REVIEW

Anemia in the Elderly: How Should We Define It, When Does It Matter, and What Can Be Done?

DAVID P. STEENSMA, MD, AND AYALEW TEFFERI, MD

Anemia signifies an underlying disease and is associated with poor clinical outcomes. In elderly patients, in whom anemia has a high prevalence (>10%), neither the hemoglobin threshold for concern nor the identity of the anemia-causing disease is easily established. This is an important shortfall, because even mild anemia can compromise patients' well-being and survival, regardless of the underlying cause. This review discusses definitions of "normal" hemoglobin levels in adults, common causes of anemia in people aged 65 years and older (eg, nutritional deficiency, renal insufficiency, inflammatory disorders, and myelodysplastic syndrome), and potential consequences of anemia in elderly patients (eg, poorer cognitive status, increased frailty, and an elevated risk of hospitalization and of complications during hospitalization). We also outline a practical initial diagnostic approach that helps determine appropriate treatment, and we weigh therapeutic options in light of new safety concerns regarding erythropoiesis-stimulating agents.

Mayo Clin Proc. **2007;82(8):958-966**

Epo = erythropoietin; ESA = erythropoiesis-stimulating agent; GI = gastrointestinal; MCV = mean corpuscular volume; MDS = myelodysplastic syndrome; NHANES III = Third US National Health and Nutrition Examination Survey; WHO = World Health Organization

Anemia is extremely frequent in elderly persons, defined in this article as those aged 65 years and older, and is growing in importance as a public health issue and a biomedical research priority.[1-3] In response to reports describing a heavy health burden from anemia in the elderly, the American Society of Hematology and the National Institute of Aging organized joint symposia in 2004 and 2005 to review the problem and define a research agenda, and the National Institutes of Health offered a special request for research proposals in 2006.[1,4] The issue is driven by demographics: the US Census Bureau estimates that currently more than 36.3 million Americans are aged 65 years or older and that by 2050 that number will increase to 85 million if current trends continue.[5] The *oldest old*, persons aged 85 years or older, are not only the fastest-growing segment of the US population, they also have the highest prevalence of anemia: 26% for men and 20% for women, when World Health Organization (WHO) definitions of anemia are used (Figure 1).[6-8] Anemia is even more common in black than in white populations (Figure 2).

From the Division of Hematology, Mayo Clinic, Rochester, MN.

Individual reprints of this article are not available. Address correspondence to David P. Steensma, MD, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (steensma.david@mayo.edu).

DEFINING ANEMIA AND "NORMAL" HEMOGLOBIN

An accurate definition of anemia is important for evaluating the causes of suboptimal hemoglobin levels, associated health outcomes, and response to interventions. The anemia definitions recommended by a WHO expert panel in 1968 based on limited population data are easy to remember, but their accuracy has been questioned (Table 1).[2,9-11] Newly proposed anemia definitions are derived primarily from 2 data sets that include hemoglobin values for large segments of the general population: the Third US National Health and Nutrition Examination Survey (NHANES III, 1988-1994) and the Scripps-Kaiser database.[8,12,13]

Focused on an ambulatory population, NHANES III assessed a national probability sample of 33,994 persons aged 2 months and older, 26,372 of whom underwent laboratory studies, including hemoglobin measurement.[12] The Scripps-Kaiser dataset includes laboratory and clinical information from 41,038 adults who attended a health appraisal clinic in Southern California between 1998 and 2002.[13] On the basis of these 2 newer databases, more people would be labeled as anemic, but the hemoglobin threshold levels proposed would be reassuringly similar to those of the WHO (Table 1), suggesting that the studies of the last few decades on the prevalence and clinical outcomes of anemia retain most of their validity.

Reference ranges for normal hemoglobin vary from laboratory to laboratory because they are usually set by the manufacturer of the automated cell counter used by a given laboratory. These reference ranges are customarily confirmed "in-house" by the institution requesting the test. For example, the Mayo Clinic Central Clinical Laboratory currently uses Coulter LH 750 impedance counters (Beckman Coulter, Miami, FL) for complete blood cell counts, and the "normal" reference range given by the manufacturer of this instrument differs from WHO norms and those suggested by NHANES III and Scripps-Kaiser data (Table 1). Variations in hemoglobin reference ranges can also be due to subtle differences in sample processing and validation methods, leading to results being "flagged" as abnormal on a laboratory printout in one facility but not in another.

Many factors can affect a healthy person's measured hemoglobin value, including ethnic background,[14] altitude of residence,[15] smoking status,[16] and physiologic fluctuations of plasma volume. These parameters are not routinely

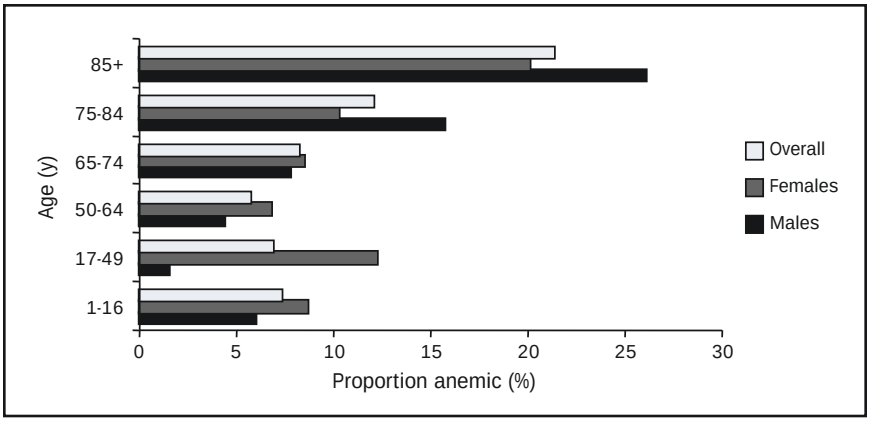

FIGURE 1. Prevalence of WHO-defined anemia (hemoglobin <13.0 g/dL for males and <12.0 g/dL for nonpregnant females) in the United States, by age and sex. SI conversion factor: to convert hemoglobin value to g/L, multiply by 10. NHANES III = Third US National Health and Nutrition Examination Survey; WHO = World Health Organization. Data from first 2 phases of NHANES III, 1988-1994.[7,8]

considered by clinical laboratories, which typically report test results adjusted for age and sex only. Therefore, interpretation of blood count results remains the responsibility of the ordering physician, who should also refer to a patient's baseline hemoglobin level when a previous measurement is available.

