Evaluating the Etiologic Cause and Optimal Treatment of Geriatric Anemia in the Primary Care Setting: A Case-Based Study

Authors: Brian Koffman, MDCM; David P. Steensma, MD, FACP

Learning Objectives: As a result of this activity, the learner will be able to

- 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
- Manage elderly patients with anemia due to nutritional deficiency, blood loss, renal failure, or suspected myelodysplasia (including appropriate referral to a specialist)

Introduction

Anemia is a very common problem in the elderly, making this clinical finding a growing concern as the proportion of older individuals in the US population continues to increase. According to current US Census Bureau projections, by 2030 there will be approximately 114.1 million Americans aged 65 years and older representing nearly 25% of the total population. By 2050, that number is anticipated to reach 156 million, more than double the estimated current population of 64.7 million persons older than 65 years.[1] The current life expectancies of 65-year-old individuals in the United States are 17 years for men and 20 years for women; this relatively lengthy lifespan argues in favor of aggressive evaluation and therapy of treatable conditions in older people.[2]

Moreover, persons older than 85 years represent the fastest growing segment of the population, with projected increase from 5.8 million today to over 19 million by 2050.[1] By age 85, most individuals have some degree of frailty and health conditions requiring chronic therapy. The National Health and Nutritional Evaluation Survey III (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. 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). Thus, the “oldest old,” persons 85 years or older, are not only the fastest growing segment of the US population, they also have the highest prevalence of anemia.
Is Anemia in Older Persons Worth Evaluating Further?

In the past, certain common conditions were considered to be a normal part of aging (eg, “senile dementia”), but it has since been recognized that these conditions are accompanied by specific pathological findings (eg, the amyloid plaques and neurofibrillary tangles of Alzheimer disease) that are present in only a subset of patients. The situation is similar with anemia. Although anemia is common in the elderly, a low hemoglobin level cannot simply be dismissed as a normal part of aging. The presence of anemia is associated with higher mortality and morbidity, especially in geriatric patients, and a cause can almost always be determined.

What Is “Normal” Hemoglobin?

It is important to have an accurate definition of anemia in order to evaluate causes, associated health outcomes, and response to interventions. In 1968, the World Health Organization (WHO) recommended anemia definitions based on analysis of a limited population.[5]

The WHO definitions of anemia in adults are

- Hemoglobin (Hgb) <13.0 g/dL for males
- Hgb <12.0 g/dL for nonpregnant females

On the basis of more recent studies of 2 large databases, the NHANES III database (described above) and the Scripps-Kaiser database (41,038 adults in Southern California), more people would be considered to be anemic, but the hemoglobin threshold levels were similar to the WHO definition.[3,5-7]

Reference ranges for normal hemoglobin vary from laboratory to laboratory and the normal range is reported along with laboratory findings. However, many other factors can influence a
healthy person’s hemoglobin level, including ethnic background, altitude of residence, smoking status, and physiologic fluctuations of plasma volume. Because clinical laboratories do not adjust for these factors, interpretation of hemoglobin test results is the responsibility of the ordering clinician.[7]

The best definition of anemia is the hemoglobin level at which poorer health outcomes occur. Several population-based studies have attempted to correlate hemoglobin levels and survival. One of the largest of these is the Cardiovascular Health Study, which followed 5888 adults in the United States aged 65 years or older for a median of 11.2 years, reported on the relationship between baseline hemoglobin level and mortality rate (Figure 2).[8] Older persons with hemoglobin measurements in the lowest quintile (<13.7 g/dL for men and <12.6 g/dL for women) had the worst survival, including the subset within that group who would have been considered non-anemic using WHO definitions of anemia.

In addition, a growing body of literature suggests that mild anemia or a “low-normal” hemoglobin level is associated with a broad range of poorer health outcomes, both in populations with specific medical conditions (eg, congestive heart failure) and in the general population. Increased mortality associated with anemia is well documented in cancer, human immunodeficiency virus infection, and other medical conditions, but it is often unclear whether these effects are due to the anemia itself or whether anemia is a biomarker of more severe disease or a lower likelihood of response to therapy.
Low hemoglobin also has a negative impact on performance status and functional independence, and this appears to the most pronounced in elderly populations. Factors associated with low hemoglobin levels in older persons include the following:[7]:

- Higher risk of recurrent falls
- Decreased mobility, bone density, skeletal muscle mass
- Poorer cognitive function
- Increased rate of major depression
- Increased frailty index
- Higher risk of hospitalization and longer duration in hospital

