ANEMIA OF CHRONIC DISEASE IN THE ELDERLY

Maren Mayhew

ABSTRACT

Many experienced clinicians feel comfortable with the diagnosis and treatment of anemia. However, the anemia of chronic diseases so prevalent in the elderly may represent a diagnostic challenge. New treatment strategies are now available for patients whose quality of life is adversely affected by this problem that is commonly ignored.

Keywords: anemia of chronic disease, low iron production, normocytic normochromic anemia

PREVALENCE AND SIGNIFICANCE

Anemia as a general condition is common in the elderly. The prevalence can reach 44% in men older than 85. The anemia of chronic disease (ACD) is a common problem in elderly patients and may represent a diagnostic challenge even for the experienced nurse practitioner. Although subtle, anemia may have a serious effect on the quality of life of the elderly patient. This article discusses common anemias in the elderly, with an emphasis on ACD and its treatment (Box 1).

The most common cause of anemia in the elderly is ACD, which was recognized as a diagnostic entity in 1962. Three causes are generally agreed on: cancer and cancer treatment, inflammation or infection, and patients with HIV who are taking zidovudine. The inflammation or infectious disease category includes malaria, rheumatoid arthritis (RA), and Crohn disease, among others. Other diseases implicated in ACD are liver disease (alcoholic cirrhosis), heart failure, chronic obstructive pulmonary disease, and diabetes. Multiple trauma can also cause ACD. The list of diseases or conditions associated with ACD continues to grow as new research uncovers the relations.

The anemia of chronic disease (ACD) is a common problem in elderly patients and may represent a diagnostic challenge even for the experienced nurse practitioner. Although subtle, anemia may have a serious effect on the quality of life of the elderly patient. This article discusses common anemias in the elderly, with an emphasis on ACD and its treatment (Box 1).

The most common cause of anemia in the elderly is ACD, which was recognized as a diagnostic entity in 1962. Three causes are generally agreed on: cancer and cancer treatment, inflammation or infection, and patients with HIV who are taking zidovudine. The inflammation or infectious disease category includes malaria, rheumatoid arthritis (RA), and Crohn disease, among others. Other diseases implicated in ACD are liver disease (alcoholic cirrhosis), heart failure, chronic obstructive pulmonary disease, and diabetes. Multiple trauma can also cause ACD. The list of diseases or conditions associated with ACD continues to grow as new research uncovers the relations.
studies. The following findings have been confirmed by several studies:

- The prevalence of anemia varies among different groups.
- Hospitalized patients have the highest rate of anemia; high rates are also found in nursing homes.
- Anemia is more prevalent in elderly men than women.
- The prevalence increases with age.
- An increased prevalence occurs in patients with Alzheimer disease.
- Increased mortality is found in anemic patients.

Anemia has significant adverse effects on the patient’s clinical, functional, and economic status. However, studies have not been done to quantify the effect of anemia on the elderly patient. The main symptom of anemia is fatigue, and fatigue clearly can have a serious effect on quality of life.

**TYPES OF ANEMIAS**

Anemia is classified either by pathophysiology or cell size (mean cell volume [MCV], equates to size) (Box 2). To understand anemia in the elderly, it is necessary to address both pathophysiology to understand cause and cell size as a method of diagnosis. These classifications have been combined in this article to facilitate discussion.

**CAUSE**

Erythropoiesis as a process normally declines during aging. This makes it difficult to sort normal aging from the effect of chronic disease. Also, it is often difficult to determine the cause of an anemia in the elderly. Studies estimating the cause of anemia in the elderly find that, for many patients, no cause can be confirmed. In many cases the cause is multifactorial. Most of the diseases listed under ACD have other mechanisms for causing anemia in addition to the ACD.