Formal definitions of anemia do not always address the complex relationship between hemoglobin level and health outcomes because only a few prospective studies have addressed this issue.[17,18] One such study was the Women's Health and Aging Study I, in which investigators followed a cohort of community-dwelling women with moderate to severe disability at the time of enrollment; 686 of these women underwent baseline hemoglobin measurement.[17] The mortality rate over the follow-up period was higher in anemic patients and steadily decreased up to a hemoglobin threshold of 13.9 g/dL (to convert to g/L [SI unit], multiply by 10). The Cardiovascular Health Study followed 5888 community-dwelling US adults 65 years or older for a median of 11.2 years,[19] and the investigators described a reverse-J-shaped relationship between baseline hemoglobin level and mortality rate (Figure 3). Those with hemoglobin measurements in the next-to-highest quintile had the best survival rate; those in the lowest quintile (<13.7 g/dL for men and <12.6 g/dL for women) had the worst. The mortality rate was also increased among the patients in the lowest quintile who would not be classified as anemic by WHO criteria; 8.5% of patients in the study, representing 7.0% of the white and 17.6% of the black study patients, met WHO criteria for anemia.[19] Therefore, anemia might be better defined on the basis of a hemoglobin range associated with the best possible health outcomes, even if such a definition results in a much larger group of people being classified as anemic. More studies with careful control for confounding comorbidities are needed before such an approach can be endorsed.[18]

CONSEQUENCES OF ANEMIA OR A LOW-NORMAL HEMOGLOBIN CONCENTRATION

A growing body of medical literature supports the contention that mild anemia or a "low-normal" hemoglobin level is associated with a broad range of poorer health-related outcomes, both in specific disease entities and all-cause mortality for the general population. For example, patients with heart failure whose hemoglobin measurements are in the lowest quartile have more symptoms, poorer hemodynamics, and greater mortality than those with higher hemoglobin levels, and these differences are particularly marked in the elderly.[20-22] Increased mortality associated with ane-

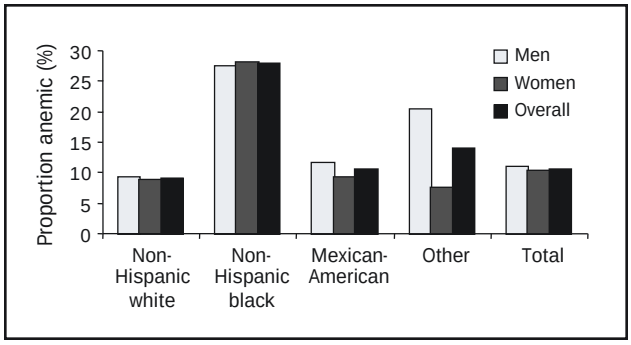

FIGURE 2. Prevalence of WHO-defined anemia in US patients aged 65 years or older, by self-declared racial or ethnic group. NHANES III = Third US National Health and Nutrition Examination Survey; WHO = World Health Organization. Data from NHANES III, 1988-1994.[7,8]

TABLE 1. **Comparison of Proposed Definitions of Lower Limit of Normal Blood Hemoglobin Concentration***

Population	WHO (1968)	NHANES III (1994)	Scripps-Kaiser (2006)	Mayo Clinic CCL (2007)
White men (g/dL)	13.0	13.8†	13.7‡	13.5
Black men (g/dL)	NRS	12.8	12.9	NRS
White women (g/dL)	12.0§	12.2	12.2	12.0
Black women (g/dL)	NRS	11.3	11.5	NRS

*SI conversion factor: to convert hemoglobin value to g/L, multiply by 10. CCL = Central Clinical Laboratory; NHANES III = Third US National Health and Nutrition Examination Survey; NRS = not reported separately; WHO = World Health Organization.
†Values in this column refer to the lowest 5% of actual NHANES III population distribution. The 5% threshold for the normal Gaussian distribution differs by less than 0.2 g/dL in each group. The range given here is for the group aged 20 to 59 years.
‡Proposed range for the group aged 20 to 59 years, also based on the 5% actual distribution in the population. In the group aged 60 years and older, the proposed lower limit for white men was 13.2 g/dL and for black men 12.7 g/dL. The proposed range does not differ by age for adult women.
§Value is for nonpregnant adult women. The WHO recommended defining anemia in pregnant women as a hemoglobin level of less than 11.0 g/dL. Reported to 2 significant digits, WHO numbers did not distinguish normal levels based on age.
Data from references.[7,9,10,12]

mia is also well described in cancer,[23] human immunodeficiency virus infection (independently of viral load),[24] and several other medical conditions.

