

# Anemia in an Aging Population

REBECCA J LAUDICINA

**ABBREVIATIONS:** ACD = anemia of chronic disease; CBC = complete blood count; CHr = reticulocyte hemoglobin; EPO = erythropoietin; HGB = hemoglobin; HCT = hematocrit; IDA = iron deficiency anemia; MA = megaloblastic anemia; MCV = mean cell volume; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; RDW = red cell distribution width; RET = reticulocyte count; SI = serum iron; sTR = serum transferrin receptor; TIBC = total iron binding capacity; TS = transferrin saturation.

**INDEX TERMS:** anemia; anemia of chronic disease; elderly; iron deficiency anemia.

Clin Lab Sci 2008;21(4):232

## LEARNING OBJECTIVES

1. State the World Health Organization criteria for defining anemia and discuss issues related to this definition.
2. Compare the prevalence of anemia in a variety of subgroups in persons over age 65.
3. Discuss the physical, cognitive, and economic impact of anemia in the elderly.
4. Characterize the major causes of anemia in the geriatric population.
5. Explain laboratory tests and results useful in identifying the cause of anemia in the elderly.

*Rebecca J Laudicina PhD is professor, Clinical Laboratory Science, Department of Allied Health Sciences, The University of North Carolina at Chapel Hill, Chapel Hill NC.*

*The Focus section seeks to publish relevant and timely continuing education for clinical laboratory practitioners. Section editors, topics, and authors are selected in advance to cover current areas of interest in each discipline. Readers can obtain continuing education credit (CE) through P.A.C.E.® by completing the continuing education registration form, recording answers to the examination, and mailing a photocopy of it with the appropriate fee to the address designated on the form. Suggestions for future Focus topics and authors, and manuscripts appropriate for CE credit are encouraged. Direct all inquiries to the Clin Lab Sci Editorial Office, IC Ink, 858 Saint Annes Drive, Iowa City IA 52245. (319) 354-3861, (319) 338-1016 (fax). ic.ink@mchsi.com*

*Address for Correspondence: Rebecca J Laudicina PhD, Division of Clinical Laboratory Science, 4110 Bondurant Hall, CB#7145, The University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7145. (919) 843-4350. Rebecca\_Laudicina@med.unc.edu*

*Rebecca J Laudicina PhD is the Focus: Anemia in Selected Populations guest editor.*

Demographic data combined with the results of recent studies indicate that anemia is a significant health concern for our aging population. As of 2006, more than 37 million people in the United States are over age 65 with that number expected to reach 80 million by the year 2050.<sup>1,2</sup> More than 10% of all individuals above age 65 have anemia. Furthermore, the prevalence of anemia increases with age, making our oldest seniors even more likely to develop anemia during their lifetimes.<sup>3</sup> The significance of these facts led to a special symposium, "Anemia and the Elderly: A Public Health Crisis in Hematology", conducted at the 2005 meeting of the American Society of Hematology.<sup>4</sup>

Although the presence of anemia may reflect an underlying or undetected medical condition, anemia is also an independent risk factor for morbidity and mortality in an array of disorders common to seniors, including cancer, renal disease, and heart disease.<sup>5</sup> Furthermore, anemia affects physical and mental functioning and interferes with the ability to conduct activities of daily living, thus affecting quality of life. Because the elderly, defined by the US Census Bureau as persons over age 65, is the fastest growing segment of the US population, anemia may be projected to have an increasing impact on our healthcare system.<sup>2</sup>

In spite of these facts, anemia in elderly patients may be overlooked in medical evaluations due to similarity of symptoms with other disorders and lack of awareness of its prevalence. Diagnosis of anemia and determination of its cause are highly dependent on the results of clinical laboratory assays. Selecting appropriate laboratory tests in an informed manner is an important consideration for quality healthcare. Clinical laboratory scientists must be prepared to take the lead in advising other health care providers on selection and interpretation of relevant assays when anemia is a possibility.

**DEFINING ANEMIA IN THE ELDERLY**

Defining anemia in the elderly is important for clinical decision making, yet what appears to be a simple matter is actually complicated by current lack of consensus about appropriate reference intervals. Traditionally, anemia in the general population has been defined by criteria developed by the World Health Organization (WHO) in 1968.<sup>6</sup> Anemia is defined for adult males and adult females as hemoglobin (HGB) concentrations of <130 g/L and < 120 g/L, respectively. This seemingly straightforward definition may oversimplify what is actually a more complex situation. The original data upon which the WHO criteria are based were collected from a relatively small, non-elderly population. Because some studies have demonstrated modest differences in HGB between younger and older adults, there are questions about what constitutes appropriate reference intervals for seniors. Several experts have suggested it is time to abandon the outdated WHO standards for newer definitions of anemia based on recent studies of the elderly.<sup>5</sup>

