Diagnosis and Management of Anemia in the Elderly

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Learning Objectives

- Differentiate among the etiological causes of anemia seen in geriatric patients
- Develop appropriate workup of elderly patients diagnosed with symptomatic anemia or anemia detected by incidental blood testing
- Incorporate strategies to manage elderly patients with anemia due to iron deficiency, nutritional deficiency or chronic disease, and determine when it is appropriate to refer to a hematologist or gastroenterologist for further evaluation
Geriatric Anemia Best Practices

- Anemia is not normal at any age
  - A treatable cause can often be determined, that may improve quality of life (QOL)
- Mean cell volume (MCV) is a free and helpful measure in narrowing differential diagnosis of geriatric anemia
  - Microcytosis, MCV <80 fL
  - Normocytosis, MCV 80-100 fL
  - Macrocytosis, MCV >100 fL
- Unexplained macrocytic anemia demands consideration of a full work-up by a hematologist

Over 65?

US Census Bureau Estimates of Population Aged ≥65 Years

Population aged ≥65 years expected to more than double from 2015-2060

In 2018...

- The life expectancy of a 65-year-old US male is: 19 years
- The life expectancy of a 65-year-old US female is: 21 years


In 2018...

- The life expectancy of a 75-year-old US male is: 12 years
- The life expectancy of a 75-year-old US female is: 13 years

Over 85?

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

Prevalence of Anemia

The oldest old aged ≥ 85 years are both the fastest growing segment of the population and have the highest rates of anemia

20% for women  26% for men

A “Normal” Hemoglobin is Variable

Lower Limits of Adult Hemoglobin (g/dL)

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>White men</td>
<td>13</td>
<td>13.8</td>
<td>12.8</td>
<td>13.7</td>
</tr>
<tr>
<td>Black men</td>
<td>NRS</td>
<td>12.8</td>
<td>11.8</td>
<td>12.9</td>
</tr>
<tr>
<td>White women</td>
<td>12</td>
<td>12.2</td>
<td>12.0</td>
<td>12.2</td>
</tr>
<tr>
<td>(11 if pregnant)</td>
<td></td>
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</tr>
<tr>
<td>Black women</td>
<td>NRS</td>
<td>11.3</td>
<td>11.3</td>
<td>11.5</td>
</tr>
</tbody>
</table>

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

Ethnic background, altitude of residence, smoking status, and physiologic fluctuations of plasma volume can influence hemoglobin

Practical Take Away

The cause of anemia in the elderly, even if mild, should be evaluated for treatment to improve quality and quantity of life
Anemia Development is Predictive of Mortality in Older Persons

- During up to 16 years of the Cardiovascular Health Study (n=3,758) those who developed anemia or experienced a HGB decline (1.18 per 1 g/dL decrease) over 3 years predicted subsequent mortality in both men and women.

  “Hemoglobin decreases identified a large group of elderly individuals at risk for subsequent adverse outcomes who would not be identified using the WHO anemia criteria. These data may allow clinicians to identify at-risk elderly individuals for early intervention to improve the quality and quantity of life”


Risk Factors for Anemia or HGB Decline

The following predicted anemia development over 3 years:

- Baseline increasing age
- African-American
- Female Gender
- Diabetes
- Kidney disease predicted anemia development over 3 years

Associations with a Low Hemoglobin in Older Persons

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

**Decreased**
- Cognitive function
- Mobility, bone density, skeletal muscle mass
- Outcomes in specific diseases (anemia as marker of disease severity)
  - Congestive heart failure (poorer hemodynamics, more symptoms, higher mortality)
  - Cancer (decreased survival)
  - HIV infection, independent of viral load


Differential Diagnosis of Geriatric Anemia

**Better Outcomes with Treatment**

The most helpful inexpensive tests for determining etiology of anemia:
- Red blood indices:
  - Mean cell volume (MCV)
  - Red cell distribution width (RDW)
- Peripheral blood smear
- Reticulocyte count
Diagnosis and Management of Anemia in the Elderly

### Anemia

**Anemia is not a disease itself, but a sign of a disease**

- Many common causes
- Stepwise work-up can save time and resources
- A cause can usually be discovered and managed

#### Causes of Anemia

- Inadequate RBC Production
  - Marrow Failure
  - Nutritional Deficiency
- Loss of RBCs
  - Bleeding (overt or occult)
- Premature RBC Destruction
  - Hemolysis (intrinsic or extrinsic)