However, it is often unclear to what extent these poor outcomes are due to the effects of the anemia itself. Anemia can be a marker for more severe disease or an indicator of lower likelihood to respond to current therapies. For instance, radiotherapy for cancer depends on adequate oxygen delivery by hemoglobin for optimal tumor cell killing. Another caveat is that anemia may affect outcome more in some patient groups than others. For example, one study found a significant association between anemia and decreased mobility and poorer survival in 1583 white patients but not in 1018 black patients.[25] A large Japanese study also found no correlation between anemia and disability.[26]

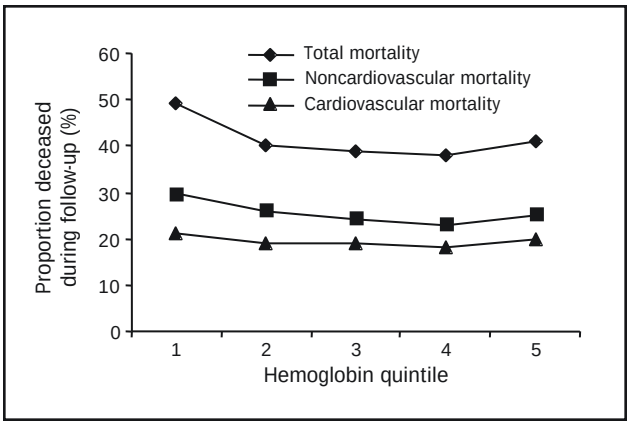

FIGURE 3. Unadjusted mortality rate over 11.2 years from the Cardiovascular Health Study, ranked by hemoglobin quintiles. *P* values for differences across quintiles were <.001 for total mortality, <.001 for noncardiovascular mortality, and .002 for cardiovascular mortality. The lowest quintile was a hemoglobin level less than 13.7 g/dL for men and less than 12.6 g/dL for women. SI conversion factor: to convert hemoglobin value to g/L, multiply by 10. Adapted from *Arch Intern Med*,[19] with permission from the American Medical Association. All rights reserved.

The potential negative impact of a low hemoglobin level on performance status, physiology, and functional independence appears to be highest in elderly patients. Among those older than 65 years, anemia has been associated with increased frailty,[27] poorer exercise performance,[28] diminished cognitive function,[29] risk of developing dementia,[30] decreased mobility,[31] increased risk of recurrent falls,[32,33] lower bone density and skeletal muscle density,[34,35] and an increased rate of major depression.[36] A 4-year National Institute of Aging–sponsored prospective study of 3607 persons aged 71 years and older looked specifically at hospitalization rates: compared with the non-anemic cohort, the 451 (12.5%) patients who were anemic at baseline (using the WHO anemia definitions) spent almost twice as many days in the hospital (25.0 vs 13.7 days; $P<.001$) and were hospitalized more frequently (65.9% vs 54.6%; $P<.001$).[37] Furthermore, when older patients are in the hospital, anemia is a risk factor for delirium.[38]

A Dutch study of 1016 community-dwelling adults aged 85 years and older found that WHO-defined anemia was also strongly associated with all-cause mortality, even in those without known comorbidities at the beginning of the study.[39] Data on 618 patients from Olmsted County, the county in which Mayo Clinic Rochester is located, corroborate these findings. The Olmsted County cohort included sicker, nonambulatory patients and residents of skilled nursing facilities, who have much higher rates of

anemia than the community-dwelling elderly (48% by WHO definition in a 900-patient study of the National Geriatrics Research Consortium[40]) and were not included in NHANES III.[41]

The health-related outcome differential between groups with higher or lower hemoglobin concentrations is more striking for white than for black populations, perhaps reflecting distinct hemoglobin distributions among ethnic groups.[14] The reasons for these differences in hemoglobin ranges by ethnic origin are complex and may be independent of socioeconomic factors.[14] Hemoglobin ranges are approximately 1 g/dL lower in black than in white populations matched for age and sex, which is partly attributable to the high incidence of α-thalassemia alleles in the former group. Only a few studies of normal hemoglobin ranges in black populations have adequately accounted for α thalassemia, which requires molecular genetic assays to diagnose definitively and is not easily detectable by hemoglobin electrophoresis.[42] In the Scripps-Kaiser database, approximately one third of the difference between the hemoglobin levels of black and white participants could be accounted for by the –3.7-kilobase α-thalassemia deletion. Sickle cell trait and creatinine levels did not contribute to these differences.[14] Although not yet attributed to a given cause, the remaining two thirds of the difference could reflect dietary and genetic factors.

PREVALENCE AND CAUSES OF ANEMIA IN THE ELDERLY

An extremely high number of elderly persons could potentially have lower than desirable hemoglobin levels. If the entire bottom quartile of hemoglobin values is associated with suboptimal outcomes, then more than 9 million elderly US citizens have a hemoglobin level that is less than ideal. When integrated, the conservative definitions of anemia of the WHO, the NHANES III findings (10.6% overall anemia rate for the population aged 65 years and older), and US Census estimates (36.3 million people aged 65 years and older) reveal that almost 4 million elderly Americans are anemic. However, nearly all anemias in the elderly are mild. Fewer than 3% of the NHANES III participants aged 65 years and older had a hemoglobin level less than 11.0 g/dL, and only 1.3% of those whose anemia was unexplained had a hemoglobin level less than 10.0 g/dL.[7]

One of the challenges of studying anemia in the elderly is the diversity of potential contributing etiologies, both those that are well understood and those that remain speculative. In an attempt to identify the most likely etiology of anemia, the laboratory component of NHANES III included measurements of total iron-binding capacity as well as whole blood folate, vitamin B_{12}, serum iron, ferritin, free erythrocyte protoporphyrin (sensitive to iron deficiency), C-reactive protein, plasma glucose, creatinine, and rheumatoid factor levels.[7] Serum erythropoietin (Epo) levels were not measured.