There is some evidence that blood HGB levels may decline slightly with age. In a longitudinal study of elderly Swedes, mean HGB declined from 140 to 138 g/L in healthy women and from 152 to 141 g/L in healthy men between ages 70 and 88.<sup>7</sup> Another study showed that although HGB levels were slightly lower in hospitalized adults (mean age 70) than in younger healthy controls (mean age 36), other RBC measures including hematocrit (HCT), mean cell hemoglobin (MCH), and red cell distribution width (RDW) were equivalent. Mean cell volume (MCV) was slightly but significantly higher for geriatric patients than for younger controls. When WHO anemia criteria were applied to the geriatric, hospitalized population, 72% of patients were classified as anemic. When lower anemia criteria (120 g/L for males and 115 g/L for females) were arbitrarily applied to the same data, only 61% of the geriatric patients were classified as anemic. Comparison of erythrocyte parameters of the newly defined anemic geriatric group to the younger non-anemic controls indicated no significant differences in HCT, MCH, RDW, or MCV.<sup>8</sup> The results of these studies suggest that HGB concentration may decline slightly with age, and therefore reference intervals specific to geriatric populations are needed. To apply WHO anemia criteria to people of advanced age may, therefore, overestimate the number who are truly anemic and may lead to unnecessary medical treatment.

Data from the Women's Health and Aging Study were used to evaluate the clinical appropriateness of the WHO anemia

criteria by investigating the relationship between HGB concentration and mobility function in female participants age  $\geq$  65. Although a consistent trend of improvement in mobility performance was found to correspond to increasing HGB levels, the study authors noted that even at low-normal HGB concentrations (12-13 g/dL), there was an adverse effect on mobility, leading the authors to question the appropriateness of the WHO definition of anemia for an older population.<sup>9</sup> In a second study by the same authors, it was found that higher HGB levels were associated with lower risk of mortality for disabled women age  $\geq$  65, and that even in the low-normal range, there was an increased risk of mortality.<sup>10</sup> Results of both studies raise concerns about the appropriateness of using WHO criteria when evaluating the elderly for anemia, in this case suggesting that the number clinically affected by anemia may be underestimated.

In support of the WHO criteria, a 10-year longitudinal study of community-based residents in the Netherlands found that anemia as defined by WHO criteria was associated with increased mortality risk for persons aged 85 and older. The mortality risk increased with lower HGB concentrations, and mortality from infectious and malignant diseases was higher in persons with anemia as defined by WHO criteria.<sup>11</sup> The authors of this study concluded that the WHO criteria for defining anemia are appropriate for the elderly and that low HGB concentrations may indicate underlying disease.

To date, revised criteria for defining anemia in the elderly have not been adopted and the WHO criteria are still widely used. Some clinical laboratories may use HGB reference intervals stratified by age, including a separate category for elderly patients.

**EPIDEMIOLOGY OF ANEMIA IN THE ELDERLY**

Anemia has been shown to be a common disorder in the elderly, and its prevalence increases with age. Data from the Third National Health and Nutrition Examination Survey 1988-1994 (NHANES III) revealed that 11.0% of non-institutionalized men and 10.2% of women over age 65 are anemic as defined by WHO anemia criteria.<sup>3</sup> Other studies confirm these findings or show that the prevalence may be even higher, especially in certain subgroups of the elderly.

The incidence of anemia was studied in 618 Minnesota residents aged  $\geq$  65. Using WHO criteria for anemia, the rate for men was 9.0% and the rate for women was 6.9%. In 75% of cases, anemia was detected in conjunction with hospitalization, but reason for admission was attributed to

anemia in only nine percent of subjects, leading the authors to conclude that the prevalence of anemia is four to six times higher than is suspected clinically.<sup>12</sup> Other studies have similarly documented a higher prevalence of anemia in elderly men than in women. This finding is in contrast to anemia prevalence for younger age groups. In persons < 55, anemia is more common in women than men.

There is also an increasing prevalence of anemia with advancing age. In community dwelling men aged ≥ 85, the prevalence of anemia was found to be 44.4%. Furthermore, the prevalence of anemia in community dwelling females is greater than the prevalence in patients referred to a medical center, suggesting that anemia may be unrecognized in a substantial portion of elderly persons.<sup>13</sup> Anemia is especially common in nursing home residents. In a study of 900 residents of skilled-nursing homes, 48% were found to be anemic by WHO criteria. The mean age of participants in this study was 79 years.<sup>14</sup>

In an analysis of data from the Cardiovascular Health Study (CHS), prevalence of anemia was found to be higher in Black than White community dwellers age ≥ 65. Using WHO criteria, anemia was present in 7.0% of whites and 17.6% of black participants.<sup>15</sup> In the NHANES III study, the prevalence of anemia was found to be 27.8% in elderly Black Americans residing in the community.<sup>3</sup>

Variation in prevalence rates among studies may be attributed to differing criteria for defining anemia, differences in populations studied, or other variables.

