A Practical Approach to the Evaluation and Management of Geriatric Anemia in Primary Care

Learning Objectives
After participating in this educational activity, participants should be able to:

1. Differentiate among the etiological causes of anemia in geriatric patients
2. Develop appropriate workup of elderly patients with symptomatic anemia or anemia detected by incidental blood testing
3. Recognize signs/symptoms of bone marrow failure and hematologic malignancy as a cause of anemia
4. Incorporate strategies to manage elderly patients with anemia due to nutritional deficiency, blood loss, renal failure or suspected myelodysplasia (including appropriate referral to a specialist)
Introduction

According to current United States (US) Census Bureau projections, there will be approximately 72.1 million Americans aged 65 years or older by 2030, representing more than 19% of the total population.[1] By 2050, the number of adults aged 65 years or older is anticipated to reach 88.5 million – almost double the estimated 47 million living in the US in 2015. Currently, 65-year-olds living in the US can be expected to live a further 17 years (men) to 19 years (women).[2] Furthermore – the “oldest old” – persons older than 85 years – represent the fastest growing age cohort of the US population, with projected increase from 5.8 million today to over 19 million by 2050.

By age 85, most individuals have some degree of frailty and health conditions requiring chronic therapy, and among these health conditions, anemia is exceptionally common. The third National Health and Nutritional Evaluation Survey (NHANES III) assessed a national probability sample of 33,994 individuals aged 2 months and older, 26,372 of whom underwent laboratory studies, including hemoglobin levels.[3,4] Among the NHANES III survey population, 20% of women and 26% of men older than 85 had anemia, more than in any other age cohort.[3,4] (Figure 1)

Figure 1. Prevalence of anemia* in the NHANES[3]

![Graph showing prevalence of anemia by age group](image)

*WHO defined as hemoglobin <13.0 g/dL for males and <12.0 g/dL for females (nonpregnant).[5] Data from first 2 phases of NHANES (1988-1994). Adapted with permission.

The burden of anemia among the elderly in the US continues to rise with the increasing life expectancy of the population.

1. Which test is diagnostically most useful in narrowing the differential diagnosis of geriatric patients with anemia?
   a. Serum creatinine
   b. Mean corpuscular volume (MCV)
c. Vitamin B12 level
d. Serum ferritin

2. A 75 year old woman who eats poorly (mostly toast with jam and inexpensive tea) due to limited income presents to her PCP with progressive fatigue over 5-6 months. She is found to have an Hb of 8.5 g/dL and a MCV of 92 fl. Her physician suspects combined iron and folate deficiency.

Which of the following tests is most sensitive to the presence of a combined nutritional deficiency?
   a. Mean corpuscular volume
   b. Mean cell hemoglobin (MCH)
c. Red cell distribution width (RDW)
d. Mean cell hemoglobin concentration (MCHC)
e. Reticulocyte count

3. Older patients with anemia are at higher risk for all the following EXCEPT:
   a. Major depression
   b. Decreased bone density
c. Poor control of type 2 diabetes
d. Decreased skeletal muscle mass
e. Reduced cognitive function

The Definition of Normal Hemoglobin (Hb)
While local laboratory normal ranges generated from local populations should be used to define anemia whenever possible, the WHO definitions of anemia in adults are:[5]
   • Hemoglobin (Hb) <13.0 g/dL for males
   • Hb <12.0 g/dL for nonpregnant females

Consequences of NOT Evaluating Geriatric Anemia
Elderly individuals at risk for anemia can be identified for early intervention to improve quality and quantity of life.

Anemia should never be considered a normal part of aging, and therefore, without consequence. Long-term follow-up (16 years) of the Cardiovascular Health Study (n=3,758) showed that anemia development (WHO criteria) and hemoglobin decline predicted subsequent mortality in men and women with respective hazard ratios (HR) of 1.39 and 1.11, per 1 g/dL decrease in Hb.[6] Lower Hb levels are also associated with significant morbidity in older persons including a higher risk of recurrent falls, poorer cognitive function, increased rate of major depression, increased frailty index, higher risk of hospitalization, longer duration in hospital and decreased mobility, bone density, skeletal muscle mass.[7] Moreover, anemia in conjunction with underlying diseases such as congestive heart failure, cancer, and HIV infection is associated with worse outcomes.[7]
**Initial Evaluation of Anemia**

It is important to remember that anemia is a sign of disease and not a disease in itself. There are multiple causes of anemia, many of which are common. An orderly approach to anemia evaluation is helpful.