Nutritional Anemia

In the NHANES III study, nutrient deficiency was suspected in approximately one third of the cases of anemia in elderly persons.[7] Most of these cases were attributed to iron deficiency, including chronic blood loss. However, folate deficiency (related to excessive alcohol use and malnutrition) and vitamin B_{12} deficiency (primarily related to atrophic gastritis) are also causes of nutritional anemia and warrant routine screening (see Diagnosis and Management, Step 1).[43-45] Although fortification of foodstuffs has made folate deficiency less common in the US population as a whole, more than 10% of elderly persons have borderline or low vitamin B_{12} levels.[43,45]

Anemia of Renal Insufficiency or Chronic Inflammation

Renal insufficiency, another easily treatable cause of anemia in the elderly, accounts for approximately 8% of the NHANES III cases. Less easily treated is the anemia of chronic inflammation (also known as the anemia of chronic disease), which was suspected in more than 20% of cases in NHANES III, either in isolation or in conjunction with renal insufficiency.[7] The contribution of chronic inflammation to anemia is hard to gauge because of the lack of an adequately sensitive and specific test to measure the type of cytokine-mediated inflammation that is associated with bone marrow suppression.

The effect of blunted hypoxia-sensing and defective Epo secretion on the lower hemoglobin values seen in older adults remains a subject of debate. Healthy elderly persons retain the ability to generate adequate amounts of Epo in response to phlebotomy.[46] However, several longitudinal studies have found that serum Epo levels increase slowly and modestly with aging as long as renal function is preserved, suggesting a need for slightly higher Epo levels to maintain a physiologic set point in old age.[47,48] Erythropoietin levels may indeed be lower than anticipated in some anemic elderly patients,[49] perhaps because creatinine-based estimates of glomerular filtration do not reliably correlate with endocrine renal function. However, little evidence exists at present for a widespread defect in Epo production or diminished sensitivity to hypoxia in older persons.

Myelodysplastic Syndrome

Primary disorders of hematopoiesis are more common in people aged 65 years and older than in younger people,

TABLE 2. **Features Suggestive of a Primary Hematological Disorder Such As Myelodysplastic Syndrome, a Myeloproliferative Disorder, or Leukemia**

History and physical examination
Splenomegaly or unexplained lymphadenopathy
Constitutional symptoms
Unexplained fevers
Unintentional weight loss
Drenching night sweats
Bone pain
History of treatment with chemotherapy (especially alkylating agents) or exposure to ionizing radiation
Laboratory findings
Neutropenia or thrombocytopenia, in addition to anemia
Oval macrocytosis in the absence of nutritional deficiency, regular alcohol use, or exposure to causative drugs
Relative or absolute monocytosis
Basophilia
Appearance of atypical cells on a peripheral blood smear
Early myeloid cells (preneutrophilic band stage)
Hypogranular or otherwise dysmorphic neutrophils
Large or hypogranular platelets
Dacrocytes

especially the myelodysplastic syndrome (MDS), which has a median age of onset in the seventh decade of life. Clinical and laboratory features suggestive of either MDS or another neoplastic myeloid disorder are listed in Table 2. Because MDS can be associated with normocytic or macrocytic anemia (rarely, microcytic[50]) and because the early morphologic changes characteristic of MDS can be subtle and difficult for hematopathologists to appreciate[51,52] (especially when only the erythroid lineage is involved), many cases of unexplained anemia in the elderly population may actually be indolent forms of MDS. This hypothesis has been confirmed in several small series, including 1 from the geriatric department of an Israeli hospital where 15% of inpatients with unexplained cytopenias, macrocytosis, or monocytosis ultimately proved to have MDS.[53,54] However, in the absence of a sensitive genetic marker for diagnosing MDS, the true prevalence of MDS in the unexplained anemia group remains uncertain, and the question must be revisited when molecular diagnostic testing for MDS improves.

Other Causes of Anemia in the Elderly

Medication and ethanol use are important contributors to anemia in the elderly, but the relative contribution of each is often unclear in the individual patient because suppression of erythropoiesis may be idiosyncratic and complicated by comorbidities. Low testosterone levels are common in the general population, especially in elderly men, but appear unlikely to be a major contributor to the overall burden of anemia.[55] Sarcopenia has also been proposed as a contributing factor to anemia[4] because decreased skeletal muscle mass is closely associated with anemia in the elderly,[35] but there is no mechanistic evidence at present.

Many cases of anemia in the elderly remain unexplained, and the causes are likely heterogeneous. Most of these patients have low C-reactive protein and interleukin 6 levels, and so their anemia is probably not due to occult inflammation.[49] Some of these patients probably have MDS. The normal age-associated reduction in bone marrow cellularity is another potential but unproven contributor to unexplained anemia. Age-dependent loss of hematopoietic clones, detected by molecular assays of clonality,[56] has been attributed by some investigators to *stem cell fatigue*, ie, a progressive demise of long-lived pluripotential hematopoietic stem cells due to senescence.

DIAGNOSIS AND MANAGEMENT

Once an elderly patient's symptoms or incidental blood test has led to the discovery of anemia, many of the same principles of anemia diagnosis and treatment apply as for a younger patient.[57,58] A practical diagnostic algorithm is presented in Figure 4.