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#### Anemia Differential Diagnosis by MCV

<table>
<thead>
<tr>
<th>MCV &lt;80 fl</th>
<th>MCV &gt;100 fl</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microcytosis</strong></td>
<td><strong>Normocytosis</strong></td>
</tr>
<tr>
<td>Iron deficiency</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>Thalassemia</td>
<td>Acute bleeding</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Renal failure (low EPO)</td>
</tr>
<tr>
<td>Sideroblastic anemias</td>
<td>Combined disorders</td>
</tr>
<tr>
<td>Rarer causes</td>
<td>Early/mild iron deficiency</td>
</tr>
<tr>
<td>Hb C</td>
<td>Hemolysis</td>
</tr>
<tr>
<td>Unstable Hb</td>
<td></td>
</tr>
<tr>
<td>Vit C def.</td>
<td></td>
</tr>
<tr>
<td>Lead poison.</td>
<td></td>
</tr>
<tr>
<td>Para-neoplastic</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Macrocytosis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>B12 or folate deficiency</td>
</tr>
<tr>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Drugs (AZT, MTX, chemoRx, etc)</td>
</tr>
<tr>
<td>Marrow disorders (esp. MDS)</td>
</tr>
<tr>
<td>Reticulocytosis</td>
</tr>
<tr>
<td>Liver disease or hypothyroidism</td>
</tr>
<tr>
<td>Artifact</td>
</tr>
</tbody>
</table>

Hb, hemoglobin; EPO, erythropoietin; AZT, azathioprine; MTX, methotrexate

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Red Cell Distribution Width (RDW)

- Included in CBC
- RDW is the variation in RBC volume (reported as part of CBC)
  \[ \text{RDW} = \frac{SD \text{ of } MCV}{MCV} \times 100 \]
- Normal RDW: 11% - 15%
- Elevated RDW (>15%) known as anisocytosis
- RDW useful in identifying anemia of mixed causes

SD, standard deviation


Reticulocytes

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

75-year-old Female with Rheumatoid Arthritis (RA)

- Receiving methotrexate and folate for RA
- Moderate RA changes in hand; otherwise normal examination
- Laboratory studies
  - HGB 10.8 g/dL, MCV 75 fL, CBC otherwise normal
  - Positive anticyclic citrullinated peptide (CCP) antibody, erythrocyte sedimentation rate (ESR) 48 mm/hour
  - Complete metabolic panel (CMP), including blood urea nitrogen (BUN) and creatinine WNL
  - Normal serum iron, total iron binding capacity, and % saturation; ferritin 523 ng/mL (normal range: 20-300 ng/mL)
  - Stool negative for occult blood x 3; last colonoscopy 3 years ago was unremarkable

Ferritin Correlates Relatively Poorly With Iron Stores

- Correlation between serum ferritin concentration and hepatic nonheme iron content as measured by the superconducting quantum interference device (SQUID)
- Ferritin is a positive acute-phase reactant: Liver production rises in response to cytokine release into bloodstream

Practical Take Away

Ferritin level is NOT a reliable measure of iron storage in the body, because it is a positive acute-phase reactant and can rise with inflammation.

Anemia of Chronic Disease/Inflammation: The Most Common Form of Normocytic Anemia

- Most cases normocytic, some microcytic
- Hepcidin-mediated (high C-reactive protein = elevated interleukin-6, a very suggestive finding)
- Not associated with every disease – must be an inflammatory component
  - Rheumatological conditions (eg, rheumatoid arthritis, lupus)
  - Inflammatory bowel disease
  - Cancer
  - Chronic infections (eg, tuberculosis, osteomyelitis)
  - Congestive heart failure (CHF), sometimes

65-year-old Male Truck Driver

- Seen for routine follow-up of type 2 diabetes, no complaints
- Early diabetic kidney disease
- Laboratory studies:
  - Hemoglobin: 10.1 g/dL; MCV: 90 fL
  - Fasting blood sugar: 151 mg/dL; HbA1c: 7.9%
  - Urine microalbumin screen: 100 mg/g creatinine (normal, <30)
  - BUN 46 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