**What Are the Primary Causes of Anemia in Older Persons?**

It is important to make the distinction that anemia is a sign of disease, not a disease in itself. Because there are dozens of potential causes of anemia, an organized approach is needed to discern the correct diagnosis and, consequently, the correct treatment of a patient’s anemia (Figure 3).[9] A specific cause can be found in almost all cases. All anemias are the result of 1 of 3 general causes:

- **Red Blood Cell (RBC) Loss Due to Bleeding.** It has been estimated that worldwide about 50% of the people are anemic, particularly in developing countries and tropical areas where endemic parasitic diseases produce blood loss.
- **Inadequate RBC Production.** Anemia due to insufficient erythropoiesis, often referred to as hypoplastic or underproductive anemia, may be due to bone marrow failure or nutritional deficiency (eg, lack of adequate stores of iron, folate, or vitamin B12).
- **Premature RBC Destruction (hemolysis).** Hemolytic anemia accounts for about 15% to 20% of all anemias, and may be due to an acquired (eg, autoimmune hemolytic anemia) or a congenital (eg, sickle cell disease or thalassemia) disorder.
One of the challenges in identifying the etiology of anemia in elderly patients is the diversity of potentially contributing factors (eg, medications and alcohol use). Thus, anemia in older persons may be multifactorial, and evaluation of low hemoglobin may be more challenging than in adolescents or young adults.

In the NHANES III study, 10% to 11% of men and women 65 years and older were anemic.[3] These anemias were generally mild, with only 2% to 3% having a hemoglobin level of <11.0 g/dL. Major causes of anemia in the NHANES III study were

- Nutritional deficiency (eg, iron, folate, vitamin B12); 50% or more of the group were related to iron deficiency, alone or in combination with folate or vitamin B12 deficiency – about one-third of cases
- Chronic disorders (kidney disease, diabetes, or inflammatory processes that have increased serum C-reactive protein, or a positive rheumatoid factor) – about one-third of cases
- “Unexplained” – about one-third of cases. Among the unexplained cases, 17% (6% of the entire patient population) had one or more criteria for the diagnosis of one of the myelodysplastic syndromes (MDS)

**Use of the Mean Corpuscular Volume to Narrow the Differential Diagnosis**

Once a diagnosis of anemia has been made from a patient’s symptoms or incidental blood test, the mean corpuscular volume (MCV) is the most valuable parameter for narrowing the possible causes of anemia in both younger and older patients (Figure 4).[9] 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 and macrocytosis due to ethanol ingestion in a patient who chronically abuses alcohol.
CASE STUDY 1

- Paul Reynolds is a 71-year-old male who presents with increasing shortness of breath. He had a history of CAD with placement of a drug-eluting stent 5 months ago, and is now receiving dual antiplatelet therapy with clopidogrel and aspirin. He denies any chest pain, but never exerts himself. He just left his cardiologist’s office where he had a clinical examination, electrocardiogram, and chest x-ray. From the cardiologist’s point of view, the patient was deemed to be hemodynamically stable with no cardiac cause for the increased dyspnea. The cardiologist has sent Mr. Reynolds back to you to further work up his shortness of breath.

- He denies any cough or other respiratory complaints or any gastrointestinal (GI) issues or change in stools.
- Physical examination reveals an obese male in no acute distress and was unremarkable.
- Labs: Hgb 10.1 g/dL; comprehensive metabolic panel (CMP) and thyrotropin (TSH) test results are all within normal ranges.

**Q1: Based on Mr. Reynolds's history and lab data, what is an appropriate next step?**

   A: Immediately stop all antiplatelet medications
   B: Check the MCV, and direct the rest of the workup based on that finding
   C: Start on ferrous sulfate 325 mg twice daily orally as a therapeutic trial, and recheck hemoglobin in 2 weeks
   D: Order serum iron, total iron-binding capacity (TIBC), % saturation, serum vitamin B12 and folate levels, and serum ferritin

This patient's hemoglobin level was below normal (10.1 g/dL), with no overt signs of bleeding or other sign of a cause. The MCV will help with differential diagnosis and guide further testing.