An organized, systematic approach to anemia evaluation is essential and in almost all cases, a specific cause can be found.

Please follow this link for a convenient smartphone application for anemia evaluation in the elderly:


**Etiology of Anemia**

There are 3 underlying causes of anemia[8]:

- **Inadequate red blood cell (RBC) production.** Due to insufficient erythropoiesis and may result from bone marrow failure or nutritional deficiency (e.g., inadequate iron stores, deficiency of folate, or vitamin B12)
- **RBC loss.** Due to bleeding (overt or occult). Most commonly caused by menstruation or gastrointestinal bleeding
- **Premature RBC destruction.** Due to hemolysis, which may be due to a defect intrinsic to the red cell or extrinsic to the red cell such as an antibody against a red cell epitope or microangiopathy. Hemolytic anemia may be due to an acquired (e.g., autoimmune hemolytic anemia) or a congenital (e.g., sickle cell disease or thalassemia) disorder

Peripheral blood smear and reticulocyte count are inexpensive and useful tests for determining the etiology of anemia. Reticulocytes are immature RBCs (typically ~1% of RBC population) that mature in the red bone marrow and then circulate for about a day before fully maturing.[9] Reticulocytes serve as a marker of marrow activity with high levels (reticulocytosis) indicating a severe loss of mature RBCs in conditions such as hemolytic anemia. Conversely low levels of reticulocytes may indicate nutritional deficiency, chronic disease, cirrhosis of the liver or bone marrow failure.

**Use of Mean Corpuscular Volume (MCV) for Differential Diagnosis of Anemia**

MCV is diagnostically most useful in narrowing the differential diagnosis of anemia and in determining initial tests in both younger and older patients (Figure 2).[8] However, it is important to remember that the presence of confounding conditions can affect a change in the MCV that differs from the expected findings. For example, iron deficiency due to portal gastropathy or macrocytosis due to alcohol abuse.

4. In a patient with microcytic anemia, the most likely differential diagnoses would include all the following **EXCEPT:**
   a. Iron deficiency
   b. Bone marrow disorder (especially MDS)
   c. Anemia of chronic inflammation
   d. Hemoglobin E trait

5. A 66-year-old African American woman presents with worsening bone pain especially at night, weight loss, and upper respiratory tract infection.
She was found to be anemic: Hb 9.8 g/dL with MCV 93 fL. Her iron studies are normal and her most recent colonoscopy a year ago was negative.

Her lab values were notable for the following: serum creatinine, serum calcium, serum globulin, and serum uric acid were all elevated above the normal range; serum albumin levels below normal range.

The patient has no lymphadenopathy or leukopenia. Subsequent evaluation showed the presence of a serum monoclonal-(M-) protein.

Which hematologic disorder should be included in the differential diagnosis of this patient?

a. Myelodysplastic syndromes (MDS)
b. Multiple Myeloma (MM) or related disorder
c. Non-Hodgkin lymphoma (NHL)
d. Chronic Lymphocytic Leukemia (CLL)

Figure 2. Anemia Differential Diagnosis by MCV

RBC Distribution Width (RDW)

RDW is the variation in MCV which is reported as part of complete blood count (CBC) test.[10] The normal range of RDW is 11%–15%, elevated RDW (>15%) is known as anisocytosis. RDW measurement is useful in identifying anemia of mixed causes such as combined nutritional deficiencies, since RDW will be elevated when there are populations of circulating RBCs of distinct sizes.
Iron Deficiency Anemia (IDA)

Iron Deficiency Anemia is the most common cause of microcytic anemia in the US.

While IDA is the most common cause of microcytic anemia in the US, up to 40% percent of IDA cases can be normocytic.[12] While dietary IDA is rare in the US, it may be seen in some strict vegetarians/vegans because plant sources contain non-heme iron, which is less well absorbed. The most common causes of IDA are abnormal uterine bleeding (20%-30%), long-term use of aspirin or other NSAIDS (10%-15%), and colorectal polyps/carcinoma (5%-10%). Diagnosis of IDA 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 (Table 1).