65-year-old Truck Driver

CONTINUED

- Iron studies
  - Serum ferritin: 98 ng/mL (normal range: 20-300 ng/mL)
  - Serum iron: 110 mcg/dL (normal range: 60-170 mcg/dL)
  - TIBC: 220 mcg/dL (normal range: 240-450 mcg/dL)
  - Transferrin saturation: 49% (normal range: 20%-50%)
CKD and Anemia

- Increased prevalence as renal function worsens
- Typically normocytic, normochromic, and hypoproliferative with low reticulocytes
- Low EPO is the predominant cause
  - EPO production may be impaired out of proportion to changes in creatine clearance
- Also 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
  - ESAs should be used after addressing all correctable causes of anemia

CKD = chronic kidney disease; EPO = erythropoietin; ESA, erythropoiesis-stimulating agent


Need to Map Serum EPO Level to HGB Level

Graphic shows the typical inverse relationship between erythropoietin levels and hemoglobin levels in anemia's not attributed to impaired erythropoietin production.

Adapted with permission of American Society of Hematology from Use of Recombinant Human Erythropoietin Outside the Setting of Uremia, Cazzola, 89(12) 1997; permission conveyed through Copyright Clearance Center, Inc.
48-year-old School Teacher

- Diagnosed with Inflammatory Bowel Disease at age 22
  - Mild to moderate and have responded to treatment with topical budesonide in conjunction with nutritional therapy
- Presents with increased 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 pallor, some abdominal discomfort; otherwise unremarkable

48-year-old School Teacher
CONTINUED

- Complete blood count:
  - **Hemoglobin:** 9.6 g/dL
  - **MCV:** 74 fl
  - Hematocrit, RBC counts, and mean corpuscular hemoglobin all below normal ranges
  - Normal white blood count, differential and platelets
- **Ferritin:** 20 ng/mL (normal range, 20-300 ng/mL)
- **Serum iron:** 48 mcg/dL (normal range: 60-170 mcg/dL)
  - Transferrin saturation 8% (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
Iron Deficiency Anemia (IDA)

- IDA is the predominant cause of microcytic anemia in the US
  - However up to 40% of patients with IDA are normocytic
- Most common causes of IDA:
  - Heavy uterine bleeding (20%-30%)
  - GI bleeding due to long-term use of aspirin/NSAIDS (10%-15%)
  - Colorectal polyps/carcinoma (5%-10%)
- Dietary IDA 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
- Once diagnosed, the cause of IDA should be evaluated

Total iron binding capacity (TIBC)

- Iron is bound to transferrin in the plasma
- TIBC is a direct measure of level of transferrin or the total capacity to bind iron
- Transferrin levels are increased in IDA and reduced in chronic inflammation

Soluble transferrin receptor (sTfR)

- Cell surface transferrin receptors internalize transferrin resulting in intracellular release of iron
- Expression of transferrin receptors increase in the absence of adequate iron stores
- sTfR levels 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

Oral Iron Therapy

- Expect HGB increase of ≥1 g/dL after one month of treatment = adequate response to treatment and confirms the diagnosis
  - Reticulocytes should increase after 7 days
- Ferrous (Fe\(^{2+}\)) salts are preferred as they are better absorbed than ferric (Fe\(^{3+}\)) salts
  - Vitamin C may increases iron absorption

<table>
<thead>
<tr>
<th>Form</th>
<th>Formulation</th>
<th>Elemental Iron</th>
<th>Typical Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>324-mg tablet</td>
<td>106 mg</td>
<td>One tablet twice per day</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300-mg tablet</td>
<td>38 mg</td>
<td>1-3 tablets 2 or 3 times per day</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325-mg tablet</td>
<td>65 mg</td>
<td>One tablet 3 times per day</td>
</tr>
</tbody>
</table>

- Adherence can be a challenge due to GI adverse events (epigastric discomfort, nausea, diarrhea, and constipation)
  - These effects may be reduced when iron is taken with meals, but absorption may decrease by 40% with food
- Eating more red meat is not enough (100 g ribeye steak = 1.94 mg iron = 254 kcal)
- Medications such as proton pump inhibitors may reduce absorption of dietary iron and iron tablets

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, eg, those who have undergone gastrectomy, gastrojejunostomy, bariatric surgery, or other small bowel surgeries
- Old formulations of HMW iron dextran should be avoided due to reactions
- Used more frequently now due to better tolerance and fast response
- Iron deficient patients usually need 1000 – 1500 mg to replete

