Chapter 15: Anemia in the Elderly With CKD

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Anemia is a common sequela of chronic kidney disease (CKD). As GFR declines, the risk of anemia increases, particularly when the GFR is <60 ml/min per 1.73 m^2.[1] Anemia is also common in the geriatric population, with a prevalence of >10% in patients greater than 65 yr old (Figure 1).[2] This poses a significant challenge in the diagnosis and management of elderly patients with anemia who have concurrent CKD. The following review discusses the definition, diagnosis, management, and outcomes of anemia in elderly patients with CKD.

DEFINITION OF ANEMIA IN THE ELDERLY

Defining normal hemoglobin levels in the elderly population is important for purposes of establishing a diagnosis and monitoring treatment effects and outcomes. In 1968, an expert panel from the World Health Organization recommended normal hemoglobin (Hg) levels be >13.0 g/dl for men and >12.0 g/dl for nonpregnant women.[3] Although the accuracy of these definitions has been called into question, more recent population-based studies, including NHANES III and the Kaiser-Scripps database, have been relatively consistent with the proposed levels.[2,4]

As previously mentioned, anemia is quite common in the elderly population. Using the WHO definition of anemia, NHANES III data have shown that the prevalence of anemia in subjects ≥65 yr old is >10.6%, significantly higher than that of the general population. However, when present in the elderly, anemia tends to be mild. From the NHANES III data, <3% of subjects 65 yr of age and older had an Hg <11.0 g/dl. Whether these modestly lower values of Hg correlate with poorer outcomes is not known.

Attention should be paid to racial and ethnic differences and other patient-centered factors in anemia prevalence in the elderly as well. Data from NHANES III showed that, among individuals 65 yr of age and older, African Americans have a higher prevalence of anemia (Figure 2).[2] Other factors that contribute to lower Hg levels must always be considered when making the diagnosis of anemia. These include altitude of residence, smoking status, normal fluctuations in plasma volume, and other patient-centered factors. These are not routinely considered when Hg concentration is reported by clinical laboratories, which typically only correct for age and sex. In addition, reference ranges for Hg may vary from laboratory to laboratory across all subjects. Thus, results of Hg testing must always be interpreted in the full context of the individual patient.

CAUSES OF ANEMIA IN THE ELDERLY

Because of the increased prevalence of lower Hg levels in the geriatric population, as well as increased risk of comorbidities leading to anemia, determining the cause of anemia can be challenging, especially in the face of CKD. Determining whether CKD is the cause of anemia, whether there is another explanation, or perhaps whether there are several etiologies of anemia has important implications for treatment and thus should be investigated rigorously before simply beginning therapy with an erythropoietic stimulating agent (ESA). Below is a discussion of the diagnosis of anemia in the elderly with CKD.

CKD AND ERYTHROPOIETIN PRODUCTION

Anemia attributable to CKD was suspected in approximately 8% of all anemia cases in the elderly, according to NHANES III. Furthermore, some studies have shown lower than expected erythropoietin (Epo) levels for the degree of anemia in ge-

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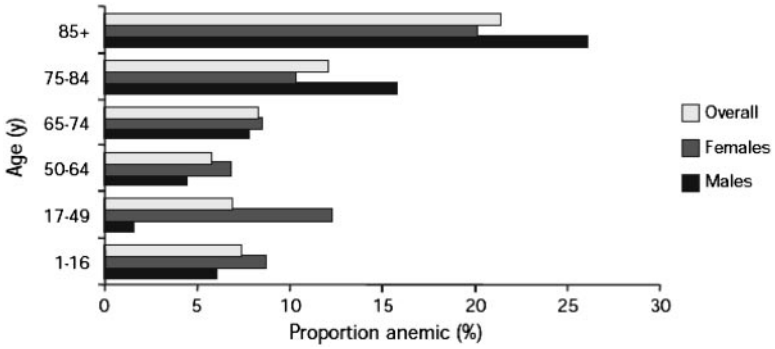