### CONSEQUENCES OF ANEMIA IN THE ELDERLY

Although in the majority of cases anemia in the elderly is mild, its impact on morbidity, mortality, and healthcare costs is significant. Several studies have implicated anemia as an independent risk factor for a variety of clinical conditions and other adverse outcomes in community dwelling adults, hospitalized patients, and residents in long term care facilities.

In a study of 17,030 community dwelling adults age ≥ 66, anemia defined as HGB < 110g/L was associated with increased risk of hospitalization and death over a three year period. Anemia was associated with first hospitalization for all causes and with hospitalization attributed to cardiovascular causes. A five-fold increased risk of mortality was found for study participants with HGB levels < 110 g/L.<sup>16</sup> A similar association between low HGB and increased mortality risk

was observed in the Cardiovascular Health Study.<sup>15</sup> In both studies, data was adjusted to control for other co-morbid conditions common to older adults, thus confirming that anemia is an independent risk factor. Anemia was shown to be an independent predictor of death and major adverse clinical events among elderly patients with stable symptomatic coronary artery disease. Anemic patients in this study were more likely than non anemic patients to be older and more likely have chronic renal failure and diabetes.<sup>17</sup> Anemia in community dwelling adults ≥65 was associated with an increased number of hospitalizations, more days spent in the hospital, and increased mortality rates.<sup>18</sup>

Anemia also negatively affects physical and neurologic functions. Anemia is associated with physical disability related to activities of daily living, inferior physical performance, and decreased muscle strength in community dwellers age ≥ 65. Performance measures showing decrements in anemic elders included standing balance, repetitive sitting and rising from a chair, and walking eight feet.<sup>19</sup> In women aged 70 to 80, mobility difficulty increased with declining HGB levels.<sup>9</sup> In hospitalized patients who had recently undergone hip fracture surgery, those with HGB values < 100 g/L were less able to walk independently post-operatively and anemia interfered with post-operative rehabilitation.<sup>20</sup> Anemia has also been shown to increase the risk of falls in older adults living in the community, those who are hospitalized, and those in long-term care facilities.<sup>21</sup> Anemia was found to be an independent risk factor for delirium in hospitalized geriatric males.<sup>22</sup> Depression and cognitive impairment are frequently reported by elderly patients with anemia.<sup>23</sup>

Anemia in the elderly has economic impact. Untreated anemia in elderly patients with predialysis chronic kidney disease was associated with a significant increase in costs of medical care when compared to the cost of care for patients without anemia.<sup>24</sup> Costs of anemia include the direct costs of laboratory tests, treatment, and management of the patient with anemia. Because of the association of anemia with other medical conditions and with physical and cognitive impairment, the costs of anemia-related effects must also be considered. As the number of elderly in our society increases, so will the number of persons at risk for anemia and the healthcare expenditures needed for anemia treatment.<sup>25</sup>

### ETIOLOGY OF ANEMIA IN THE ELDERLY

Anemia in the elderly can be attributed to a variety of causes including anemia of chronic disease (anemia of inflammation), nutritional deficiencies, renal disease, acute or chronic

blood loss, hemolytic disorders, and others. In some studies, anemia in a significant subset of subjects is attributed to unknown or unexplained causes.

The third National Health and Nutrition Examination Survey 1988-1994 (NHANES III) provided data for a comprehensive study of the prevalence of anemia and its causes.<sup>3</sup> A HGB assay was performed as a screening test for anemia on 4,199 non institutionalized adults aged  $\geq 65$ , and tests used to classify the cause of anemia were performed (or calculated) on a subset of 2,096 participants. Additional tests included serum iron (SI), total iron-binding capacity (TIBC), transferrin saturation (TS), serum ferritin (SF), folate, cobalamin ( $B_{12}$ ), C-reactive protein (CRP), serum creatinine, creatinine clearance, glucose, rheumatoid factor, and hepatitis C antibody. Anemia was defined according to the WHO criteria of  $<120$  g/L HGB for women and  $<130$  g/L HGB for men. Based on results of laboratory data and information collected from a personal interview, causes of anemia were determined. Approximately one-third of anemia in the study group was attributed to deficiencies of iron,  $B_{12}$ , or folate with deficiencies of iron accounting for half of these cases. Iron deficiency was attributed to blood loss or nutritional deficiency. Another third of subjects had anemia of inflammation, anemia of chronic renal disease, or both. One-third of cases were classified as unexplained anemia. Most cases of anemia were mild; only 2.8% of women and 1.6% of men had HGB values  $\leq 110$  g/L.

In a study of 60 anemic nursing home residents, 23.3% had iron deficiency anemia, 13.3% had anemia of chronic disease, and 10.0% had anemia of renal insufficiency. Other causes were found for 8.3% of residents and 45.9% of causes were listed as idiopathic.<sup>26</sup> In a larger study of 481 residents of a multilevel geriatric institution, a high prevalence of anemia was found (31.4%). The most common causes were anemia of chronic disorders (65.6%), anemia of chronic renal failure (13.2%), and anemia due to deficiencies of iron, folate, or  $B_{12}$  (4%). In only 15% of cases was the cause unknown. Anemia was considered to be mild in over half of the cases.<sup>27</sup> The differences in results for these studies may be due to variations in methods, average age of subjects, or clinical settings.