<table>
<thead>
<tr>
<th>Form</th>
<th>Elemental Iron</th>
<th>Typical single dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMW iron dextran (e.g. InFed®) – can give as total dose infusion</td>
<td>50 mg/mL</td>
<td>Up to TDI</td>
</tr>
<tr>
<td>Sodium ferric gluconate (Nulecit™)</td>
<td>12.5 mg/mL</td>
<td>62.5 or 125 mg</td>
</tr>
<tr>
<td>Iron sucrose (Venofer®)</td>
<td>20 mg/mL</td>
<td>100 mg</td>
</tr>
<tr>
<td>Ferumoxytol (Feraheme®)</td>
<td>30 mg/mL</td>
<td>510 mg</td>
</tr>
<tr>
<td>Ferric carboxymaltose (Injectafer®)</td>
<td>50 mg/mL</td>
<td>750 mg</td>
</tr>
</tbody>
</table>

LMW, low molecular weight; HMW, high molecular weight.


Normocytic-Normochromic Anemias: Hemolytic Anemia

- ↑ lactate dehydrogenase (LDH) due to increased cell destruction, ↑ indirect bilirubin (increased HGB catabolism), ↓ haptoglobin, and sometimes ↑ reticulocyte count (bone marrow regenerative effort if healthy marrow)
- DAT can further guide the work-up (but up to 10% of healthy people have +DAT)
- Schistocytes (fragmented red blood cells)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Schistocytes on peripheral blood smear?</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

Evaluate for disseminated intravascular coagulation (DIC) or other microangiopathic process such as hemolytic uremic syndrome (HUS)/hemorrhagic thrombotic purpura (TTP)

- Microangiopathic hemolytic anemia (MAHA) associated with defective valve
- Autoimmune hemolytic anemia (AIHA)
- Flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH)
- Osmotic fragility test to assess for spherocytes
- RBC enzyme analysis, HGB electrophoresis

Diagnosis and Management of Anemia in the Elderly

**Microcytic-hypochromic Anemias: Thalassemia/Sickle Cell Disease**

Consider HGB analysis to identify possible hemoglobinopathies in patients from suspected ethnic groups with microcytic anemia, normal RDW and normal ferritin.

<table>
<thead>
<tr>
<th>Test</th>
<th>a-thalassemia</th>
<th>b-thalassemia</th>
<th>Sickle-cell disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family History / Ethnicity</strong></td>
<td>SE Asian, Middle Eastern, Chinese, African</td>
<td>Chinese, other Asians, African Americans</td>
<td>Sub-Saharan Africa, Mediterranean basin, Middle Eastern, Indian</td>
</tr>
<tr>
<td><strong>HBG electrophoresis / HPLC</strong></td>
<td>Adults: normal†</td>
<td>↑HbA2, ↓HbA, and probably ↑HbF</td>
<td>HbS ± HbC</td>
</tr>
<tr>
<td><strong>Genetics (typically recessive inheritance)</strong></td>
<td>Deletion of HBA1 and HBA2 genes on chromosome 16</td>
<td>Mutations in the HBB gene on chromosome 11 (&gt;170 known)</td>
<td>Specific mutations in the 6th codon of HBB gene (HbS and or HbC)*</td>
</tr>
<tr>
<td><strong>Determinants of disease severity</strong></td>
<td>Number of affected alleles (1-4)</td>
<td>Number of affected alleles (1-2) and mutation type</td>
<td>Number of affected alleles (1-2), Hb variant and if thalassemia also present</td>
</tr>
<tr>
<td><strong>Trait</strong></td>
<td>Asymptomatic*</td>
<td>Intermedia: Hemolysis which may need transfusions</td>
<td>Major: Lifelong transfusions, chelation</td>
</tr>
<tr>
<td><strong>Intermedia</strong></td>
<td>± transfusions</td>
<td>Major: Lifelong transfusions, chelation</td>
<td></td>
</tr>
<tr>
<td><strong>Major</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
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</tr>
</tbody>
</table>

HPLC, high-performance liquid chromatography

*HbS=hemoglobin S (glu→val substitution at codon 6); HbC=hemoglobin C (glu→lys substitution at codon 6); HbSC=HbS/HbC compound heterozygote; HbSS=homozygous for HbS

†Newborns: may have HbH or Hb Bart's

*Persons with trait are asymptomatic and require no treatment or long-term monitoring. They usually do not have IDA.