Step 1. Use the Mean Corpuscular Volume to Narrow Differential Diagnosis and Determine Initial Tests

The mean corpuscular volume (MCV) is 1 of the most diagnostically useful parameters for evaluating anemia in younger and older populations alike. However, the presence of coexisting disorders with opposite effects on the MCV (eg, iron deficiency and alcohol abuse) should be kept in mind. A low MCV is strongly suggestive of iron deficiency anemia, especially if it is an acquired abnormality; a congenitally low MCV suggests thalassemia. However, because iron deficiency anemia can occur with normal MCV, serum ferritin measurement is recommended as 1 of the first tests for microcytic or normocytic anemia in the elderly. Occult gastrointestinal (GI) bleeding, which remains a major cause of anemia in older patients, must be ruled out. Dietary iron deficiency is rare in the United States, and therefore serologic evidence of iron deficiency (eg, ferritin <20 ng/mL [to convert to pmol/L {SI unit}, multiply by 2.247]) mandates consideration of anatomic evaluation of the GI tract. Higher ferritin values may still be consistent with iron deficiency, especially if an inflammatory condition coexists. For patients with normal findings on an initial GI evaluation, repeated testing may be indicated if they continue to be iron deficient despite iron replacement therapy. Ferritin is an imperfect measurement of iron deficiency, and ferritin measurement may need to be supplemented by other tests (eg, soluble transferrin receptor assay).

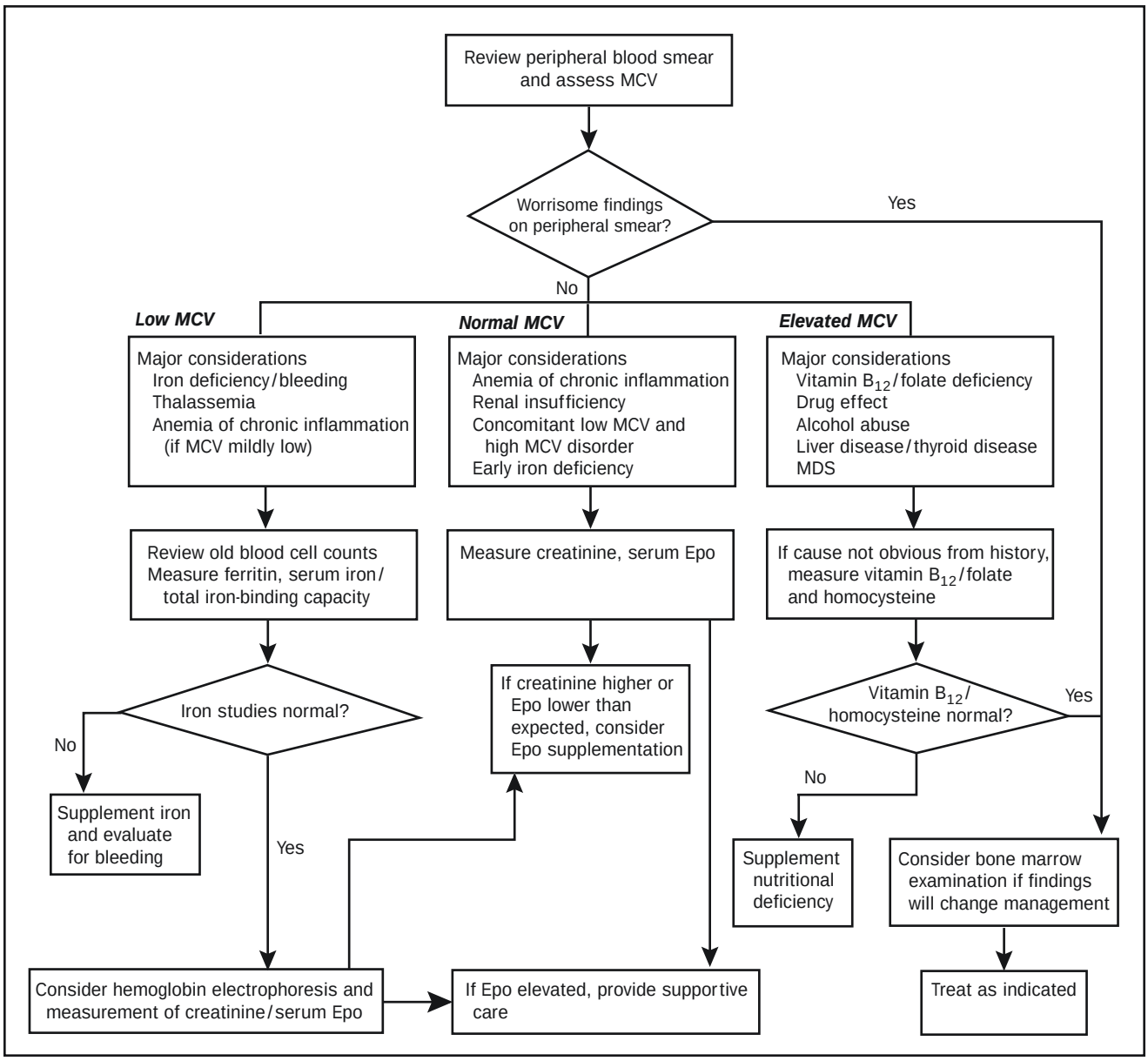

FIGURE 4. A proposed algorithm for evaluation of low hemoglobin in older patients. Epo = erythropoietin; MCV = mean corpuscular volume; MDS = myelodysplastic syndrome.

Similarly, an increased MCV warrants measurement of serum homocysteine and vitamin B_{12} levels to evaluate for either vitamin B_{12} or folate deficiency. For borderline vitamin B_{12} levels (at the lower end of the "normal" range), assessment of methylmalonic acid may confirm tissue-level vitamin B_{12} deficiency. In normocytic anemia, initial tests should include determination of serum creatinine and Epo levels. Macrocytic anemia that cannot be attributed to either drug effect or vitamin B_{12}/folate deficiency should raise the possibility of MDS, but liver disease or alcohol abuse must always be considered as alternative explanations for the macrocytosis.