Figure 1. Prevalence of anemia in the United States by age (NHANES III). Prevalence of WHO-defined anemia (hemoglobin <13.0 g/dl for males and <12.0 g/dl for nonpregnant females) in the United States, by age and sex. NHANES III, Third US National Health and Nutrition Examination Survey; WHO, World Health Organization. Data from first two phases of NHANES III, 1988–1994. From: Steensma DP, Tefferi A: Anemia in the elderly: how should we define it, when does it matter, and what can be done? *Mayo Clin Proc* 82: 958–966, 2007, reprinted with permission.[16]

riatric patients. Some have theorized that the elderly have a decreased ability to produce Epo in response to hypoxia or that there is decreased hypoxia-sensing in the kidney with increasing age and thus a higher Epo requirement to maintain the same Hg level.[5,6] However, one study has shown that normal, healthy elderly individuals have the capacity to produce adequate Epo in response to phlebotomy.[7] Whether this translates into an ability to maintain Epo production and Hg levels in the setting of chronic blood loss or other perturbations in Hg concentration is not known. Thus, to date, there is no solid evidence that the elderly have a decreased ability to produce Epo when kidney function is normal.

One possible explanation for the observation of lower than expected Epo levels is that CKD may be present to some degree in some elderly subjects despite the results of GFR estimating equations. This may be because of the fact that the equations to estimate GFR are suspect in the elderly as the population of subjects in the studies used to create these equations did not include very elderly patients. Second, the correlation of estimated GFR to renal endocrine function is not as well studied in the elderly. For the general population, anemia caused by CKD can present as early as eGFR of about 60 ml/min per 1.73 m^2. Whether this relationship between eGFR and Epo production is similar for the elderly population is not known. Therefore, eGFR alone cannot be used reliably to exclude anemia of CKD in the geriatric population.

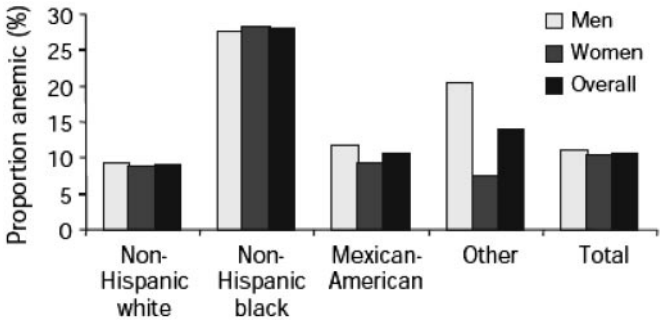

Figure 2. Prevalence of anemia in the United States by race and ethnicity. Prevalence of WHO-defined anemia in US patients 65 yr of age or older, by self-declared racial or ethnic group. NHANES III, Third US National Health and Nutrition Examination Survey; WHO, World Health Organization. Data from NHANES III, 1988–1994. From: Steensma DP, Tefferi A: Anemia in the elderly: how should we define it, when does it matter, and what can be done? *Mayo Clin Proc* 82: 958–966, 2007, reprinted with permission.[16]

NUTRITIONAL ANEMIA

Inadequate nutrition is a common problem in the elderly. Iron deficiency, both nutritional and because of chronic blood loss, accounts for most cases of nutritional anemia, representing about one third of anemia cases in the elderly in the NHANES III cohort. Diagnosis of iron deficiency should be made with free iron, total iron binding capacity, and ferritin levels. As is the case in the general CKD population with iron deficiency, ferritin levels are not reliably low because of chronic inflammation and thus should not be used to exclude iron deficiency anemia. Similarly, mean corpuscular volume (MCV) is not always low in CKD, despite iron deficiency anemia, so a normal MCV should not exclude the diagnosis. Based on early studies, an iron/total iron binding capacity (TIBC) ratio $\leq$16% or a serum ferritin <12 ng/ml is necessary to make the diagnosis of iron deficiency anemia.[8,9]

Other causes of nutritional anemia must be investigated in the elderly also. Particularly, folate and B_{12} deficiencies are more frequently present than in the general population. One study found that >10% of the elderly had borderline or low B_{12} levels.[10] As was the case with iron deficiency, one must be careful not to exclude the diagnosis of B_{12} or folate deficiency solely by MCV when concurrent CKD is present.