The etiology of ACD is not fully understood. It appears to be caused by inflammatory cytokines such as interleukin, tumor necrosis factor, and interferon alfa and beta. These cytokines play three roles. The first role is that red blood cell survival is slightly decreased. This leads to anemia. The second role is a depressed response to the anemia. The body produces erythropoietin, but the amount is low compared to what a normal body would make with the same severity of anemia. The bone marrow fails to increase the production of red blood cells sufficient to compensate for the anemia. The third role is that inflammation causes iron to be retained in the reticuloendothelial system rather than being released to the RBCs developing in the marrow. Inflammation causes a direct inhibition of this process. The patient has iron but is unable to use it, so there is no iron deficiency per se.

**Chronic Renal Failure**

The main cause of anemia in patients with CRF is insufficient production of erythropoietin by the diseased kidneys. This is an absolute decrease in production because of the kidney damage, not a relative decrease as in ACD. This process leads to decreased RBC production, and the resulting anemia is more severe than that seen in ACD.
Gastrointestinal Blood Loss and Nutritional Deficit
Iron deficiency in the elderly is often caused by acute or chronic gastrointestinal (GI) blood loss. Folate and vitamin B12 deficiencies are also seen in the elderly because of inadequate intake or absorption. It may be symptoms of these other deficiency problems that bring the ACD to the attention of the clinician.

DIAGNOSIS OF ANEMIA

Signs and Symptoms
Most anemias are discovered on routine laboratory tests. The patient often does not complain of or evidence any symptoms. Other disease states may be aggravated or found concurrent with anemia.

The most common symptom of anemia is fatigue. Although some might assume that the most important symptom to manage in palliative medicine is pain, fatigue is one of the top two symptoms (along with anorexia) for distress in patients who are terminally ill. In fact, fatigue is a problem in 75% to 90% of patients with terminal illness. It is described as tiredness, a general lack of energy not relieved by rest, diminished mental capacity, and weakness. It may be so severe it causes profound difficulty in performing activities of daily living. Fatigue contributes to decreased exercise tolerance, frailty, immobility, and depression. Fatigue is a common complaint in the elderly and it is hard to know when it is significant. Researchers suggest it is underdiagnosed and undertreated. Many diseases in the elderly can cause fatigue directly and may also produce anemia, which can in turn increase the fatigue. This makes it extremely difficult to diagnose the true cause of the fatigue. A good example of this is the deconditioning the patient experiences as a result of cancer, which is common in addition to anemia.

It is essential for the clinician to determine what part anemia might play in contributing to fatigue. Assess the severity of the fatigue by talking to the patient to determine the effect on the patient’s quality of life. The degree of patient distress and disability will help determine how aggressive the clinician should be in the treatment of the anemia.

Research suggests that anemia found in association with heart failure is correlated with increased mortality. Approximately 17% of patients with heart failure have anemia, 60% of which may be found to be ACD. Anemia contributes to the disease progression of heart failure, and the anemia can exacerbate ischemic heart disease or cause high-output failure.

Differential Diagnosis

The diagnosis of ACD is one made by exclusion, and it is ultimately a clinical diagnosis. ACD may coexist with other causes of anemia, especially iron deficiency. The presence and type of anemia is established by a complete blood cell (CBC) count, reticulocyte count, and iron studies (Table 1).

The laboratory tests will determine not only the structural characteristics but also the severity of the anemia. Most anemias initially present as normocytic. As they progress, different characteristics become more apparent. Serum ferritin concentration is directly corre-
lated to the reticuloendothelial iron stores. Reduced serum ferritin means low iron stores; this is the only cause of low serum ferritin. Tests will document that the iron stores in ACD are normal. Another test that should be obtained is the transferrin saturation. The transferrin saturation is the ratio of serum iron to TIBC and will be low in both ACE and iron-deficiency anemia.

Other causes of anemia should be excluded before ACD can be diagnosed. Thus, the clinician must search for CRF, iron deficiency and blood loss, vitamin B₁₂ and folate deficiencies, and other problems as dictated by the laboratory results. The diagnosis of iron-deficiency anemia is confirmed by bone marrow examination. This test is expensive and painful and requires patient cooperation; thus, it is often not feasible in the elderly.¹

To summarize, ACD is a mild normocytic normochromic anemia characterized by low reticulocyte index, low serum iron, and low TIBC, with normal or increased ferritin, in a patient with a systemic (an inflammatory component) disease.