Anemia of chronic disease (ACD), also referred to as anemia of inflammation, is clearly responsible for many cases of anemia observed in the elderly. ACD is more common in the elderly than in any other age group.<sup>28</sup> The occurrence of ACD-associated diseases including cancer, autoimmune disorders, kidney disease, and acute and chronic infections,

increases with advancing age. Protein calorie malnutrition is another cause of ACD. ACD develops when there is acute or chronic immune activation. The impact of pro-inflammatory cytokines such as interleukin-1 (IL-1), interleukin-6 (IL-6), and tissue necrosis factor  $\alpha$  (TNF- $\alpha$ ), on erythropoiesis includes alterations in iron homeostasis, production of erythroid progenitors and erythropoietin (EPO), and red cell survival, thus causing anemia by several mechanisms.<sup>29</sup> Anemia of renal disease is considered to be a distinct form of anemia, and is typically due to decreased EPO production.

Nutritional deficiencies also occur in the elderly and are responsible for some cases of anemia. Mild, preclinical cobalamin (vitamin  $B_{12}$ ) deficiency is common, affecting 5%-30% of the elderly. The risk of cobalamin deficiency increases with age, but not all persons with cobalamin deficiency develop megaloblastic anemia. In the elderly, the deficiency arises most commonly from inability to split cobalamin from foods, making it unavailable for transport by intrinsic factor. Folate deficiency can develop from dietary insufficiencies or alcohol abuse. Due to widespread use of food additives and dietary supplements, folate levels in the general population have risen significantly, and folate deficiency is no longer considered common in the elderly.<sup>28</sup> Iron deficiency is more common in younger women than in postmenopausal women. Iron deficiency in elderly women and men is most likely a result of gastrointestinal or genitourinary bleeding rather than inadequate dietary intake. Iron deficiency anemia may exist concurrently with ACD or megaloblastic anemia in some patients.

The underlying mechanisms by which idiopathic or unexplained anemia develops in the elderly are incompletely understood. It is possible that some aspect of the process of aging alone may contribute to the development of anemia, leading to speculation about the existence of "anemia of aging". However, hematopoiesis in healthy elderly persons who are not subjected to hematopoietic stress is similar to hematopoiesis in healthy younger adults. Hematopoietic precursors remain normal in number, and cell counts in the peripheral blood do not change with advancing age in healthy adults.

It may be that the elderly have impairment in the hematopoietic system that results in reduced capacity to deal with hematopoietic stress. Elderly anemic patients fail to show increases in erythrocyte progenitors and reticulocytes as would be expected in younger anemic patients.<sup>30</sup> A longitudinal analysis of EPO levels in healthy adults initially without anemia demonstrated that EPO levels increase with age. The



increase may reflect normal compensation for subclinical bleeding, increased red cell turnover, or increased resistance of red cell precursors to EPO in which case the EPO is an effort to maintain optimal HGB levels. The rate of EPO increase was greater for persons who remained healthy during the study than it was for persons who developed diabetes or hypertension. Study participants who developed diabetes or hypertension and anemia during the study showed a significantly diminished EPO response, and were thus unable to compensate for the anemia.<sup>31</sup> Increases in pro-inflammatory cytokines, including IL-6, IL-1, and TNF- $\alpha$ , have been observed in healthy elderly persons.<sup>32</sup>

It is also possible that some cases of unexplained anemia in the elderly result from unrecognized inflammatory conditions. Before attributing the cause to “anemia of aging”, it may be beneficial to rule out subclinical conditions associated with ACD in a geriatric patient. Myelodysplastic syndromes are also a cause of anemia in persons typically over age 50 and should be considered when accompanied by dysplasia and cytopenia in leukocytes or platelets. Anemia may also be a presenting feature in patients with chronic or acute leukemias which are seen in older persons. It is unlikely that other causes of anemia such as hemoglobinopathies, thalassemia, and inherited red cell defects will be initially diagnosed in older adults as they are often sufficiently severe to be recognized in much younger individuals. A complete discussion of all possible causes of anemia is beyond the scope of this article. For more detailed information, the reader may wish to consult a hematology reference book.<sup>33</sup>

#### DETECTING ANEMIA IN THE ELDERLY

In many elderly persons, the onset of anemia is gradual. Most anemic adults are asymptomatic until HGB fall below 80 g/L, although elderly patients may be symptomatic at HGB levels of 100 g/L, especially if cardiac reserves are impaired.<sup>34</sup> Because they may adjust their daily activities to accommodate for physiologic changes, the elderly may be unaware of symptoms. When symptoms associated with anemia such as fatigue, dyspnea, mental confusion, depression, disorientation, or weakness are reported to a health care provider, they may be attributed to aging alone if the patient is elderly. Although pallor, especially in the conjunctiva, can be a useful diagnostic clue to anemia, there are no other clinical signs specific to anemia. For these reasons, it is easy to overlook anemia in geriatric patients.<sup>35</sup> In addition, symptoms of anemia may be masked by those of comorbidities. In some cases, providers may fail to appreciate the clinical significance of a mild anemia in the elderly patient.<sup>36</sup>

