

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

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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.

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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).

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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

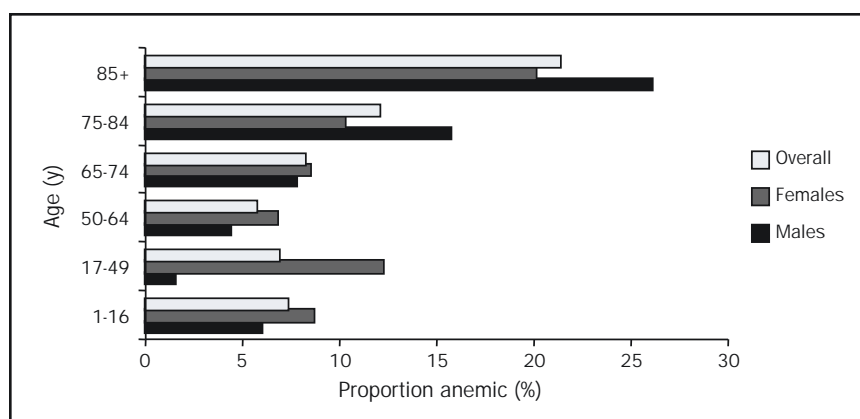


FIGURE 1. Prevalence of WHO-defined anemia (hemoglobin <13.0 g/dL for males and <12.0 g/dL for nonpregnant females) in the United States, by age and sex. SI conversion factor: to convert hemoglobin value to g/L, multiply by 10. NHANES III = Third US National Health and Nutrition Examination Survey; WHO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

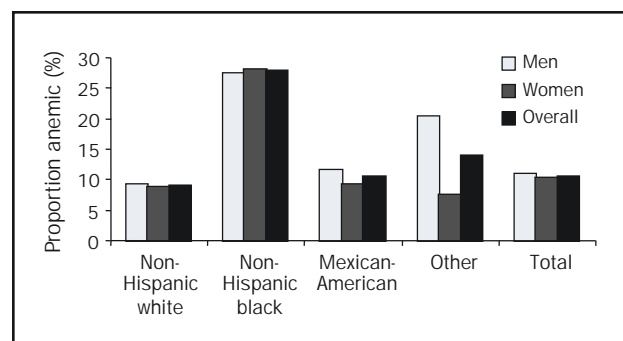


FIGURE 2. Prevalence of WHO-defined anemia in US patients aged 65 years or older, by self-declared racial or ethnic group. NHANES III = Third US National Health and Nutrition Examination Survey; WHO = World Health Organization. Data from NHANES III, 1988-1994.^{7,8}

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

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

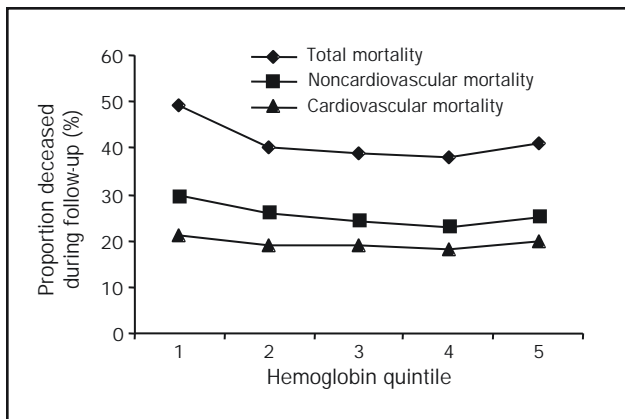


FIGURE 3. Unadjusted mortality rate over 11.2 years from the Cardiovascular Health Study, ranked by hemoglobin quintiles. P values for differences across quintiles were $< .001$ for total mortality, $< .001$ for noncardiovascular mortality, and $.002$ for cardiovascular mortality. The lowest quintile 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.

anemia than the community-dwelling elderly (48% by WHO definition in a 900-patient study of the National Geriatrics Research Consortium⁴⁰) 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. Sick 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 B₁₂, 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 B₁₂ 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 B₁₂ 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
Dacryocytes

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, microcytic⁵⁰) 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 anemia⁴ 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).