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**Evaluation of Microcytic-hypochromic Anemias**

Consider HGB analysis in patients from suspected ethnic groups with microcytic anemia, normal RDW and normal ferritin.

<table>
<thead>
<tr>
<th>MCV Low</th>
<th>RBC Count normal or ↑</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP normal</td>
<td>sTfR/log ≥1.55</td>
</tr>
<tr>
<td>Ferritin ≥50</td>
<td>↑HbA2 or HbF</td>
</tr>
<tr>
<td>Ferritin 50-150</td>
<td>HbS analysis</td>
</tr>
<tr>
<td>Ferritin &gt;150</td>
<td>Anemia of chronic disease</td>
</tr>
<tr>
<td>CRP ↑</td>
<td>↓HbA2 or HbF</td>
</tr>
<tr>
<td>Ferritin &lt;50</td>
<td>High RDW Low hepcidin*</td>
</tr>
<tr>
<td>Ferritin &lt;50</td>
<td>Iron deficiency anemia</td>
</tr>
<tr>
<td>Ferritin &lt;50</td>
<td>RDW variable High hepcidin*</td>
</tr>
<tr>
<td>Ferritin &lt;50</td>
<td>Globin cluster on chromosome 16 deletion</td>
</tr>
</tbody>
</table>

*Assays for serum hepcidin are in development. CRP, C-reactive protein; RBC = red blood cell; sTfR = soluble transferrin receptor; Hb = hemoglobin

Laboratory Work-Up of Macrocytic Anemias

- MCV >100 fl
  - Normal reticulocyte count

- No macrocytes on peripheral blood smear
  - Oval macrocytes
    - Vitamin B₁₂
    - Folate
  - Round macrocytes
    - Liver
    - Thyroid

- Consider lab error or:
  - Cold agglutinins
  - Hyperleukocytosis
  - Hyperglycemia

- Normal
- Low
- Bone marrow & cytogenetics
  - Evaluate as indicated

*If MCV is very high (>110 fl), suspect: B₁₂/folate deficiency, RBC agglutination


Vitamin B₁₂ Deficiency

- Most common cause of macrocytic anemia but can take years to develop
- Increase risk of neurological complications and cardiovascular disease¹-⁴
- B₁₂ deficiency can occur in vegans due to low intake of animal source foods¹,²
  - While dairy and eggs have vitamin B₁₂, many vegetarians/most vegans will eventually require supplements
- Pernicious anemia is a severe vitamin B₁₂ deficiency typically caused by autoimmune gastritis³,⁴
- Methodological problems can affect the sensitivity/specificity of current vitamin B₁₂ assays⁵
  - Vitamin B₁₂ deficiency may be confirmed by measurement of methylmalonic acid (MMA) or homocysteine
  - An elevated level of methylmalonic acid (MMA) is more specific and sensitive
  - If only homocysteine levels are elevated, then a folate deficiency may exist
- Daily high-dose oral vitamin B₁₂ tablets (1000 to 2000 μg) are as effective as monthly intramuscular injections in correcting blood and neurologic abnormalities³
- Pernicious anemia / malabsorption require lifelong vitamin B₁₂ therapy³
- The natural bioidentical forms of vitamin B₁₂ – methylcobalamin, adenosylcobalamin and hydroxycobalamin – are preferred over the synthetic cyanocobalamin (better bioavailability/safety)⁵
  - Use the least-expensive natural form of B₁₂, such as methylcobalamin

### 71-year-old Female: Retired Nurse

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

### 71-year-old Retired Nurse CONTINUED

- Laboratory studies:
  - Hemoglobin 9.8 g/dL, MCV 103 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
  - 3 years ago, screening colonoscopy was negative
Practical Take Away

- If gastrointestinal bleeding, nutritional causes, chronic inflammation and renal failure have been ruled out, anemia work up should continue and may indicate the need for a bone marrow examination even if anemia is the only cytopenia.