An abnormally low HGB may be the first clue that the elderly patient is anemic, but it is interesting to note that current practice guidelines do not recommend anemia screening for asymptomatic elderly patients. Routine anemia screening by HGB and hematocrit (HCT) are not recommended for patients age  $\geq 65$  in guidelines issued by the Institute for Clinical Systems Improvement, citing lack of supporting evidence for a recommendation.<sup>37</sup> Screening of asymptomatic adults for anemia is not included in the *Recommendations of the US Preventive Services Task Force*<sup>38</sup> and is not recommended by the American Academy of Family Physicians.<sup>39</sup> Preoperative testing for anemia is only recommended for patients with severe comorbidities such as cardiovascular or renal disease prior to major surgeries.<sup>40</sup> The National Kidney Foundation recommends annual testing for anemia in patients with chronic kidney disease.<sup>41</sup>

Although screening guidelines are lacking, some providers may test for anemia in healthy patients or in those with diagnosed clinical conditions as part of regular health assessments. Some researchers and geriatric specialists believe that anemia is often poorly recognized and managed, and that routine screening of older individuals for anemia should be considered.<sup>36</sup> When anemia is documented, the cause should be thoroughly investigated in order to initiate appropriate and timely treatment.<sup>42</sup> Treatment may slow disease progression and prevent it from worsening, thus improving patient outcomes.<sup>43</sup>

#### DETERMINING CAUSES OF ANEMIA

Although anemia testing begins with reviewing HGB and HCT values, a complete blood count (CBC) is typically performed on an automated instrument. Other useful tests for anemia evaluation included in the CBC are erythrocyte count, mean cell volume (MCV), mean cell hemoglobin (MCH), mean cell hemoglobin concentration (MCHC), reticulocyte count (RET), red cell distribution width (RDW), and a microscopic examination of erythrocytes on a Wright stained blood smear. Erythrocyte indices (MCV, MCH, and MCHC) are useful for classifying anemia based on red cell size and HGB content, thus providing a first step in determining cause of anemia. Other parts of the CBC such as the leukocyte concentration, leukocyte differential and morphology, and platelet concentration may be helpful in evaluating patients for other conditions causing anemia such as myelodysplastic syndromes or leukemia.<sup>44</sup> A new measurement, the reticulocyte hemoglobin (CHr), is reported by some hematology analyzers when RET counts are ordered. CHr has been shown to be an early indicator of developing iron deficiency, before HGB levels decline.<sup>45</sup>

Confirmatory tests for investigating the possible cause of anemia in an elderly patient include serum iron (SI), total iron binding capacity (TIBC), transferrin saturation (TS), serum ferritin (SF), soluble transferrin receptor (sTR), cobalamin, and folate. These tests are important when a deficiency of iron, cobalamin, or folate is suspected and in some cases of anemia due to other causes. The sTR assay is helpful in differentiating iron deficiency anemia from anemia of chronic disease. A bone marrow examination is ordered if leukemia, myelodysplastic syndrome, or aplastic anemia is suspected but is not needed for assessing iron status.

For cost effectiveness, selection of confirmatory tests should proceed based on information gained from the CBC, physical examination, and patient history. Useful algorithms for evaluating anemia in the elderly appear in the references.<sup>35, 42</sup>

The following sections include brief descriptions of key laboratory findings for the most common causes of anemia in elderly patients. For more information on these disorders or other causes of anemia, the reader should consult a hematology reference book.<sup>33</sup>

#### ANEMIA OF CHRONIC DISEASE

Anemia of chronic disease (ACD) is usually characterized as normocytic and normochromic, although in about one-third of patients, the anemia is microcytic and hypochromic. It is usually mild, with typical HGB and HCT levels ranging from 90 to 110 g/L.<sup>46</sup> A decreased serum iron, low to normal TIBC, normal or increased SF, and normal TfR are typical in ACD and are useful in differentiating ACD from iron deficiency. The RET is usually decreased and TS is normal or low in ACD.<sup>47</sup> There is no specific treatment for ACD in general, and the anemia usually resolves with effective treatment for the underlying disorder. ACD due to cancer and rheumatoid arthritis may respond favorably to treatment with EPO. ACD and IDA may be found in combination. In this situation, interpretation of confirmatory tests is difficult.