**TREATMENT**

**General Principles**

It is tempting to base treatment of ACD solely on laboratory values. However, other factors must be considered. Treatment must be based on the cause of the anemia, and, if the anemia is severe or causing symptoms, it must be treated and not ignored. Otherwise, it is usually not necessary to treat ACD. Treatment in that case would consist of optimal control of the underlying cause (Box 3).

Commonly, patients with ACD have a hemoglobin level of around 30 and a hematocrit of about 10 and manage well. The anemia has developed slowly, and the patient has adjusted to it. Patients with heart failure have a decreased ability to tolerate anemia. They may become symptomatic even with hemoglobin or hematocrit at a higher level. Some patients with ACD complain of fatigue. Others decrease their activity level to alleviate the fatigue and do not complain.

However, these changes, even if small, may lead to a decreased quality of life. The patients are less able to care for themselves and do what they want to do. They need a higher level of care, sometimes necessitating placement in a nursing home or care center. The clinician may consider physical therapy to improve their endurance if they are able to tolerate it. Other patients need energy conservation techniques, such as doing the most difficult activities at a time when they are feeling their best and taking frequent rest periods. Consider other therapy if these methods are not sufficient.

Transfusions can be useful for immediate treatment in severe, symptomatic anemia. The drawbacks to the use of transfusions include allergic reactions, limited blood supply, and risk of disease transmission. The patient also must go to a facility to receive the transfusion, thus increasing the cost, work, and expense.

Iron-deficiency anemias can be treated with oral iron. The usual recommended dose is between 150 and 200 mg elemental iron daily. Higher doses are needed when iron is poorly absorbed. The recommended dietary intake of iron for older persons is 10 mg/day. Adverse effects of iron therapy are abdominal discomfort, nausea, vomiting, and constipation. These adverse reactions can lead to decreased food intake, bowel impaction, and other problems, including unnecessary GI examinations, and can lead to decreased compliance with iron therapy. One study showed significantly lower incidence of adverse effects and effective treatment of iron deficiency with the use of doses as low as 15 mg instead of 150 mg.¹¹ This study is particularly impressive in that the subjects were older than 80. An additional factor to consider is

**Box 3. Clinical Practice Implication**

A. Monitor for fatigue in the patient
B. Monitor for anemia through routine CBC counts
C. If a patient complains of fatigue, do a thorough assessment to determine the cause of the fatigue
D. If the patient has anemia (confirmed through laboratory work)
   1. Evaluate the laboratory findings
   2. Perform additional tests as needed to determine the cause of the anemia
E. To treat
   1. Treat any medical condition that is amenable to treatment
   2. Treat any other cause for the anemia
F. If the anemia does not improve
   1. Evaluate the effect the anemia is having on the patient’s quality of life
   2. If it is significant, consider whether treatment with epoetin might help
Intravenous iron sucrose (Venofer) is indicated for treatment of iron-deficiency anemia in patients undergoing chronic hemodialysis who are receiving supplemental erythropoietin therapy.\(^{12}\) It is also used for iron-deficiency anemia in patients who cannot tolerate oral iron. It is given intravenously by infusion or by slow injection over a period of at least 15 minutes. Slow infusion rates decrease the risk of hypotension. The dose is 5 mL iron sucrose (100 mg elemental iron). Common adverse reactions include allergy, hypotension, cramps or leg cramps, nausea, headache, vomiting, and diarrhea.