Case Study 1

Elsa is a 72 year old woman of European descent who presents to her primary care physician (PCP) with progressive dyspnea over 5-6 months. She was a former heavy smoker (quit 17 years ago) who suffers from COPD and is currently using short-acting and long-acting bronchodilators. She has no history of congestive heart failure (CHF), pulmonary hypertension or chronic kidney disease and is otherwise hemodynamically stable with no other overt cause for the increased dyspnea. Her most recent colonoscopy 2 years ago was negative and she denies melena. Her PCP suspects iron deficiency anemia after recently reading an article on iron deficiency in patients with COPD.[11]

Selected laboratory results:

- CBC: Hemoglobin of 10.6 g/dL (normal female range 12.1 to 15.1 g/dL) with normal white blood count, differential and platelets. MCV 72 fL (normal range 80-100 fL).
- Reticulocyte count, folate and B12 tests all within normal range.
- Iron studies: Ferritin 8 ng/mL (normal range, 20-300 ng/mL); transferrin saturation 9% (normal range 20%-50%); TIBC elevated.

What would you do next for this patient?

- a. Refer for GI evaluation
- b. Give RBC transfusion
- c. Give an erythropoiesis stimulating agent (epoetin, darbepoetin)
- d. **Give oral ferrous iron supplement**
- e. Give intravenous iron
### Table 1. Workup of Microcytic-Hypochromic Anemias

<table>
<thead>
<tr>
<th>Cause</th>
<th>Clinical/lab clues</th>
<th>Next test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>• Low ferritin</td>
<td>• GI evaluation, unless bleeding source obvious</td>
</tr>
<tr>
<td></td>
<td>• Low iron with high TIBC = low TfSat</td>
<td>• Consider sprue (antigliadin Ab)</td>
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<tr>
<td></td>
<td>• High sTfR</td>
<td></td>
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<tr>
<td></td>
<td>• High RDW</td>
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<td></td>
<td>• High platelets</td>
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<tr>
<td></td>
<td>• Low hepcidin*</td>
<td></td>
</tr>
<tr>
<td>Anemia of chronic disease/inflammation</td>
<td>• Normal or high ferritin</td>
<td>• ESR, CRP to confirm inflammation</td>
</tr>
<tr>
<td></td>
<td>• Low iron/low TIBC</td>
<td>• Specific immunological evaluation</td>
</tr>
<tr>
<td></td>
<td>• Low sTfR</td>
<td>• Serum EPO level</td>
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<tr>
<td></td>
<td>• RDW variable</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High hepcidin*</td>
<td></td>
</tr>
<tr>
<td>Thalassemia syndromes</td>
<td>• Normal or high ferritin, normal RDW</td>
<td>• β thalassemia: High Hb A2</td>
</tr>
<tr>
<td></td>
<td>• β thalassemia: Mediterranean/African</td>
<td>• If suspected α thalassemia: Molecular testing (often only needed for prenatal counseling)</td>
</tr>
<tr>
<td></td>
<td>• α thalassemia: Asian/Melanesian; typically normal Hb electrophoresis in α thalassemia trait and α thalassemia silent carriers; abnormal Hb electrophoresis in HbH; abnormal Hb electrophoresis in Hb Barts (lethal condition detectable only in newborns)</td>
<td></td>
</tr>
<tr>
<td>Rarer causes</td>
<td>• Sideroblastic anemias: High RDW/dimorphic picture</td>
<td>• Sideroblastic anemia: Bone marrow exam</td>
</tr>
<tr>
<td></td>
<td>• Vitamin C deficiency: Petechiae, loose teeth; typically alcoholic or malnourished</td>
<td>• Vitamin C deficiency: Vitamin C level</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin C: African, chronic hemolysis</td>
<td>• Hemoglobin C/E: Hemoglobin electrophoresis/HPLC</td>
</tr>
<tr>
<td></td>
<td>• Hemoglobin E: SE Asian, chronic hemolysis</td>
<td></td>
</tr>
</tbody>
</table>

Table adapted from[8] by permission of Mayo Foundation for Medical Education and Research. All rights reserved
*Assays for serum hepcidin are in development
sTfR, soluble transferrin receptor. In vitro diagnostic (IVD) assays for sTfR are widely available clinically
TfSat, transferrin saturation; TIBC, total iron-binding capacity
RDW, red cell distribution width
HPLC, high-performance liquid chromatography

Serologic evidence of iron deficiency (e.g., serum ferritin <20 ng/mL) indicates the need for assessing the GI tract. Because ferritin is an acute phase reactant it is an imperfect measure of total body iron stores[13] since higher levels may still be consistent with iron deficiency, especially if the patient has an inflammatory condition. Ferritin may therefore need to be supplemented by
other tests (e.g., soluble transferrin receptor assay, which is not an acute phase reactant and is unaffected by inflammation). The soluble transferrin receptor assay is particularly useful in differentiating iron deficiency, which is associated with elevated soluble transferrin receptor levels, from anemia of inflammation and chronic disease which is associated with lower levels.