#### Anemia of renal disease

Anemia of renal disease is considered a category of anemia distinct from ACD. HGB concentration begins to decrease when the level of blood urea nitrogen rises above 30 mg/dL. The anemia is typically normocytic and normochromic, and HGB levels are between 50 and 80 g/L. Poikilocytosis is moderate to severe with burr cells, acanthocytes, and schistocytes present. RET counts are decreased.<sup>48</sup> Other useful assays include tests of renal function such as creatinine, urea nitrogen, and the urinalysis. EPO is used to treat anemia of renal disease. When

patients are treated with hemodialysis, bleeding and loss of iron or folate may result in anemia due to other causes.

#### Iron deficiency anemia

Anemia due to iron deficiency (IDA) is microcytic and hypochromic, especially once the HGB level falls below 100 g/L. In severe cases, elliptocytes may accompany microcytes and hypochromic red cells on blood films. Typically HGB and HCT are somewhat lower than seen in ACD. Because other anemias, most notably the thalassemias, are also characterized by low MCV, MCH, and MCHC, additional tests are needed for confirmation of IDA. Low SI, TS, and SF combined with elevated RDW, TIBC and sTR are typical for IDA and are needed to differentiate it from ACD and thalassemia. Ferritin is an especially sensitive marker for emergent iron deficiency and will be decreased before full-blown anemia develops. The CHr is also a useful marker, with low levels seen in developing iron deficiency. Because IDA in elderly adults is most commonly a result of iron loss due to chronic gastrointestinal bleeding, treatment includes stopping the blood loss and replacing iron with oral supplements. Ferritin levels may be periodically re-ordered to assess the efficacy of treatment. EPO is not typically used to treat IDA.

#### Megaloblastic anemia

Megaloblastic anemia (MA) is macrocytic and normochromic with numerous morphologic abnormalities evident in erythrocytes, including macroovalocytes, Howell-Jolly bodies, and basophilic stippling. MCV is usually >110 fL RDW is elevated and RET is normal or decreased. Hypersegmentation of neutrophils is an early and common indicator of MA, and pancytopenia is typical. Assays for serum cobalamin and serum folate are needed to document deficiencies of one or both as a cause of MA. Other relevant laboratory tests include assays for methylmalonic acid, antibodies to parietal and gastric cells, bilirubin, lactic dehydrogenase, and homocysteine.<sup>49</sup> Treatment consists of cobalamin or folate replacement, and additional laboratory tests are needed to monitor the effectiveness of therapy.

Other causes of macrocytosis include alcoholism, liver disease, and reticulocytosis. Usually MCV is less elevated in these conditions than in MA. An elevated MCV should not be ignored as it can indicate the presence of these clinical conditions, especially unsuspected alcohol abuse. Elevated RET are a key feature of hemolytic anemias and severe blood loss. A complete discussion of macrocytic anemias is beyond the scope of this article, and the reader should consult a hematology reference book for more information.<sup>33</sup>

CONCLUSIONS

The prevalence of anemia is high in people over age 65 in the US and is especially common among the eldest seniors, men, and African Americans. Several studies have shown that anemia is an independent risk factor for morbidity and mortality and may impair physical and cognitive function and quality of life for senior citizens. Early diagnosis and treatment of anemia can improve health outcomes in several medical conditions.<sup>43</sup> Detecting the presence of anemia and identifying its cause depends on information provided by the clinical laboratory, thus ordering the correct tests is important. With our rapidly aging US population, the overall incidence and impact of anemia on the healthcare system is expected to increase.

In spite of a large number of relevant studies performed to date, unanswered questions about anemia in the elderly remain. They include:

- Should the healthy elderly be routinely screened for anemia?
- What reference intervals should be used to evaluate seniors for the presence of anemia?
- Does an “anemia of aging” exist and if so, how should it be managed?
- What is the most cost effective use of laboratory tests to evaluate anemia and determine its cause?
- How can health care providers become more aware of the prevalence and causes of anemia in elderly patients?

*Clin Lab Sci encourages readers to respond with thoughts, questions, or comments regarding this Focus section. Email responses to ic.ink@mchsi.com. In the subject line, please type “CLIN LAB SCI 21(4) FO ANEMIA IN SELECTED POPULATIONS”. Selected responses will appear in the Dialogue and Discussion section in a future issue. Responses may be edited for length and clarity. We look forward to hearing from you.*

REFERENCES

1. US Census Bureau. 2006 population estimates. Available from <http://factfinder.census.gov>. Accessed 2008 May 9.
2. Hobbs FB. Population profile of the United States:the elderly population. Available from <http://census.gov/population/www/pop-profile/elderpop.html>. Accessed 2008 May 9.
3. Guralnik JM, Eisenstaedt RS, Ferrucci L, and others. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood* 2004;104:2263-8.
4. Guralnik JM, Ershler WB, Schrier SL, and others. Anemia in the elderly: A public health crisis in hematology. *Hematology* 2005. The American Society of Hematology. Available from <http://asheducationbook.hematologylibrary.org/cgi/content/full/2005/1/528>.

Accessed 2008 May 8.