**Q2: His MCV is 74 fL. What would be your next step?**

   A: Order serum iron, TIBC, % iron saturation, and ferritin levels
   B: Order serum vitamin B12 and folate levels
   C: Hematology consult for consideration of bone marrow aspirate and biopsy
   D: Arrange for transfusion of 2 units of packed RBCs

In the elderly, a low MCV (microcytic anemia) is strongly suggestive of iron deficiency anemia, especially if it is an acquired condition; however, iron deficiency anemia can also occur with normal MCV (normocytic anemia).[7]

**Q3: Iron studies confirm iron deficiency anemia. You would next**

   A: Ask for gastroenterology consultation for endoscopy
   B: Refer the patient to hematology
   C: Arrange for intravenous iron infusions
   D: Discontinue all antiplatelet medications

Occult GI bleeding is a major cause of anemia in older patients and must be ruled out whenever iron deficiency is detected. Because dietary iron deficiency is rare in the United States, serologic evidence of iron deficiency (eg, serum ferritin <20 ng/m) indicates the need for assessing the GI tract. Higher ferritin levels may still be consistent with iron deficiency, especially if the patient has an inflammatory condition. It should be recognized that ferritin is an imperfect measure of total body iron stores[10] and may need to be supplemented by other tests (eg, soluble transferrin receptor assay, which, unlike serum ferritin, is unaffected by inflammation, as the transferrin receptor is not an acute phase reactant). 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 (AI/ACD), which is associated with lower levels. A patient with normal findings on GI evaluation and continued iron deficiency despite iron replacement should be referred to a hematologist.
Common Causes of Microcystosis (MCV <80 fL) (Figure 5)[9]

- In the United States, iron deficiency is the most likely cause.
- Thalassemia: inherited inability to synthesize globin coupled with an erythropoietic drive results in an elevated number of small RBCs, leading to low hematocrit and hemoglobin but a normal or high RBC count. There is only one other situation that clinically gives rise to a low MCV and a high red count: a patient with polycythemia vera who has had bleeding or who has been bled by phlebotomy. It is worthwhile referring patients with thalassemia to a hematologist, because hemoglobin assays and molecular testing are often necessary to define the thalassemia subtype, and thalassemia has reproductive implications.
- ACD is usually a normochromic-normocytic anemia, but it may be microcytic, particularly with chronicity.

Less Common Causes of Microcytosis (Figure 5)

- Rarer causes of microcytosis include sideroblastic anemia (acquired idiopathic sideroblastic anemias are considered a form of MDS), congenital/acquired disorders (eg, hemoglobin C, hemoglobin E), vitamin C deficiency, and lead poisoning.

The Red Cell Distribution Width (RDW), while not specific for a cause of anemia, in some cases can be a useful parameter in differentiating iron deficiency from thalassemia and the ACD by providing an objective measure of variation in red cell size. In classic iron deficiency, the RDW reflects a broad distribution of red cell sizes (anisocytosis) and, therefore, is elevated. In contrast, the RDW tends to be relatively low in thalassemia syndrome and ACD. Also, for unclear reasons, the bone marrow responds to iron deficiency and blood loss by an increase in platelets; this platelet count elevation may be subtle, but often is present in iron deficiency.
Common Causes of Normocytic Anemia (MCV ≥80 or ≤100 fL)

- AI/ACD is the most common form of normocytic anemia, although some cases of AI/ACD may be microcytic (Figure 5). Because AI/ACD is hepcidin-mediated, a high C-reactive protein (a surrogate marker for elevated hepcidin and interleukin-6) is a very suggestive finding of AI/ACD. AI/ACD is not associated with every chronic medical condition; there must be an inflammatory component, eg, rheumatoid arthritis, systemic lupus erythematosus, inflammatory bowel disease, cancer, chronic infections, and sometimes congestive heart failure.[4]

- Acute or relatively recent blood loss, for which the bone marrow has not yet had time to compensate, may also present as normocytic anemia.

- Chronic renal failure is associated with low production of erythropoietin by the kidneys and with varying degrees of anemia.

- Combined or mixed disorders, in which both small and large red cells are present. For example, in celiac disease, both iron deficiency (low MCV) and folic acid deficiency (high MCV) may be present due to proximal small bowel malabsorption; these opposing effects on MCV may balance out to a normochromic-normocytic anemia, but the RDW should be elevated.
- Early or mild iron deficiency.
- Autoimmune hemolytic anemia (AIHA) may be normocytic or macrocytic. AIHA is characterized by mainly spherocytes and reticulocytes in blood smears. Spherocytes have low MCV, but reticulocytes (young red cells) are larger and a high count will increase the MCV. The net effect is normocytosis with a high RDW.[11]