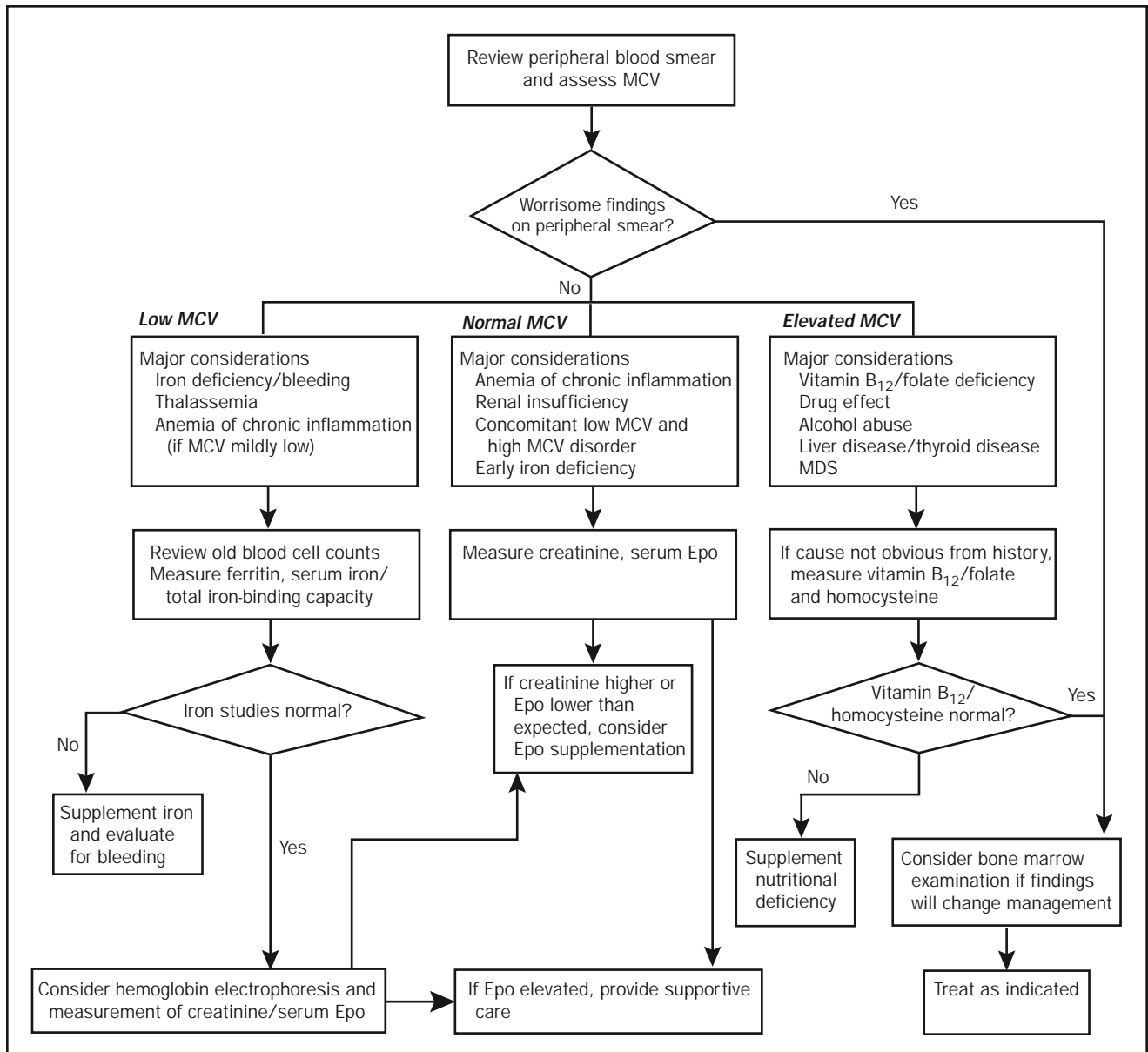


FIGURE 4. A proposed algorithm for evaluation of low hemoglobin in older patients. Epo = erythropoietin; MCV = mean corpuscular volume; MDS = myelodysplastic syndrome.

Similarly, an increased MCV warrants measurement of serum homocysteine and vitamin B₁₂ levels to evaluate for either vitamin B₁₂ or folate deficiency. For borderline vitamin B₁₂ levels (at the lower end of the “normal” range), assessment of methylmalonic acid may confirm tissue-level vitamin B₁₂ 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 B₁₂/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 B₁₂, 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.

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