MALIGNANCY

The elderly are at increased risk for malignancy. Several types can cause anemia and must be considered whenever an elderly patient presents with anemia. The two most important categories are gastrointestinal (GI) malignancies and hematologic malignancies. GI malignancies lead to chronic blood loss and iron deficiency anemia, so stool testing for occult blood should be considered. However, colonoscopy should be considered even if the stool for occult blood is negative in the presence of an unexplained iron deficiency anemia in an elderly patient with CKD.

Hematologic malignancies in general can cause anemia because of disruption of hematopoiesis in the bone marrow. Two that have a particular predilection for elderly patients are myelodysplastic syndrome (MDS) and multiple myeloma. Both diseases have peaks in the seventh decade of life and can be insidious in onset, with only subtle laboratory findings to point to the diagnosis. Several studies have shown that MDS is probably underdiagnosed in this population and may account for a significant number of cases of anemia in the elderly that do not have an identifiable cause.[11] Multiple myeloma can also be easily missed in the workup of a patient with anemia. Thus, an elderly patient with CKD and anemia, in most cases, should be screened for the presence of paraproteins.

APPROACH TO DIAGNOSIS OF ANEMIA IN THE ELDERLY

Initial evaluation of anemia in the elderly should include a review of the complete blood count, including red blood cell morphology and parameters such as MCV. Worrisome findings on the peripheral blood smear should prompt consideration of referral to Hematology. Abnormal MCV should be worked up appropriately (*e.g.,* high MCV warrants folate, B_{12}, and homocysteine levels, consideration of alcohol or medications, liver or thyroid disease).

A normal MCV should not completely rule out either high or low MCV causes of anemia, although their diagnosis is less likely. Renal function should be estimated to determine the possibility of anemia caused by renal disease. Concomitant iron deficiency must always be evaluated in the face of CKD and worked up if present. An appropriately elevated Epo level with normal iron studies should prompt referral to Hematology to investigate for hematologic malignancies. If the workup of an elderly CKD patient's anemia has not yielded a diagnosis at this point, consideration should be given to obtaining an Epo level because, as previously discussed, relative Epo deficiency may be present in the elderly even with near "normal" eGFR.

TREATMENT AND OUTCOMES

After treating any underlying nutritional deficiencies noted earlier, and with persistent anemia, one should consider therapy for anemia of CKD. The mainstays of treatment are ESAs and iron. ESAs have been shown to be effective in raising Hg levels appropriately in the elderly.[12] Concomitant iron deficiency being frequently present in this group, iron supplementation is commonly part of treatment. Several formulations of oral iron are available for consideration. In some patients with CKD, oral iron is ineffective in raising available iron stores, especially in the elderly who frequently show poorer GI absorption of iron.[13] Such patients may benefit from the introduction of intravenous iron. Although the ability of these agents to raise Hg levels is documented, the benefits of raising the Hg are still somewhat murky.

Most studies documenting the benefit of anemia treatment have been conducted in ESRD patients, whereas there are fewer studies in predialysis patients with CKD. Most of these studies have had a reasonable number of subjects $\geq$65 yr of age, so results may be generalizable to the geriatric population to some degree. Improvement in health-related quality of life (HRQOL), cognition, left ventricular mass, and decreased need for transfusions have been documented in the general ESRD population, and it is reasonable to believe that the same benefits would be conferred on the elderly ESRD population. The benefits of anemia treatment in predialysis CKD are more controversial. Although a few studies have shown higher HRQOL, lower left ventricular mass, and a possible decrease in progression of CKD in those subjects treated for anemia, the evidence is not strong, and no study has shown a survival advantage to treatment.