Step 2. Carefully Evaluate the Need for Bone Marrow Examination

The generalist may find it difficult to decide whether and when to refer the mildly anemic patient to a hematologist for a bone marrow aspiration and biopsy with cytogenetic analysis. In making this decision, the physician should evaluate the clinical context and consider whether the

findings from such tests would likely alter the course of treatment.

Once other frequent causes of anemia have been excluded, the most common finding on marrow examination would likely be either MDS or a nondiagnostic marrow aspirate suspicious for possible MDS. The myelodysplastic syndrome is only curable via allogeneic stem cell transplantation, which is a difficult undertaking at any age and particularly perilous for patients older than 60 years.[59] Additionally, the 3 Federal Drug Administration–approved therapies for MDS (lenalidomide, azacitidine, and decitabine) cause substantial neutropenia and thrombocytopenia and have not been proved to extend overall survival. Thus, bone marrow examination would be unlikely to alter clinical management in most elderly patients with anemia due to MDS because they would be candidates only for therapy with hematopoietic growth factors, and their likelihood of response to epoetin alfa or darbepoetin alfa therapy can be determined by measuring their serum Epo levels (highest likelihood of response, Epo <100 IU/L; unlikely to respond, Epo >500 IU/L).[60] However, MDS is not the only diagnostic possibility for unexplained anemia; multiple myeloma and other serious disorders can also present as mild anemia. Therefore, the decision to refer a patient for marrow examination should be made on an individual basis.

Step 3. Avoid the Indiscriminate Use of Epo Therapy for Mild Anemia

At present, there are no clinical guidelines to suggest how best to manage older patients with mild anemia, or even whether such anemia can or should be "managed" without correction of the underlying etiology. Those with nutritional deficiency (iron, vitamin B_{12}, folate) or severe anemia due to renal failure or inflammation should, of course, receive supplementation with the deficient nutrient or with recombinant Epo, respectively. However, the proper approach to patients with unexplained anemia is more difficult to determine, especially if that anemia is relatively mild and the patient is not clearly symptomatic.

Transfusion of red blood cells reliably increases hemoglobin levels, but the risks of transfusion (eg, acute reactions, infections, volume overload, systemic iron overload) are such that long-term transfusion is not a real consideration in patients with a baseline hemoglobin greater than 10 g/dL. Before the advent of recombinant erythropoiesis-stimulating agents (ESAs) (epoetin alfa and darbepoetin alfa), androgens such as testosterone and fluoxymesterone were widely used for anemia of any cause, including unexplained anemia in elderly patients. However, androgens are less effective than ESAs at augmenting hemoglobin and are associated with a broad range of systemic adverse events (eg, hirsutism, acne, testicular atrophy, peliosis hepatis, elevated hepatocellular cancer risk, and stimulation of androgen-sensitive malignancies such as prostate cancer). Therefore, androgens are less commonly used today, and their appropriate role in unexplained anemia in elderly patients is unclear.

A small placebo-controlled prospective trial demonstrated that ESAs increase hemoglobin levels and quality-of-life measurements in elderly patients with anemia (median hemoglobin of study participants, 10.5 g/dL), including unexplained anemia.[61] However, the widespread use of ESAs in elderly patients with mild anemia cannot be recommended without more evidence from prospective trials, both because it would be exceedingly expensive in such a large patient group and because questions about the safety of ESAs have been raised. Since 2003, for instance, 5 studies in anemic patients with cancer receiving chemotherapy or radiotherapy have either been stopped early because of adverse events in the active ESA therapy arm, or, when completed, have showed negative effects with ESA therapy compared to placebo or supportive care alone.[62] In all 5 of these studies, the hemoglobin target was greater than 12.0 g/dL. A study of more than 900 patients with cancer-associated anemia that was not due to chemotherapy used a hemoglobin goal of 12.0 g/dL but was also stopped early because of poorer survival in the darbepoetin alfa arm.[63] Finally, in a randomized study of 1432 patients with anemia due to renal failure, those treated with epoetin alfa to reach a target hemoglobin level of 13.5 g/dL had more adverse events and no improvement in cardiac function compared with those treated to a target hemoglobin level of 11.3 g/dL.[64]

On March 9, 2007, the Federal Drug Administration added a black box warning to the package inserts for epoetin alfa and darbepoetin alfa recommending that patients not be treated to a hemoglobin level greater than 12.0 g/dL. Until further data are available, anemia in the elderly should be evaluated and remediable causes treated, but the anemia itself should not be treated unless the patient is severely symptomatic or in danger of needing a transfusion (eg, hemoglobin <10.0 g/dL).

CONCLUSION

Anemia in the elderly is an extremely common problem that is associated with increased mortality and poorer health-related quality of life, regardless of the underlying cause of the low hemoglobin. Future research is needed to define the optimal hemoglobin levels for health, to refine diagnostic testing to sort out the etiology of the unexplained anemias, and to evaluate rigorously therapies designed to augment erythropoiesis.

REFERENCES

1. Schrier SL. Hematology, ASH, and the anemia of the aged [editorial]. *Blood.* 2005;106:3341-3342.

2. Spivak JL. Anemia in the elderly: time for new blood in old vessels? [editorial]. *Arch Intern Med.* 2005;165:2187-2189.

3. Eisenstaedt R, Penninx BW, Woodman RC. Anemia in the elderly: current understanding and emerging concepts. *Blood Rev.* 2006 Jul;20: 213-226. Epub 2006 Feb 10.

4. Guralnik JM, Ershler WB, Schrier SL, Picozzi VJ. Anemia in the elderly: a public health crisis in hematology. *Hematology Am Soc Hematol Educ Program.* 2005:528-532.

5. US Census Bureau. Age data. Available at: www.census.gov/population /www/socdemo/age.html and www.census.gov/prod/2006pubs/07statab /pop.pdf. Accessed June 22, 2007.