**Role of Hepcidin**

Hepcidin is a 25-amino acid liver peptide hormone that is the central regulator of body iron metabolism.\[14,15\] Hepcidin levels are induced by increased iron stores and inflammation, and reduced by hypoxia, anemia, and ineffective bone marrow erythropoiesis. Increased hepcidin levels lead to iron sequestration by macrophages, contributing to the pathogenesis of anemia of chronic disease. Decreased levels of hepcidin are observed in iron deficiency and primary iron overload diseases such as hereditary hemochromatosis. Increased levels of hepcidin are seen during infection, decreasing the available host iron pool that is essential for survival of invading pathogens. Assays for this useful biomarker are in development.

Elevated hepcidin levels cause disordered iron homeostasis by impairing dietary iron absorption and iron mobilization from body stores.

**Treatment of IDA**

If there is no evidence of a GI hemorrhage or source of bleeding, IDA can be treated with oral iron (120 mg/day for 3 months, in adults) with a Hb increase of 1 g/dL after one month of treatment defining an adequate response to treatment and confirming the diagnosis.\[12\] Ferrous salts are preferred because they are absorbed much more readily and vitamin C can increase absorption in some patients. Adherence to oral iron therapy can be a challenge due to GI adverse effects which may be reduced when iron supplementation is taken with meals (however absorption may decrease by 40%). Medications such as proton pump inhibitors may reduce absorption of dietary and supplemental iron, since stomach acid is necessary for maximal iron absorption. Although more costly, intravenous iron is considered better tolerated and more effective than oral iron treatment in improving ferritin and may be used in patients who cannot tolerate/absorb oral iron, e.g., those who have undergone gastrectomy, gastrojejunostomy, bariatric surgery, or other small bowel surgeries.\[12\] Multiple preparations of intravenous iron are now available. High molecular weight iron dextran should be avoided due to greater risk of life-threatening anaphylaxis compared to low molecular weight iron dextran and other newer preparations such as iron sucrose or ferric carboxymaltose.

There is no universally accepted threshold for RBC transfusion in patients with IDA. While guidelines often specify hemoglobin thresholds for when to transfuse, it is the patient's clinical condition and symptoms that should drive the decision.\[16\]

A patient with normal findings on GI evaluation and continued iron deficiency despite iron replacement should be referred to a hematologist.
Anemia of Chronic Kidney Disease (CKD)
The kidneys are the primary source for the production of erythropoietin (EPO), the hormone that stimulates the bone marrow to produce RBCs. Anemia in the elderly is not just due to progressive nephron loss with aging because EPO levels actually increase over time, potentially compensating for other factors contributing to anemia in older patients (Figure 3).[17]
Anemia increases in prevalence with CKD progression due to impaired renal secretion of EPO.[18] Anemia is common in patients with end-stage renal disease (ESRD) or stage ≥3 CKD and is typically normocytic, normochromic and hypoproliferative. Patients with CKD have disordered iron homeostasis with low serum transferrin saturation and normal to high serum ferritin, but with iron depletion in the bone marrow.

**Treatment of Anemia of CKD**
Correction of iron deficiency with oral or intravenous iron supplementation can reduce severity of anemia of CKD. Erythropoiesis Stimulating Agents (ESAs) should only be used after addressing all correctable causes of anemia.[18,19]
Case Study 3
Jim is a 78-year-old retired man and former agricultural worker. Complains of less stamina and new dyspnea when walking, but no chest pain. He reports light alcohol use (2-3 beers a week) and that he was a former smoker (pack a day), but quit when he retired 14 years ago.

Physical examination: lungs clear, mild sinus tachycardia (heart rate ~102/min); exam otherwise unrevealing. Fecal occult blood negative x 2. His most recent screening colonoscopy 2 years ago was negative

Laboratory studies:
Hemoglobin 9.6 g/dL, MCV 102 fL (normal range 80-100 fL); other CBC values within normal range.

Folate, B₁₂, thyroid stimulating hormone (TSH), serum ferritin, serum iron, % iron saturation all normal.

Peripheral smear showed oval macrocytes.