**Common Causes of Macrocytosis (MCV >100 fL)**
- Vitamin B12 or folate deficiency. An increased MCV warrants measurement of RBC folate and serum vitamin B12 levels. In the event of a borderline vitamin B12 level at the lower end of normal range, the presence or absence of true tissue-level vitamin B12 deficiency may be confirmed by methylmalonic acid assessment in serum and urine.[7]
- Alcohol abuse can cause macrocytosis by several mechanisms in addition to its association with folate deficiency and with bleeding and reticulocytosis. Ethanol is directly toxic to erythroid precursors and results in abnormal megaloblastoid maturation, in which the nucleus and cytoplasm of the developing red cell mature out of synchrony. In addition, in patients with alcoholic liver cirrhosis, lipid alterations may alter the RBC membrane.
- Some drugs (eg, azathioprine, methotrexate, chemotherapies [hydroxyurea]) cause macrocytosis through a variety of mechanisms, including inducing megaloblastoid red cell maturation in the bone marrow.
- Cigarette smoking can cause macrocytosis in some cases, but the prevalence of macrocytosis among cigarette smokers is not known.
- Primary bone marrow disorders, especially MDS, are often associated with a higher MCV. It is important to work together with a hematology consultant to diagnose and manage this group of diseases.

**Less Common Causes of Macrocytosis**
- Advanced cirrhotic liver disease or severe hypothyroidism can cause macrocytosis by altering red cell membrane lipid composition.
- An artifact, such as agglutination or rouleaux, may cause spurious macrocytosis due to multiple clumped red cells moving together through the flow chamber of an automated analyzer together, making the analyzer detect an apparent very large red cell. A peripheral blood smear will identify such artifacts; as a result, a laboratory workup of macrocytic anemia should include evaluation of the peripheral smear by a hematologist or pathologist (Figure 6).[9]
- Hyperglycemia. When red cells are stored in the citrate or EDTA tube in the presence of a high blood sugar (hyperglycemia), they can swell and produce an artifactual increase in red cell size.
- Reticulocytes are larger than more mature RBCs; therefore, reticulocytosis after hemorrhage or in AIHA may be associated with a high MCV. The typical finding on the peripheral blood smear is polychromasia; specific stains for reticulocytosis will allow an accurate count.
The type of macrocyte present on peripheral smear may help in the differential diagnosis. Round macrocytes are usually seen in liver disease or thyroid disease. Oval macrocytes are the typical finding with vitamin B12 and folate deficiency, with other forms of megaloblastoid anemia such as drug or alcohol effect, and with bone marrow failure syndromes. If serum vitamin B12 and folate tests are normal, an artifact has been ruled out, and the patient has no history of excess alcohol use and is not taking a drug known to cause macrocytic anemia such as methotrexate, then a bone marrow disorder is likely. Such patients should be referred to a hematologist for a bone marrow aspirate and biopsy, including cyogenetic assays. If the vitamin B12 or folate levels are low, the patient should be evaluated and managed appropriately.
CASE STUDY 2

James Anthony, an 80-year-old, semi-retired auto mechanic and gas station owner, presents for a routine physical examination. He has no symptoms other than in the last few months he has been feeling more tired than normal, but he attributes this to his age. His only medication includes an occasional over-the-counter ranitidine for gastroesophageal reflux. He had a colonoscopy 2 years earlier, findings were normal. Physical examination is unremarkable, but he is found to have anemia (Hgb 10.1 g/dL) on a routine complete blood cell count (CBC). Except for slightly elevated total and low-density lipoprotein cholesterol levels, his laboratory results, including CMP and TSH values, are normal. He recalls that his mother received regular vitamin B12 injections from her family clinician when she was older.

Q1: Given Mr. Anthony’s history and lab results, what would you conclude regarding his fatigue?

A: It is most likely due to vitamin B12 deficiency and should respond to weekly vitamin B12 injections
B: A full psychological assessment should be done, as his physical and lab findings are not likely factors in his fatigue
C: His fatigue is most likely a normal part of aging and he only needs reassurance
D: His fatigue is probably due to anemia and should be evaluated further

The patient’s fatigue may be related to his mild anemia. Anemia is never normal, and it should be worked up.

Q2. What is the most important result to check on Mr. Anthony’s CBC?

A: RBC count
B: Platelet count and white cell count and differential, as normal platelet and white cell count make a serious blood disorder unlikely
C: MCV, as this is the most helpful initial indicator of possible etiology of the anemia
D: Hematocrit, as this is the most sensitive test for true anemia

MCV is the most useful test for narrowing the differential diagnosis of anemia, and will guide further testing.
Q3: His MCV is mildly elevated at 104 fL. What would be your next step?
   A: Serum iron, TIBC, and % saturation
   B: Hemoglobin electrophoresis
   C: C-reactive protein
   D: Serum vitamin B12 and folate levels

An increase MCV warrants evaluation for vitamin B12 or folate deficiency, and possible screening for alcohol abuse. If those are normal, a hematologist consultation would be appropriate.