6. Hobbs FB. The elderly population. Available at: www.census.gov/population /www/pop-profile/elderpop.html. Accessed June 22, 2007.

7. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* 2004 Oct 15;104:2263-2268. Epub 2004 Jul 6.

8. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics. Plan and operation of the Third National Health and Nutrition Examination Survey, 1988-94. *Vital Health Stat 1.* 1994 Jul;32:1-407.

9. World Health Organization. Nutritional anemia: report of a WHO Scientific Group. *World Health Organ Tech Rep Ser.* 1968;405:5-37.

10. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood.* 2006 Mar 1;107:1747-1750. Epub 2005 Sep 27.

11. Woodman R, Ferrucci L, Guralnik J. Anemia in older adults. *Curr Opin Hematol.* 2005;12:123-128.

12. Hollowell JG, van Assendelft OW, Gunter EW, Lewis BG, Najjar M, Pfeiffer C, Centers for Disease Control and Prevention, National Center for Health Statistics. Hematological and iron-related analytes—reference data for persons aged 1 year and over: United States, 1988-94. *Vital Health Stat 11.* 2005 Mar;247:1-156.

13. Beutler E, Felitti VJ, Koziol JA, Ho NJ, Gelbart T. Penetrance of 845G→A (C282Y) *HFE* hereditary haemochromatosis mutation in the USA. *Lancet.* 2002;359:211-218.

14. Beutler E, West C. Hematologic differences between African-Americans and whites: the roles of iron deficiency and alpha-thalassemia on hemoglobin levels and mean corpuscular volume. *Blood.* 2005 Jul 15;106:740-745. Epub 2005 Mar 24.

15. Ruiz-Arguelles GJ. Altitude above sea level as a variable for definition of anemia. [letter]. *Blood.* 2006;108:2131.

16. Nordenberg D, Yip R, Binkin NJ. The effect of cigarette smoking on hemoglobin levels and anemia screening. *JAMA.* 1990;264:1556-1559.

17. Chaves PH, Xue QL, Guralnik JM, Ferrucci L, Volpato S, Fried LP. What constitutes normal hemoglobin concentration in community-dwelling disabled older women? *J Am Geriatr Soc.* 2004;52:1811-1816.

18. Boehringer PA, Darden IL. The quest for the normal hemoglobin concentration [letter]. *Blood.* 2006;108:777.

19. Zakai NA, Katz R, Hirsch C, et al. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort: the Cardiovascular Health Study. *Arch Intern Med.* 2005;165:2214-2220.

20. Horwich TB, Fonarow GC, Hamilton MA, MacLellan WR, Borenstein J. Anemia is associated with worse symptoms, greater impairment in functional capacity and a significant increase in mortality in patients with advanced heart failure. *J Am Coll Cardiol.* 2002;39:1780-1786.

21. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure: the prospective randomized amlodipine survival evaluation (PRAISE). *J Am Coll Cardiol.* 2003;41:1933-1939.

22. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. *Circulation.* 2003;107:223-225.

23. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer.* 2001;91:2214-2221.

24. Fangman JJ, Scadden DT. Anemia in HIV-infected adults: epidemiology, pathogenesis, and clinical management. *Curr Hematol Rep.* 2005;4:95-102.

25. Patel KV, Harris TB, Faulhaber M, et al. Racial variation in the relationship of anemia with mortality and mobility disability among older adults. *Blood.* 2007 Jun 1;109:4663-4670. Epub 2007 Feb 6.

26. Ishine M, Wada T, Akamatsu K, et al. No positive correlation between anemia and disability in older people in Japan [letter]. *J Am Geriatr Soc.* 2005; 53:733-734.

27. Chaves PH, Semba RD, Leng SX, et al. Impact of anemia and cardiovascular disease on frailty status of community-dwelling older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci.* 2005;60:729-735.

28. Penninx BW, Guralnik JM, Onder G, Ferrucci L, Wallace RB, Pahor M. Anemia and decline in physical performance among older persons. *Am J Med.* 2003;115:104-110.

29. Chaves PH, Carlson MC, Ferrucci L, Guralnik JM, Semba R, Fried LP. Association between mild anemia and executive function impairment in community-dwelling older women: the Women's Health and Aging Study II. *J Am Geriatr Soc.* 2006;54:1429-1435.

30. Atti AR, Palmer K, Volpato S, Zuliani G, Winblad B, Fratiglioni L. Anaemia increases the risk of dementia in cognitively intact elderly. *Neurobiol Aging.* 2006;27:278-284.

31. Chaves PH, Ashar B, Guralnik JM, Fried LP. Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women: should the criteria currently used to define anemia in older people be reevaluated? *J Am Geriatr Soc.* 2002;50:1257-1264.

32. Penninx BW, Pluijm SM, Lips P, et al. Late-life anemia is associated with increased risk of recurrent falls. *J Am Geriatr Soc.* 2005;53:2106-2111.

33. Dharmarajan TS, Norkus EP. Mild anemia and the risk of falls in older adults from nursing homes and the community. *J Am Med Dir Assoc.* 2004; 5:395-400.

34. Cesari M, Pahor M, Lauretani F, et al. Bone density and hemoglobin levels in older persons: results from the InCHIANTI study. *Osteoporos Int.* 2005 Jun;16:691-699. Epub 2004 Sep 28.

35. Cesari M, Penninx BW, Lauretani F, et al. Hemoglobin levels and skeletal muscle: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci.* 2004;59:249-254.

36. Onder G, Penninx BW, Cesari M, et al. Anemia is associated with depression in older adults: results from the InCHIANTI study. *J Gerontol A Biol Sci Med Sci.* 2005;60:1168-1172.