When reviewing the benefits of anemia therapy, one question that remains is: What level of Hg should be targeted? At this point, the target Hg level for individuals with CKD is not agreed on, particularly for the elderly. Two recent studies have cast doubt on the goal of targeting normal Hg levels. The Correction of Hemoglobin and Outcomes in Renal Insufficiency (CHOIR) trial was a randomized study of predialysis patients with CKD and anemia. One group was targeted to an Hg of 13.5 g/dl, whereas another group was targeted to an Hg of 11.3 g/dl.[14] Average subject age was about 66 yr old. Achieved Hg for the higher Hg group was actually lower, just below 13 g/dl. There was increased risk of one of the primary or secondary outcomes in the higher Hg group compared with the lower Hg group, with no benefit in HRQOL (Figure 3). The Cardiovascular Risk Reduction in Early Anemia Treatment with Epoetin Beta (CREATE) also studied higher Hg level in predialysis patients with CKD.[15] No benefits were shown in the group targeted to higher Hg, although excess risk of events was not statistically significant in this study. Mean age of subjects in CREATE was about 59 yr old.

This excess mortality with the use of ESAs is of particular importance in the elderly population with CKD. This is because the elderly are at higher risk of having the comorbidities associated with the vascular events that occurred more frequently in the higher Hg groups. Thus, when treating anemia of CKD in the elderly, one should not aim for high Hg levels, especially if the patient has a history of any kind of vascular disease, pro-thrombotic state such as malignancy, or poorly controlled hypertension. Based on the results of the two studies mentioned previously, the evidence supports restoring Hg levels to a level between 10.0 and 12.0 g/dl.

CONCLUSION

The diagnosis and workup of anemia in an elderly patient with CKD is, in the end, the same as for any patient. However,