Q4: Mr. Anthony's serum vitamin B12 level was 560 pg/mL (normal range: 200 - 900 pg/mL) and his RBC folate level was also normal. What is the most appropriate next step?
   A: Reassure the patient that there is no worrisome cause for his anemia
   B: Suggest a hematology consult for a possible bone marrow biopsy to rule out MDS
   C: Prescribe an iron supplement
   D: Order homocysteine and methylmalonic acid to check for occult B12 deficiency

While a serum vitamin B12 level less than 350 pg/mL may be associated with tissue-level vitamin B12 deficiency, a serum vitamin B12 level greater than 500 pg/mL is almost never associated with tissue-level deficiency. Referral to a hematologist is appropriate, as Mr. Anthony is likely to have a primary bone marrow disorder such as MDS, especially given his age and occupational exposure. The hematologist’s workup would likely include evaluation of a peripheral smear and a bone marrow biopsy to rule out MDS.

**Myelodysplastic Syndromes (Formerly “Preleukemia”)**

MDS are a group of neoplastic bone marrow disorders that are most often found in older patients. MDS are associated with peripheral blood cytopenias and a risk of progression to a treatment-refractory form of acute myeloid leukemia. The median age at diagnosis of MDS is approximately 70 years in the United States, but MDS may occur in younger patients, especially those who have been exposed to prior chemotherapy (particularly alkylating agents), some toxins including benzene, or radiation.

Over 90% of patients with MDS have anemia at the time of diagnosis, while less than half have neutropenia or thrombocytopenia. RBC transfusions are often required for management. The bone marrow is typically hypercellular, and the cells are abnormal in appearance (“dysplastic”); bone marrow blasts may be increased. The natural history of MDS is that approximately 25% of patients will progress to acute myeloid leukemia (MDS was called preleukemia in the past, but this term was misleading because most patients never developed leukemia), 50% will die from complications of cytopenias (most commonly infection and bleeding), and the remaining 25% will die from other non-MDS causes.
MDS: Diagnosis and Treatment

MDS may be the most common hematologic malignancy among individuals older than 65, with recent estimates of approximately 45,000 new cases per year in the Medicare population. By comparison, acute monocytic leukemia occurs in fewer than 12,000 adults per year in the United States. Overall the rate at which MDS is diagnosed has increased over the past 20 years, likely due, in part, to the formal definition of MDS as a distinct hematologic malignancy and consequent greater clinician awareness, improved diagnostic techniques, and the aging population.

It is not clear what proportion of elderly anemic patients has MDS. Among the NHANES III population, two-thirds of older patients with anemia had a potential cause for their anemia (ie, a nutritional deficiency or chronic disease), though it is possible that some of these patients also had MDS. The frequency of MDS among the one-third of “unexplained anemia” cases in elderly persons is unknown. In a study of 3275 geriatric patients hospitalized for acute care or short-term rehabilitation who were carefully evaluated for blood abnormalities, 245 (7.5%) had unexplained cytopenia, macrocytosis, or monocytosis, and 37 (15%) were diagnosed with MDS.

Historically, most patients with MDS were treated with supportive care alone. Unfortunately, supportive care has not improved over time. A survey of the cumulative survival of MDS patients receiving only best supportive care between the years 1970 and 2005 showed no significant improvement in outcomes during that interval. Prior to 2004, the only treatments available for most patients with MDS were erythropoiesis stimulating agents, androgenic steroids, cytotoxic chemotherapy, and allogeneic hematopoietic stem cell transplantation. Over the past several years, however, several new agents for treatment of patients with MDS have become available that may modify the natural history of the disease (Figure 7).
RBC transfusion dependence is a significant burden for many MDS patients (39% in low risk; 79% in high risk).[15] Patients who are transfusion-dependent have a significantly shorter overall survival.[16] Other issues with transfusions include the fact that they provide only temporary improvement, the increased risk of infection or a transfusion reaction, the possible risk of iron overload after multiple transfusions (a ferritin level of 1000 ng/mL is associated with poorer outcomes in MDS, and is usually approximately 10-20 units of blood, a number quickly reached by many MDS patients), the impact on blood supply (MDS accounts for about 3% of all RBC transfusions), a negative impact on quality of life, inconvenience for the patient, and expense.[17,18]

Hematopoietic stem cell transplantation remains the only cure for MDS, but older patients are usually ineligible for transplant due to their age and comorbidities. Prior to 2000, less than 5% of all MDS patients were considered candidates for transplant. However, with greater use of reduced intensity conditioning approaches in older patients and the availability of alternative nonsibling stem cell sources such as umbilical cord blood, the proportion of patients eligible for transplantation is growing.