What would you do next for this patient?

a. Hematology consult for bone marrow biopsy
b. GI consult for EGD and repeat colonoscopy
c. Hemoglobin electrophoresis
d. EPO levels
e. Refer for GI evaluation

Workup of Macrocytic Anemia
The type of macrocyte present on peripheral smear may inform the differential diagnosis of macrocytic anemia (Figure 4).[8] Round macrocytes are typically seen in advanced liver disease or severe thyroid disease. Oval macrocytes are more common and are seen with vitamin B₁₂ or folate deficiency, certain drugs that alter metabolism such as methotrexate, alcohol abuse, or bone marrow failure syndromes. If the vitamin B₁₂ or folate levels are low, the nutritional deficiency should be evaluated and corrected. Once RBC agglutination artifact, serum vitamin B₁₂/folate, alcohol and drug use (e.g., methotrexate) have been ruled out, the patient should be referred to a hematologist for a bone marrow evaluation including cytogenetics.
Algorithm for Evaluation of Anemia in Older Patients

The algorithm shown in (Figure 5) provides a systematic approach for evaluating anemia in older individuals, integrating the decision points that have evolved for differential diagnosis.[7] In practice, this strategy can identify the underlying cause of anemia in most patients and enable them to receive appropriate therapy.
Figure 5. Proposed Algorithm for Evaluation of Low Hemoglobin in Older Patients*

EPO, erythropoietin
MCV, mean corpuscular volume
MDS, myelodysplastic syndrome

Anemia Due to Bone Marrow Failure and Hematologic Malignancy

During normal hematopoiesis a common hematopoietic stem cell gives rise to myeloid and lymphoid precursors. The myeloid lineage normally produces granulocytes, erythrocytes, thrombocytes, macrophages and mast cells whereas the lymphoid lineage produces B-, T-, NK- and plasma cells. Hematologic disorders may derive from the myeloid and lymphoid lineages (Figure 6). [20] Historically, hematological malignancies have also been classified according to the primary location of the malignancy: leukemia (blood), lymphomas (lymph nodes), or myeloma (bone marrow). Cancer-related anemia is prevalent, affecting 30% to more than 90% of patients with solid tumor malignancies and is associated with poorer survival and local tumor control. [21] When other causes of anemia have been ruled out, hematologic disorders and either hematologic or solid tumor malignancies should be considered in the differential diagnosis. Given that newer treatments are improving outcomes in many hematologic malignancies, improved disease recognition and appropriate referral from the PCP to hematologist has the real potential to improve patient outcomes.
Myelodysplastic Syndromes (MDS): MDS are clonal marrow stem-cell disorders, characterized by blood cytopenias due to ineffective hematopoiesis and by progression to acute myeloid leukemia (AML) in up to one third of patients.\[22\] The majority of cases of MDS occur in the elderly (the median age at diagnosis is 71 years), with most cases arising de novo, but about 15\% of cases occurring after chemotherapy or radiotherapy for a previous cancer. MDS is sometimes associated with prior exposure to environment or industrial toxins. The range in number of new cases of MDS is probably 3-4 fold higher than the annual incidence based on the 2006-2010 SEER registry due to a limitation in these registry guidelines that required the capture of only one malignancy in the myeloid lineage and did not require blood count or bone marrow biopsy for MDS confirmation.\[23\] By these criteria, there may be 40-60,000 new cases of MDS in the US annually. If there were indeed 60,000 new cases, MDS would be the second most common hematological malignancy after Non-Hodgkin Lymphoma and a top 10 cancer in frequency.\[24\] In NHANES III, \~6\% of the total anemic population met at least one diagnostic criteria for MDS.\[3\]

A hallmark feature of MDS is that 90\% of patients have anemia that is typically macrocytic.

The vast majority (90\%) of patients with MDS have anemia that is typically, but not always, macrocytic.\[22\] Neutropenia and thrombocytopenia are seen at diagnosis in about a third to one-half of patients, and rarely seen in the absence of anemia. MDS is associated with cytogenetic changes that occur with or without gene mutations and extensive gene hypermethylation that may decrease normal expression of tumor suppressor genes. Prognostic
risk stratification in MDS is based on percentage of marrow blasts, number and importance of cytopenias, and abnormal karyotype.[22] Higher-risk MDS is associated with decreased time to AML evolution and shorter survival duration. The majority of patients with higher-risk MDS are transfusion dependent.[22] Patients with unexplained macrocytic anemia should be referred to a hematologist for bone marrow evaluation since there are effective therapies for MDS that extend survival and/or reduce or eliminate transfusion requirements.