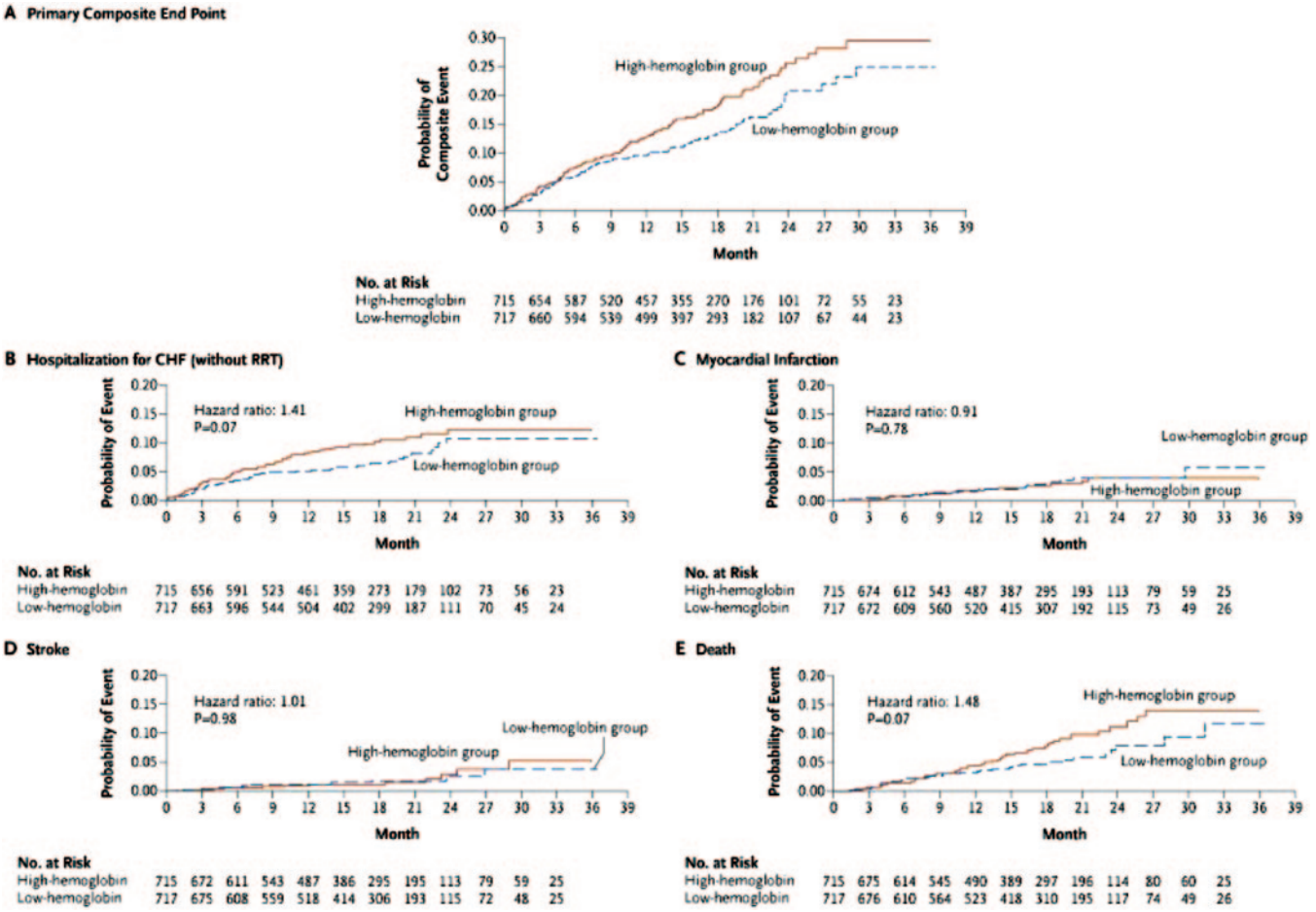

Figure 3. Primary and secondary endpoints for higher *versus* lower Hg groups in the CHOIR Study. Kaplan–Meier estimates of the probability of the primary composite endpoint and secondary endpoints of individual components—hospitalization for congestive heart failure (CHF) without renal replacement therapy (RRT), myocardial infarction, stroke, and death. (Reprinted from Singh AK, Szczech L, Tang KL, *et al.*: Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 355: 2085–2098, 2006).[14]

epidemiologic information and special diagnostic considerations must be taken into account since the elderly are more likely to have a concomitant cause of anemia in the face of CKD. Treatment with ESAs is effective, and iron supplementation, initially oral but intravenous if ineffective, should be considered in the regimen given the frequency of iron deficiency in these individuals. When choosing a target Hg level, it is important to remember that higher Hg levels may be associated with increased cardiovascular and thrombotic events. The elderly are at risk for conditions that raise the risk of these events, so anemia must be treated judiciously. A target Hg of 10.0 to 12.0 g/dl is an acceptable target based on available evidence.

TAKE HOME POINTS

- Anemia in the elderly with CKD is often multifactorial, with iron deficiency being common
- Special consideration must be given to diagnoses common in this population, including GI blood loss and hematologic causes (MDS, multiple myeloma)
- ESAs and iron supplementation are effective in treating anemia of CKD in this population
- Hg should be targeted to a level between 10.0 and 12.0 g/dl

DISCLOSURES

None.

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REVIEW QUESTIONS: ANEMIA IN THE ELDERLY WITH CKD

1. According to NHANES III data, the prevalence of anemia in persons ≥65 yr of age is approximately:
   a. 1%
   b. 5%
   c. 10%
   d. 20%

2. The most common cause of anemia in the elderly is:
   a. Nutritional anemia (including iron deficiency)
   b. Chronic kidney disease
   c. Occult malignancy
   d. Hematologic abnormalities (including myelodysplastic syndrome)

3. Which of the following is true regarding erythropoietin (Epo) production in the elderly?
   a. In patients with normal kidney function, Epo production is decreased in the elderly compared with the nonelderly
   b. In elderly patients, estimated GFR correlates better with Epo production than in nonelderly patients
   c. One study has shown that normal, healthy, elderly subjects could not produce adequate Epo in response to phlebotomy
   d. To date, there is insufficient evidence to conclude that the elderly have a diminished capacity to produce Epo in response to anemia

4. Which potential benefit of ESA therapy for predialysis CKD patients has NOT been demonstrated in any study to date?
   a. Decreased mortality
   b. Decreased left ventricular hypertrophy
   c. Decrease in progression of CKD
   d. Increase in health-related quality of life

5. Results of the CHOIR and CREATE trials support a target Hg level less than:
   a. 10 g/dl
   b. 11 g/dl
   c. 12 g/dl
   d. 13 g/dl

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