Between 2004 and 2006, 3 specific therapies were approved for MDS by the Food and Drug Administration (FDA): azacitidine, lenalidomide, and decitabine. Clinical trials of the newer MDS therapies have demonstrated benefit compared with supportive care in MDS populations. For instance, the AZA-001 randomized, prospective trial compared azacitidine with a control arm of “conventional care,” which consisted of best supportive care alone, low-dose Ara-C, or standard chemotherapy, in patients with higher-risk MDS. Treatment with azacitidine resulted in an

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improvement in median overall survival from 15 months to 24.4 months, a difference of 9.4 months.[19] This was the first time a therapy had been demonstrated to improve survival in a subgroup of MDS patients.

For the nearly 10% of MDS patients whose bone marrow cells have a deletion of the long arm of chromosome 5 (del(5q)), the oral immunomodulatory drug lenalidomide can be particularly effective.[20,21] In a study of lenalidomide in a selected population of MDS patients with del(5q), about two-thirds of enrolled patients became transfusion independent, the median increment in hemoglobin was 5.4 g/dL, and these responses lasted a median of over 2 years. Another study showed that there is also a subset of patients with MDS who do not have del(5q): about one-quarter of the patients without del(5q) also became transfusion independent, although the responses did not last as long as in the del(5q) patients (median 41 weeks).[22]

In a phase III trial, decitabine demonstrated a significant improvement in response rate compared with best supportive care across multiple MDS disease subsets.[23] Although it takes several months to achieve response with either azacitidine or decitabine, patients who do respond often become transfusion independent.[19,24]

In summary, whereas 10 years ago treatment options were limited for patients with MDS, there are now several effective therapies to consider. However, it is not clear whether earlier therapy for MDS improves outcomes compared with later initiation of treatment, and the benefits of these therapies need to be balanced with adverse effects associated with these agents, especially for geriatric patients who may have multiple comorbidities. Typical or common treatment-related adverse effects with the 3 FDA-approved therapies include the following:

Azacitidine and decitabine[25,26]
- Cytopenias
- Febrile neutropenia, especially in first 2 cycles
- Skin reactions (with subcutaneous azacitidine)
- GI side effects (diarrhea, nausea, vomiting)
- Aphthous ulcers of the mouth
- Maculopapular rash

Lenalidomide[27]
- Cytopenias
- Peripheral neuropathy
- Concern about teratogenicity (lenalidomide is chemically related to thalidomide)
- Rash
- Fatigue
- Venous thromboembolism (rare when used as monotherapy as in MDS)
Algorithm for Evaluation of Anemia in Older Patients
The algorithm shown in Figure 8 provides a structured approach for evaluating low hemoglobin 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.

Best Practices Pearls
- 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 patient functional status
- Use 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 considered in patients with unexplained macrocytic anemia
Figure 8. Proposed Algorithm for Evaluation of Low Hemoglobin in Older Patients.

1. Review peripheral blood smear and assess MCV.
   - Worrisome peripheral smear? Yes/No
     - Low MCV (<80 fl)
       - Major Considerations: Iron deficiency/bleeding, Thalassemia, Anemia of chronic inflammation (if MCV mildly low)
       - Review old blood cell counts, Measure ferritin, serum iron/total iron-binding capacity
       - Iron studies normal? No/Yes
         - Supplement iron and evaluate for bleeding
         - Consider hemoglobin electrophoresis and measurement of creatinine/serum EPO
       - If EPO elevated, provide supportive care
     - Normal MCV (80-100 fl)
       - Measure creatinine, serum EPO
       - If creatinine higher or EPO lower than expected, consider EPO supplementation
       - If cause not obvious from history, measure vitamin B12/folate and homocysteine
     - Elevated MCV (>100 fl)
       - Major Considerations: Vitamin B12/folate deficiency, Drug effect, Alcohol abuse, Liver/thyroid disease, MDS
       - Vitamin B12/homeocysteine normal? Yes/No
         - Supplement nutritional deficiency
         - Consider bone marrow examination if findings will change management
         - Treat as indicated