Treatment of patients with lower-risk MDS, especially for anemia, includes hematopoietic growth factors, lenalidomide, and transfusions. Higher-risk MDS is treated with hypomethylating agents (azacitidine, decitabine) and, whenever possible, allogeneic stem-cell transplantation.[22]

The oral immunomodulatory drug lenalidomide is indicated for transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q [del(5q)] abnormality with or without additional cytogenetic abnormalities. In a phase 2 study, about two-thirds of patients with del(5q) MDS became transfusion independent, with a median hemoglobin increase 5.4 g/dL, and responses were durable lasting a median of >2 years.[25] Responses were also seen in patients with low- or intermediate-1-risk MDS who did not have del(5q), albeit less robust: about one-quarter of them became transfusion independent, and responses were less durable (median 41 weeks).[26]

In a randomized, prospective phase 3 trial of patients with higher-risk MDS, treatment with the hypomethylating agent azacitidine which affects gene expression was associated with a median overall survival of 24.4 months, an improvement of 9.4 months compared with “conventional care”. [27] This was the first time a therapy had been demonstrated to improve survival in a subgroup of MDS patients. In the phase 3 ADOPT trial, 63% of patients with MDS (all types) became RBC transfusion independent after 7 cycles of therapy with decitabine, another hypomethylating agent.[28]

**Leukemia:** The four most common subtypes of leukemia most likely be encountered in the primary care setting are acute lymphoblastic (ALL; 6,020 new cases in the US in 2014), acute myelogenous (AML; 15,720 new cases in the US in 2014), chronic lymphocytic (CLL; 18,860 new cases in the US in 2014), and chronic myelogenous (CML; 5,980 new cases in the US in 2014).[24] CLL is often more akin to NHL than to a leukemia.[29-31] ALL predominantly occurs in children (75%-80% of cases), whereas AML, CLL and CML are more common in adults. AML is the most common form of acute leukemia affecting adults (80% of cases, median age at diagnosis 66) and the leading cause of leukemia death. Patients with acute leukemia may present with constitutional symptoms (fever, fatigue, weight loss). Bleeding and bruising are also common. Anemia is common in AML. Acute leukemia can also present with leukopenia, combined with anemia or thrombocytopenia.

Leukocytosis is the hallmark finding in chronic leukemia. Constitutional symptoms are less common, occurring in 15% of patients with CLL and in approximately one-third of patients with CML. Bleeding and bruising are also less common presenting features in the chronic leukemias. Hepatosplenomegaly and lymphadenopathy are common physical examination findings in CLL and splenomegaly is common in CML.

Cases of suspected leukemia should be referred to a hematologist for evaluation of a peripheral blood smear, and in some cases, evaluation of a bone marrow specimen, in order to confirm diagnosis and initiate treatment. The diagnosis of CLL does not require a bone marrow exam and is based on a clonal expansion of B lymphocytes in the peripheral blood, confirmed by immunophenotyping. The diagnosis of CML requires cytogenetic or molecular testing of the
bone marrow or peripheral blood for a specific abnormality called the Philadelphia chromosome (a reciprocal translocation between chromosomes 9 and 22). The abnormal BCRABL gene fusion created by the Philadelphia chromosome is found in 95% of patients with CML and encodes a tyrosine kinase that causes uncontrolled cellular proliferation. This targeted approach of inhibiting the tyrosine kinase enzyme is not curative, but can maintain long-term control of the disease.

**Lymphoma:** NHL is the most common type of lymphoma with 70,800 new cases expected in the US in 2014.[24] Hodgkin Lymphoma (HL) is less common with 9,190 new cases expected in 2014. The most common presenting symptom of lymphoma is painless lymphadenopathy.[32,33] “B symptoms” (unexplained fever, night sweats, and recent weight loss) may also be present and are associated with poorer prognosis. The majority of NHL are associated with anemia or other cytopenia. NHL affects mainly the elderly (median age at diagnosis, 66 years) whereas HL has a bimodal age distribution affecting younger and older adults. The diagnosis of lymphoma is confirmed by accurate pathological evaluation of a lymph node. Essential workup of lymphoma includes CBC, serum lactate-dehydrogenase (LDH) levels, comprehensive metabolic panel and CT evaluation, often supplemented by positron emission tomography (PET) scanning. Depending on the type and stage of lymphoma, treatments may include watchful waiting, chemotherapy, targeted biologic therapy or hematopoietic stem cell transplant.[32,33]

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**Case Study 4**
Sarah is a 67-year-old retired woman and avid cyclist. She now complains of greater fatigue when cycling and persistent bone pain at night. Her past medical history is unremarkable and she never smoked nor was there any significant alcohol use. Physical examination was unrevealing and her most recent screening colonoscopy was negative.