### Table 2. Dosage and Administration of Epoetin

<table>
<thead>
<tr>
<th>Disease</th>
<th>When to Use</th>
<th>Starting Dose</th>
<th>Increase Dose When</th>
<th>Maximum Dose</th>
<th>Decrease or Stop</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF</td>
<td>—</td>
<td>50-100 U/kg</td>
<td>8 wk, CBC</td>
<td>300 U/kg</td>
<td>HCT 36% or increase of more than 4 points in 2-wk period</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TIW</td>
<td>not increased</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>by 5-6 points</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cancer or cancer therapy</td>
<td>Serum erythropoietin level &lt;200 mU/mL</td>
<td>150 U/kg TIW</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>HIV</td>
<td>On zidovudine, serum erythropoietin level &lt;500 mU/kg</td>
<td>100 U/kg TIW</td>
<td>In 8 wk, if response not satisfactory</td>
<td>300 U/kg</td>
<td>NA</td>
</tr>
<tr>
<td>Surgery</td>
<td>—</td>
<td>100 U/kg weekly</td>
<td>—</td>
<td>600 U/kg</td>
<td>—</td>
</tr>
</tbody>
</table>

Information from drug package insert. TIW, three times week.

that with oral iron therapy bowel movements turn black, masking any GI bleeding that might be present.

Epoetin Alfa Treatment

Epoetin is an additional therapeutic option that was shown to be effective in treating many anemias of decreased RBC production. The use of this drug has been studied most extensively in the treatment of anemia of CRF, whereby it is generally effective if the patient is adequately dialyzed.\(^{13}\) It is also used for iron-deficiency anemia in patients who cannot tolerate oral iron. It is given intravenously by infusion or by slow injection over a period of at least 15 minutes. Slow infusion rates decrease the risk of hypotension. The dose is 5 mL iron sucrose (100 mg elemental iron). Common adverse reactions include allergy, hypotension, cramps or leg cramps, nausea, headache, vomiting, and diarrhea.

In cancer, the response rate has been 40% to 80%, depending on the study.\(^{14}\) In RA, most patients have shown a positive response to epoetin.\(^{15}\)

Epoetin is being tried for patients with heart failure and anemia. Darbepoetin was shown to increase the hemoglobin level and to improve symptoms. However, a decrease in mortality in these patients with heart failure was not documented.\(^{16}\)

An interesting new use of epoetin is for the prevention of blood transfusions during surgery. The scarcity of blood for transfusions has lead to a search for alternatives for patients undergoing elective surgery. Although donation of autologous blood is the preferred alternative, elderly patients are often unable to make new RBCs quickly enough. Epoetin has been shown to facilitate the production of autologous blood that can be donated before elective surgery.\(^{17}\) Patients who will benefit most are patients with a hematocrit of 33 to 39 whose blood loss during surgery is expected to be 1000 and 3000 mL.

Epoetin is relatively expensive as a treatment.\(^{18}\) It costs about $300 per dose of 20,000 units, which would total about $1,200 per month, given weekly.
Epoetin therapy may be reimbursed under Medicare Part B, providing strict requirements are followed. The companies who deliver the medication and fill out the reimbursement forms for the medication are a good source for information about reimbursement requirements in your area. See Table 2 for specific dosage and administration information in anemias caused by other diseases and Box 4 for additional information about the use of epoetin.

**Darbepoetin alfa (Aranesp)** is another medication that is closely related to erythropoietin. It is indicated for anemia, secondary to renal failure, and anemia secondary to cancer chemotherapy. Off-label indication for this product is anemia secondary to malignancy. Absorption of this product is slow with the peak concentration occurring at 24 to 72 hours in patients with CRF and 71 to 123 in patients with cancer.

**Summary**

Anemia is a common finding in the elderly. One of the frequent problems responsible for this condition is ACD, which is caused by decreased RBC production. It is generally not treated. However, if the anemia is causing significant fatigue, which is interfering with the patient's quality of life, treatment with epoetin may be effective. Epoetin...
does not have a specific indication by the Food and Drug Administration listed for use in ACD, but many clinicians are beginning to use it successfully to improve the quality of life in elderly patients with ACD.

References


Maren Mayhew, MS, ANP, GNP, CRNP, has worked in office, nursing home, and home care settings in the Washington, DC, area for more than 25 years. She has also served as a faculty member in several NP programs. She has coedited five books for nurse practitioners, including A Pharmacology Textbook for Primary Care Providers. In accordance with national ethical guidelines, she has disclosed that she has no financial relationships with business or industry. She may be reached at marenmayhew@comcast.net.