5. Spivak J. Anemia in the elderly: time for new blood in old vessels? *Arch Intern Med* 2005;165:2187-9.
6. Nutritional Anaemias. World Health Organ Tech Rep Ser 1968;405:5-37.
7. Nilsson-Ehle H, Jagenburg R, Landahl S, and others. Blood hemoglobin declines in the elderly: implications for reference intervals from age 70 to 88. *Eur J Haematol* 2000;65:190-4.
8. Nandigam V, Nandigam K, Badhe BA, and others. Is adult definition of anemia applicable to a geriatric population? A study of erythrocyte parameters in Indian geriatric inpatients. *J Am Geriatr Soc* 2004;52:1589-90.
9. Chaves Ph, Ashar B, Guralnik JM, and others. 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;50:1257-64.
10. Chaves PH, Xue QL, Guralnik JM, and others. What constitutes normal hemoglobin concentration in community-dwelling disabled older women. *J Am Geriatr Soc* 2004;52:1811-6.
11. Izaks GJ, Westendorf RG, Knook DL. The definition of anemia in older persons. *JAMA* 1999;281:1714-7.
12. Ania BJ, Suman VJ, Fairbanks VF, and others. Incidence of anemia in older people: an epidemiologic study in a well-defined population. *J Am Geriatr Soc* 1997;45:825-31.
13. Ania BJ, Suman VJ, Fairbanks VF, and others. Prevalence of anemia in medical practice; community versus referral patients. *Mayo Clin Proc.* 1994;69:730-5.
14. Artz AS, Fergusson D, Drinka PJ, and others. Prevalence of anemia in skilled-nursing home residents. *Arch gerontol geriat* 2004;38:201-6.
15. Zakai NA, Katz, R, Hirsch C, and others. A prospective study of anemia status, hemoglobin concentration, and mortality in an elderly cohort. *Arch Intern Med* 2005;165:2214-20.
16. Culleton BF, Manns BJ, Zhang J, and others. Impact of anemia on hospitalization and mortality in older adults. *Blood* 2006;107:3841-6.
17. Muzzarelli S, Pfesterer. Anemia as independent predictor of major events in elderly patients with chronic angina. *Am Heart J* 2006;152:991-6.
18. Penninx BW, Pahor M, Woodman RC, and others. Anemia in old age is associated with increased mortality and hospitalization. *J Gerontol Med Sci* 2006;61A:474-9.
19. Penninx BW, Pahor M, Cesari M, and others. Anemia is associated with disability and decreased physical performance and muscle strength in the elderly. *J Am Geriatr Soc* 2004;52:719-24.
20. Foss NB, Kristensen MT, Kehlet H. Anaemia impedes functional mobility after hip fracture surgery. *Age Aging* 2008;37:173-8.
21. Dharmarajan TS, Avula S, Norkus EP. Anemia increases risk for falls in hospitalized older adults: an evaluation of falls in 362 hospitalized, ambulatory, long-term care, and community patients. *J Am Med Dir Assoc* 2007;8 Suppl 2:e9-e-15.
22. Joosten E, Lemiengre J, Nelis T, and others. Is anaemia a risk factor for delirium in acute geriatric populations? *Gerontology* 2006;52:382-5.
23. Katz IR, Beaston-Wimmer P, Parmelee P, and others. Failure to thrive in the elderly: exploration of the concept and delineation of psychiatric components. *J Geriatric Psychiatry Neurol* 1993;6:161-9.
24. Lefebve P, Duh, MS, Buteau S, and others. Medical costs of untreated anemia in elderly patients with predialysis chronic kidney disease. *J Am Soc Nephrol* 2006;17:3497-502.