**Laboratory studies:**
- **CBC:** Hemoglobin 9.1 g/dL; WBC 3.2 x 10^3/µL (normal range 3.8-10.8 x 10^3/µL); MCV and platelets normal
- **Creatinine:** 1.5 mg/dL (normal range 0.7-1.4 mg/dL); serum calcium: 10.6 mg/dL (normal range 8.5 - 10.3 mg/dL); serum globulin 4.8 g/dL (normal range 2.3-3.5 g/dL); serum uric acid: 7.7 mg/dL (normal female range: 2.5 - 7.5 mg/dL); albumin 2.9 mg/dL (3.5 - 5 g/dL); all other values within normal range.

What would you do next for this patient?
- a. Hematology consult for bone marrow biopsy
- b. GI consult for EGD and repeat colonoscopy
- c. **Serum free light chain test**
- d. EPO levels

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**Multiple Myeloma (MM):** MM is the second most common blood cancer after NHL and the incidence and mortality rates are approximately two-fold higher in African Americans compared to whites.[24] Approximately 24,050 new cases of MM are expected in 2014.[24] MM is a malignancy resulting from hyperproliferation of mature antibody producing B-cells (plasma cells) in the bone marrow.[34] A consequence of MM is the over production of cytokines and
other factors that disrupt normal marrow function leading to low blood count, abnormal immune function, and lytic lesions. The median age at diagnosis is 69 years for women and 71 years for men. It is important for PCPs to recognize that MM is a disease spectrum, spanning a continuum from monoclonal gammopathy of undetermined significance (MGUS), smoldering (asymptomatic) myeloma, to symptomatic MM.[35] Early diagnosis and referral to a hematologist is essential to avoid the sequelae of advanced disease such as organ dysfunction, bone lesions, anemia, infections, and kidney failure. This is especially true given a variety of available treatment options for MM that offer the potential to make MM a chronic disease with early intervention.[35]

Early diagnosis of MM is a challenge due to non-specific presenting symptoms. The most common presenting symptoms are bone pain, fatigue (due to anemia), weight loss, neurologic symptoms and infections (Figure 7).[36] Patients may also present with renal failure. Lymphadenopathy and hepatomegaly are rare. Routine blood tests that aid in the initial workup are CBC, ESR and chemistry panel.[36,37]

**Figure 7. Presenting Features of MM**

*Adapted from[36]*

Prevalence of selected presenting features in a series of 1,027 patients with MM.

Anemia is seen in approximately ¾ of patients with MM and is normocytic-normochromic and associated with formation of rouleaux.

Anemia in MM is common (73% of cases), normocytic-normochromic and associated with formation of rouleaux (stacks of 3-12 RBCs).[36,37] Detection of a monoclonal (M-) protein in serum or urine or imbalance in free light chains (i.e., ratio of kappa to lambda) is central to diagnosis and monitoring of MM. M-proteins are also a hallmark of MGUS and can sometimes be seen in association with CLL or lymphomas. Detection of M-protein should trigger referral to a hematologist for consideration of bone marrow evaluation, skeletal survey or other testing. *(Table 2)* outlines the diagnostic evaluation of MM according to NCCN guidelines.[37] MRI or PET/CT may also be useful as clinically needed to evaluate the extent of disease involvement.
Table 2. Diagnostic Evaluation of MM*

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding in MM</th>
</tr>
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<tbody>
<tr>
<td>CBC, differential</td>
<td>↓Hb ↓WBC ↓platelets</td>
</tr>
<tr>
<td>Chemistry: BUN, creatinine, electrolytes, calcium, albumin, LDH, uric acid</td>
<td>↑creatinine, ↑calcium, ↑uric acid, ↓albumin</td>
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<tr>
<td>SPEP with quantitative immunoglobulins</td>
<td>↑M-protein in serum ± ↓normal antibodies</td>
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<tr>
<td>Immunofixation</td>
<td>Identifies M-protein heavy/light chain type</td>
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<tr>
<td>β2-microglobulin</td>
<td>↑(marker of tumor burden)</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>↑(marker of myeloma growth factor)</td>
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<tr>
<td>24-hour UPEP with immunofixation</td>
<td>↑monoclonal protein (Bence-Jones), proteinuria</td>
</tr>
<tr>
<td>Serum free light chain (sFLC)</td>
<td>↑ free light chain (λ or κ)</td>
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<tr>
<td>Bone marrow biopsy, cytogenetics, FISH, IHC</td>
<td>&gt;0% plasma cells, prognostic information</td>
</tr>
<tr>
<td>Skeletal survey</td>
<td>Osteolytic lesions, osteoporosis</td>
</tr>
</tbody>
</table>