37. Penninx BW, Pahor M, Woodman RC, Guralnik JM. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol A Biol Sci Med Sci.* 2006;61:474-479.

38. Joosten E, Lemiengre J, Nelis T, Verbeke G, Milisen K. Is anaemia a risk factor for delirium in an acute geriatric population? *Gerontology.* 2006;52:382-385. Epub 2006 Aug 17.

39. Izaks GJ, Westendorp RG, Knook DL. The definition of anemia in older persons. *JAMA.* 1999;281:1714-1717.

40. Artz AS, Fergusson D, Drinka PJ, et al. Prevalence of anemia in skilled-nursing home residents. *Arch Gerontol Geriatr.* 2004;39:201-206.

41. Ania BJ, Suman VJ, Fairbanks VF, Rademacher DM, Melton LJ III. Incidence of anemia in older people: an epidemiologic study in a well defined population. *J Am Geriatr Soc.* 1997;45:825-831.

42. Jackson RT, Jackson FL. Reassessing 'hereditary' interethnic differences in anemia status. *Ethn Dis.* Winter 1991;1:26-41.

43. Green R, Miller JW. Vitamin B_{12} deficiency is the dominant nutritional cause of hyperhomocysteinemia in a folic acid-fortified population. *Clin Chem Lab Med.* 2005;43:1048-1051.

44. Andres E, Loukili NH, Noel E, et al. Vitamin B_{12} (cobalamin) deficiency in elderly patients. *CMAJ.* 2004;171:251-259.

45. Loikas S, Koskinen P, Irjala K, et al. Vitamin B_{12} deficiency in the aged: a population-based study. *Age Ageing.* 2007 Mar;36:177-183. Epub 2006 Dec 21.

46. Goodnough LT, Price TH, Parvin CA. The endogenous erythropoietin response and the erythropoietic response to blood loss anemia: the effects of age and gender. *J Lab Clin Med.* 1995;126:57-64.

47. Ble A, Fink JC, Woodman RC, et al. Renal function, erythropoietin, and anemia of older persons: the InCHIANTI study. *Arch Intern Med.* 2005;165: 2222-2227.

48. Ershler WB, Sheng S, McKelvey J, et al. Serum erythropoietin and aging: a longitudinal analysis. *J Am Geriatr Soc.* 2005;53:1360-1365.

49. Ferrucci L, Guralnik JM, Bandinelli S, et al. Unexplained anaemia in older persons is characterised by low erythropoietin and low levels of pro-inflammatory markers. *Br J Haematol.* 2007;136:849-855.

50. Steensma DP, Gibbons RJ, Higgs DR. Acquired alpha-thalassemia in association with myelodysplastic syndrome and other hematologic malignancies. *Blood.* 2005 Jan 15;105:443-452. Epub Sep 9.

51. Steensma DP, Dewald GW, Hodnefield JM, Tefferi A, Hanson CA. Clonal cytogenetic abnormalities in bone marrow specimens without clear morphologic evidence of dysplasia: a form fruste of myelodysplasia? *Leuk Res.* 2003;27:235-242.

52. Steensma DP, Tefferi A. The myelodysplastic syndrome(s): a perspective and review highlighting current controversies [published correction appears in *Leuk Res.* 2005;29:117]. *Leuk Res.* 2003;27:95-120.

53. Mahmoud MY, Lugon M, Anderson CC. Unexplained macrocytosis in elderly patients. *Age Ageing.* 1996;25:310-312.

54. Beloosesky Y, Cohen AM, Grosman B, Grinblat J. Prevalence and survival of myelodysplastic syndrome of the refractory anemia type in hospitalized cognitively different geriatric patients. *Gerontology.* 2000;46:323-327.

55. Ferrucci L, Maggio M, Bandinelli S, et al. Low testosterone levels and the risk of anemia in older men and women. *Arch Intern Med.* 2006;166:1380-1388.

56. Gale RE, Fielding AK, Harrison CN, Linch DC. Acquired skewing of X-chromosome inactivation patterns in myeloid cells of the elderly suggests stochastic clonal loss with age. *Br J Haematol.* 1997;98:512-519.

57. Tefferi A. Practical algorithms in anemia diagnosis [letter]. *Mayo Clin Proc.* 2004;79:955-956.

58. Tefferi A, Hanson CA, Inwards DJ. How to interpret and pursue an abnormal complete blood cell count in adults. *Mayo Clin Proc.* 2005;80:923-936.

59. Wallen H, Gooley TA, Deeg HJ, et al. Ablative allogeneic hematopoietic cell transplantation in adults 60 years of age and older. *J Clin Oncol.* 2005 May 20;23:3439-3446. Epub 2005 Apr 11.

60. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al, Scandanavian MDS Group. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. *Br J Haematol.* 2003;120:1037-1046.

61. Agnihotri P, Ahuja M, Telfer MC, et al.Chronic anemia and fatigue in elderly patients: results of the first randomized double-blind placebo-controlled cross-over study with epoetin alfa [abstract]. *Blood.* 2005;106. Abstract 3553.

62. Crawford J. Erythropoietin: high profile, high scrutiny [editorial]. *J Clin Oncol.* 2007 Mar 20;25:1021-1023. Epub 2007 Feb 20.

63. Glaspy J, Smith R, Aapro M, et al. Results from a phase III, randomized, double-blind, placebo-controlled study of darbepoetin alfa (DA) for the treatment of anemia in patients not receiving chemotherapy or radiotherapy [abstract]. Presented at: American Association for Cancer Research Annual Meeting; Los Angeles, CA; April 17, 2007. Abstract LB-3.

64. Singh AK, Szczech L, Tang KL, et al, CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med.* 2006; 355:2085-2098.