## FOCUS: ANEMIA IN SELECTED POPULATIONS

25. Robinson B. Cost of anemia in the elderly. *J Am Geriatr Soc* 2003;51(Suppl):S14-S17.
26. Artz AS, Fergusson D, Drinka PJ, and others. Mechanisms of unexplained anemia in the nursing home. *J Am Geriatr Soc* 2004;52:423-7.
27. Chernetsky A, Sofer O, Rafael C, and others. Prevalence and etiology of anemia in an institutionalized geriatric population. *Harefuah* 2002;141:591-4.
28. Carmel R. Anemia and aging: an overview of clinical, diagnostic and biological issues. *Blood Rev* 2001;15:9-18.
29. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005;352:1011-23.
30. Rothstein G. Disordered hematopoiesis and myelodysplasia in the elderly. *J Am Geriatr Soc* 2003;51(Suppl):S22-S26.
31. Ershler WB, Sheng S, McKelvey J, and others. Serum erythropoietin and aging: A longitudinal analysis. *J Am Geriatr Soc* 2005;53:1360-5.
32. Ershler WB. Biological interactions of aging and anemia: A focus on cytokines. *J Am Geriatr Soc* 2003;51(Suppl):S2-S9.
33. Lichtman MA, editor. *Williams hematology*. 7<sup>th</sup> ed. New York: McGraw-Hill; 2006.
34. Montoya VL, Wink D, Sole ML. Adult anemia: determine clinical significance. *Nurse Pract* 2002;27:38-53.
35. Smith DL. Anemia in the elderly. *Am Fam Physic* 2000;62:1565-72.
36. Balducci L, Ershler WB, Krantz S. Anemia in the elderly: clinical findings and impact on health. *Crit Rev Oncol Hematol* 2005;58:156-65.
37. Preventive services for adults. Institute for Clinical Systems Improvement; 2007. Available from <http://www.guideline.gov/algorithm/6046/NGC-6046.html>. Accessed 2008 May 12
38. Guide to Clinical Preventive Services, 2007: Recommendations of the U.S. Preventive Services Task Force. AHRQ Publication No. 07-05100, September 2007. Rockville MD: Agency for Healthcare Research and Quality. Available from <http://www.ahrq.gov/clinic/pocketgd07/>. Accessed 2008 May 15.
39. American Academy of Family Physicians (AAFP). Summary of recommendations for clinical preventive services. Revision 6.4. Leawood (KS): American Academy of Family Physicians (AAFP); 2007 Aug. 15 p. Available from [http://www.guideline.gov/summary/summary.aspx?doc\\_id=11830&cnbr=006077&string=periodic+AND+health+AND+examination](http://www.guideline.gov/summary/summary.aspx?doc_id=11830&cnbr=006077&string=periodic+AND+health+AND+examination). Accessed 2008 May 15.
40. National Institute for Clinical Excellence. Preoperative tests: The use of routine preoperative tests for elective surgery. National Institute for Clinical Excellence 2003. Available from [http://www.nice.org.uk/nicemedia/pdf/Preop\\_Fullguideline.pdf](http://www.nice.org.uk/nicemedia/pdf/Preop_Fullguideline.pdf). Accessed 2008 May 15.
41. National Guideline Clearinghouse. KDOQI clinical Practice guidelines and clinical practice recommendations for anemia in chronic kidney disease. 2007 update of hemoglobin target. Available from [http://www.guideline.gov/summary/summary.aspx?doc\\_id=11651&cnbr=006019&string=kdoqi](http://www.guideline.gov/summary/summary.aspx?doc_id=11651&cnbr=006019&string=kdoqi). Accessed 2008 May 15.
42. Balducci L. Epidemiology of anemia in the elderly: information on diagnostic evaluation. *J Am Geriatr Soc* 2003;51(Suppl):S2-S9.
43. Lipschitz D. Medical and functional consequences of anemia in the elderly. *J Am Geriatr Soc* 2003;51(Suppl):S10-S13.
44. McKenzie SB. Introduction to anemia. In: McKenzie SB, editor. *Clinical laboratory hematology*. 3<sup>rd</sup> ed. New Jersey: Pearson Prentice Hall; 2004.
45. Mast AE, Blinder MA, Lu Q, and others. Clinical utility of the reticulocyte hemoglobin content in the diagnosis of iron deficiency. *Blood* 2002;99:1289-91.
46. Doig K. Disorders of iron and heme metabolism. In: Rodak BF, Fritsma GA, Doig K., editors. *Hematology: clinical principles and applications*. 3<sup>rd</sup> ed. Missouri: Elsevier; 2007.
47. McKenzie SB. Anemias of disordered iron metabolism and heme synthesis. In: McKenzie SB, editor. *Clinical laboratory hematology*. 3<sup>rd</sup> ed. New Jersey: Pearson Prentice Hall; 2004.
48. Laudicina RJ. Hypoproliferative anemias. In: McKenzie SB, editor. *Clinical laboratory hematology*. 3<sup>rd</sup> ed. New Jersey: Pearson Prentice Hall; 2004.
49. Doig K. Anemias caused by defects of iron metabolism. In: Rodak BF, Fritsma GA, Doig K., editors. *Hematology: clinical principles and applications*. 3<sup>rd</sup> ed. Missouri: Elsevier; 2007.

### New Titles at the ASCLS Online Store

- |                                                                                                                                                                                                                                                          |                                                                                                                                                                                                                                                                                                                |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>■ <b>Bloodborne Pathogens in the Workplace</b> - interactive educational CD</li> <li>■ <b>Blood Specimen Collection FAQs</b> - answers to hundreds of frequently asked questions; ideal resource; book</li> </ul> | <ul style="list-style-type: none"> <li>■ <b>Clinical Chemistry Reviews</b> - new lipid/ cardiac module available; by Larry Kaplan, PhD &amp; Amadeo Pesce, PhD; CD</li> <li>■ <b>Quick Guide to Clinical Chemistry</b> - pocket-sized reference; tests categorized by clinical condition; paperback</li> </ul> |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**For more information, visit [www.ascls.org](http://www.ascls.org), click on Online Store or Continuing Education/What's New? or email [joanp@ascls.org](mailto:joanp@ascls.org).**

American Society for Clinical Laboratory Science, 6701 Democracy Blvd., Suite 300, Bethesda, MD 20817

