myelodysplastic Syndromes
  - Chronic Myeloid Neoplasms
    - Chronic Myeloid Lymphoid Neoplasms
  - Lymphoid Neoplasms
    - Hodgkin Lymphoma
    - Non-Hodgkin Lymphoma
  - Myeloid Neoplasms
    - Myeloma

Notes:

- MCV >100 μL³, suspect: B₁₂ deficiency
- Low intake of animal source foods; may be seen in vegetarians/vegans
- Severe vitamin B₁₂ deficiency most commonly caused by autoimmune gastritis (pernicious anemia)
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Improving Outcomes in Geriatric Anemia: A Guide to the Differential Diagnosis of Treatable Causes

**Key Features of Myelodysplastic Syndromes (MDS)**

- **Malignant hematopoietic clonal proliferations**
- **Progressive cytopenias**
- **Dysplastic features**
- **Inability to find a specific cause**

**Disease features**

- **Molecular genetic testing for mutations can complicate diagnosis but is reasonable in elderly patients**
- **Specific mutation(s) may define MDS even in the presence of clonal mutations**

**Hematopoietic growth factors**

- **ESAs**
- **G-CSF**, **GM-CSF**

**Commonly Employed Treatments for MDS: Evolution in the Last 15 Years**

- **2001**
  - **Hematopoietic growth factors**, especially **ESAs**
  - **Decitabine**
  - **Low-dose cytarabine**
  - **Hematopoietic stem cell transplant in <5% of patients**

- **2016**
  - **ESA** use less
  - **G-CSF**, **GM-CSF**
  - **TPO receptor agonists**
  - **Immunosuppressive therapy (IST)**
  - **Decitabine (rejectable; FDA approved 2006)**
  - **Ara-C (rejectable; FDA approved 2004)**
  - **Lenalidomide (oral; FDA approved 2005)**
  - **Hematopoietic cell transplant in up to 20% of patients**
  - **Investigational immunotherapies including PD-1 checkpoint inhibitors combined with azacitidine, CAR-T cell therapy**

**If there are ~60,000 new MDS cases per year then....**

- **MDS is the 2nd most common hematological malignancy after Non-Hodgkin Lymphoma (NHL) and a top 10 cancer in frequency**

**Estimated new cases in 2016 [men and women]**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS</td>
<td>6,680</td>
<td>6,250</td>
</tr>
<tr>
<td>Lymphomas</td>
<td>2,830</td>
<td>2,020</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1,030</td>
<td>1,000</td>
</tr>
<tr>
<td>Myeloma</td>
<td>780</td>
<td>780</td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>510</td>
<td>510</td>
</tr>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>470</td>
<td>470</td>
</tr>
<tr>
<td>Other</td>
<td>2,170</td>
<td>2,170</td>
</tr>
<tr>
<td>Long</td>
<td>254,830</td>
<td>254,830</td>
</tr>
</tbody>
</table>

Comparisons: 60,900 new cases of chronic lymphocytic leukemia (CLL) and 20,500 cases of multiple myeloma in 2016

**Key Takeaway**

- **It is important to diagnose/rule out MDS and other chronic myeloid neoplasms because:**
  - Effective therapies are available
  - Even if the cause of anemia is not due to MDS or another chronic myeloid neoplasm, the hematologist may be able to find a specific cause
Many Patients With MDS Become Transfusion Dependent

- Transfusions are needed in 39% (lower risk) to 79% (higher risk) of MDS patients.
- Transfusion requirements are associated with significantly reduced OS.
- Issues with transfusions:
  - Temporary improvement
  - Risk of infection, reaction
  - Need for iron chelation after multiple transfusions
  - Impact on blood supply (MDS accounts for ~3% of transfusions)
  - Costly (blood product processing, drugs/consumables, staff/overhead, management of complications and hospitalization)

MDS is Worth Diagnosing Because Effective Therapies Are Available

<table>
<thead>
<tr>
<th>Drug</th>
<th>Subtype</th>
<th>Duration</th>
<th>Approval for Chronic Leukemia</th>
<th>Approval for MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dacogen</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azacitidine</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Decitabine</td>
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