*Adapted from[37]

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FISH=fluorescence in situ hybridization; IHC=immunohistochemistry; LDH=lactate dehydrogenase; SPEP=serum protein electrophoresis; UPEP=urine protein electrophoresis

A sensitive quantitative and automated serum free light chain (sFLC) assay has been developed[38] that is recommended in the NCCN and in the International Myeloma Working Group guidelines for use in the initial diagnostic workup of multiple myeloma and related disorders.[37,39] It is helpful for PCPs to get a baseline test for sFLC in a patient with a monoclonal protein (M-spike) to provide valuable information for follow-up and response to treatment when referred to a hematologist.

There has been unprecedented progress in the development of novel therapies for MM such that the former gold standard treatment, autologous hematopoietic stem cell transplant is typically no longer used as primary therapy, but rather used later in the treatment paradigm.[35,37] Currently approved novel therapies to treat symptomatic MM include the oral immunomodulatory drugs lenalidomide and pomalidomide, and the proteasome inhibitors bortezomib and carfilzomib. The availability of multiple novel therapies is improving survival and turning MM into a chronic disease for many patients (Figure 8).[35]
Figure 8. Patient Overall Survival from Time of Diagnosis in MM (Six-Year Interval Kaplan-Meier Estimates)*

ASCT=Autologous Stem Cell Transplant; MEL(200)=melphalan (200 mg/m²)

*From[35]

Summary

- **Anemia should not be considered a normal part of the aging process** and should be evaluated
  - A cause can often be determined, and treatment may alter outcomes and improve quality of life (QOL)
- **Use mean corpuscular volume (MCV)** to narrow differential diagnosis of geriatric anemia and determine initial tests
  - Microcycosis, MCV <80 fL
  - Normocycosis, 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**
- Consider multiple myeloma and related disorders in the differential diagnosis of patients with **unexplained normocytic-normochromic and non-specific symptoms** of bone pain, weight loss, neurologic symptoms and infections
  - It is important to get a **baseline serum free light chain (sFLC) test** in suspected cases
Post-test

1. Which test is diagnostically most useful in narrowing the differential diagnosis of geriatric patients with anemia?
   a. Serum creatinine
   b. Mean corpuscular volume (MCV)
   c. Vitamin B12 level
   d. Serum ferritin

2. A 75 year old woman who eats poorly (mostly toast with jam and inexpensive tea) due to limited income presents to her PCP with progressive fatigue over 5-6 months. She is found to have an Hb of 8.5 g/dL and a MCV of 92 fL. Her physician suspects combined iron and folate deficiency.

   Which of the following tests is most sensitive to the presence of a combined nutritional deficiency?
   a. Mean corpuscular volume (MCV)
   b. Mean cell hemoglobin (MCH)
   c. Red cell distribution width (RDW)
   d. Mean cell hemoglobin concentration (MCHC)
   e. Reticulocyte count

3. Older patients with anemia are at higher risk for all the following EXCEPT:
   a. Major depression
   b. Decreased bone density
   c. Poor control of type 2 diabetes
   d. Decreased skeletal muscle mass
   e. Reduced cognitive function

4. In a patient with microcytic anemia, the most likely differential diagnoses would include all the following EXCEPT:
   a. Iron deficiency
   b. Bone marrow disorder (especially MDS)
   c. Anemia of chronic inflammation
   d. Hemoglobin E trait

5. A 66-year-old African American woman presents with worsening bone pain especially at night, weight loss and upper respiratory tract infection.

   She was found to be anemic: Hb 9.8 g/dL with MCV 93 fL. Her iron studies were normal and her most recent colonoscopy a year ago was negative.
Her lab values were notable for the following: serum creatinine, serum calcium, serum globulin and serum uric acid were all elevated above the normal range; serum albumin levels below normal range.

The patient has no lymphadenopathy or leukopenia. Subsequent evaluation showed the presence of a serum monoclonal-(M-) protein.

Which hematologic disorder should be included in the differential diagnosis of this patient?

a. Myelodysplastic syndromes (MDS)
b. Multiple Myeloma (MM) or related disorder
c. Non-hodgkin lymphoma (NHL)
d. Chronic Lymphocytic Leukemia (CLL)