Simplified Classification of Hematologic Malignancies

Myelodysplastic Syndromes (MDS)

- **Typical Patients**
  - Median age at diagnosis ~70
  - Prior chemotherapy in 5%-10%
  - Prior radiation Exposure in <5%

- **Common Disease Features**
  - >95% of patients have cytopenias, most commonly anemia; <50% have neutropenia or thrombocytopenia at diagnosis
  - MDS Paradox: Bone marrow usually hypercellular but cytopenias present
  - Cells look abnormal ("dysplastic"); Blasts may be increased
  - Approximately ½ of patients have abnormal chromosomes

- **Typical Clinical Course**
  - "Preleukemia" → Death from infection, bleeding, complications of anemia (50%)
  - AML (25%)
  - Death from other causes (25%)

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It is important to diagnose 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
Diagnosis and Management of Anemia in the Elderly

Clonal Mutations and Increased Cardiovascular Risk

- Molecular genetic testing for mutations is reasonable in elderly patients with unexplained anemia, especially if cytopenia exist
- ≥10% of patients aged >70 years have detectable clonal mutations
- Clonal hematopoiesis of indeterminate potential (CHIP) is common in healthy aging population. Confers 0.5%-1.0% annual risk of progression and increased all-cause mortality
- **CHIP carriers had a 1.9X greater risk of coronary heart disease** than noncarriers (95% CI, 1.4 to 2.7) in nested case–control analyses from two prospective cohorts [(BioImage and Malmö Diet and Cancer (MDC)]
- **Participants with CHIP had a 4.0X greater risk of MI** than noncarriers in two retrospective case–control cohorts for the evaluation of early-onset MI [Atherosclerosis, Thrombosis, and Vascular Biology Italian Study Group (ATVB) and the Pakistan Risk of Myocardial Infarction Study (PROMIS)]
- **Mutations in DNMT3A, TET2, ASXL1, and JAK2 were each individually associated with coronary heart disease.** CHIP carriers with these mutations also had increased coronary-artery calcification, a marker of coronary atherosclerosis burden

Unexplained Anemia in the Elderly

**How Common is MDS?**

In the NHANES III 5.8% of the total anemic population (~17% of those with unexplained anemia) met ≥1 diagnostic criteria for MDS\(^1\)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional</td>
<td>33.3%</td>
</tr>
<tr>
<td>Chronic Disease</td>
<td>33.3%</td>
</tr>
<tr>
<td>Meeting criteria for MDS</td>
<td>27.5%</td>
</tr>
<tr>
<td>Unidentified cause</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

\(^2\) Cogle CR, et al. *Blood*. 2011;117:7121-7125. (Using an algorithm that required one or more MDS claims and accounted for recommended diagnostic services during the year before the first claim; 2005 data)
Diagnosis and Management of Anemia in the Elderly

60,000 new MDS cases per year

- MDS is the 2nd most common hematological malignancy after Non-Hodgkin Lymphoma (NHL) and a top 10 most frequent cancers

Comparison: 20,110 new cases of chronic lymphocytic leukemia and 8850 new cases of testicular cancer expected in 2017


MDS is Worth Diagnosing Because Effective Therapies Are Available

- ESA (erythropoiesis-stimulating agent) help but less often needed with new treatments
- Oral iron chelation for iron overload (BLACK BOX WARNING)
- G G-CSF (granulocyte-colony stimulating factor), GM-CSF (granulocyte-macrophage-colony stimulating factor) TPO (thrombopoieti) receptor agonists
- Immunosuppressive therapy (not FDA approved)
- Approved Meds
  - Decitabine (injectable; FDA approved 2006)
  - Azacitidine (injectable; FDA approved 2004)
  - Lenalidomide (oral; FDA approved 2005)
- Multiple new drugs in trials with promising results
- Hematopoietic allogeneic stem cell transplant in up to 20% of patients (RIC, URD, umbilical cord) potentially curative

Diagnosis and Management of Anemia in the Elderly

Proposed Algorithm for Evaluation of Low Hemoglobin in Older Patients

Geriatric Anemia Best Practices

- **Anemia is not normal at any age**
  - A treatable cause can often be determined, that may improve quality of life (QOL)

- **Mean cell volume (MCV)** is free and helpful in narrowing differential diagnosis of geriatric anemia
  - Microcytosis, MCV <80 fL
  - Normocytosis, MCV 80-100 fL
  - Macrocytosis, MCV >100 fL

- **Unexplained macrocytic anemia** demands consideration of a full work-up by a hematologist