The purpose of this monograph is to provide a concise update on the management of anemia for multidisciplinary health professionals who work in long-term care (LTC) facilities. New information on the pathophysiology of anemia, and the availability of potentially effective therapy for anemia associated with chronic kidney disease (CKD), which is prevalent in the LTC population, have provided an impetus for clinicians to consider evaluating and treating this condition more actively than has been the case in the past. The monograph is intended to provide an overview of these new directions in the management of anemia in LTC.

Is anemia too often the missing diagnosis in LTC residents? A case example:

A 92 year-old cognitively intact female nursing home resident with congestive heart failure (CHF) and chronic renal insufficiency experienced an increase in edema in her legs, weight gain, and shortness of breath on minimal exertion. These exacerbations of her symptoms, as well as several falls, lead to increasingly frequent hospitalizations. Her CHF medications were maximized but she continued to complain of weakness. Her multiple health problems – obviously serious in the setting of advanced age – appeared to explain her physical decline.

Neither the family nor the patient was ready to “give up”. Additional steps were taken to further evaluate the patient.

Laboratory testing performed during her most recent hospitalization revealed a hemoglobin (Hgb) value of 9.0, well below the generally accepted value for anemia (<12 g/dL). Her hemoglobin values had declined over the years, and no bleeding source had ever been identified. Her creatinine had gone from 1.3 to 1.6 over the last 4 years and at age 92 she “weighed her age”. She was given an erythropoiesis stimulating protein to treat the condition and, over three months her hemoglobin improved. Her weakness improved and other vague symptoms, including dizziness and lack of appetite, also got better. She was able to stay out of the hospital for the next 8 months.

Anemia in LTC: What is the scope of the condition?

Despite an estimated prevalence of over 40% within LTC facilities, anemia may not always be “on the radar screen”. There are a host of explanations why the condition may be overlooked. The symptoms and signs of anemia in the elderly such as fatigue, weakness, and dyspnea are not specific and can be attributed to old age, making it a condition somewhat easy to overlook. Even skin pallor, which can be a helpful diagnostic clue in younger patients, may be hard to recognize in an elderly patient. Mild anemia in particular may not result in a comprehensive analysis of its cause – especially when there are other serious co-morbidities present.

Emerging research over the past decade has revealed a high prevalence of anemia in the elderly population – those with chronic disease and those who otherwise appear healthy. Data from the non-institutionalized U.S. population assessed in the third
National Health and Nutrition Examination Survey (NHANES III) showed anemia prevalence rates rose rapidly after age 50 to >20% at age 85 and older. In all, over 3 million people in the U.S. aged 65 years and older are anemic. (See Figure 1)

While many questions remain to be answered, the implications of anemia on the health and well-being of elderly residents of LTC facilities can be substantial. In a climate of ever-increasing healthcare costs, it is also important to note that although specific data on the economic impact associated with anemic elderly patients are limited, a recent survey found adverse health effects associated with the condition increases costs.

Anemia in elderly patients may be implicated in a host of federal nursing home quality indicators, including rates of decline in mobility and being bedfast, cognitive impairment, and decline in activities of daily living such as eating and bathing. Anemia may also be associated with an increased risk of falls in elders who live in the community as well as LTC facilities.

Anemia is known to impact several outcomes. It can reduce exercise tolerance and, by contributing to frailty, lead to an increase in hospitalizations and transitions in care. In fact, an increased need for hospitalization has been associated with elderly people with anemia who reside in nursing homes or the community when compared with a cohort without anemia. Also, anemia has been shown to result in longer hospital lengths of stay and an increase in mortality after hip fractures when compared to those without anemia.

Recent studies have shown an association between anemia and increased severity of a number of conditions in elders, including diabetes, cardiovascular disease (CVD) and chronic kidney disease (CKD).

**What is the pathophysiology of anemia in the LTC population?**

To understand the potential clinical impact of anemia and to appreciate the pharmacologic treatment of this disorder, anemia must be thought of first and foremost as increasing the risk of tissue hypoxia. The heart responds to tissue hypoxia by increasing cardiac output, decreased vascular resistance, and decreased blood viscosity, allowing cardiac output to rise without an increase in blood pressure. Cardiac pump failure follows along the Frank-Starling curve.

A summary of potential symptoms and signs of anemia illustrates that many body systems may be adversely affected by the hypoxic insult of anemia, including the central nervous system, gastrointestinal tract, vascular system, and cardiorespiratory systems. (See Figure 2)

Erythropoiesis, the process of producing red blood cells, occurs almost exclusively in the bone marrow. When low concentrations of oxygen in the blood are detected, the hormone erythropoietin (EPO) is released by the kidneys, stimulating the marrow to increase red blood cell production. Erythropoiesis can be affected by multiple factors, including chronic disease, damage to erythroid progenitor cells by pro-inflammatory cytokines and free radicals, blood loss,
vitamin deficiencies, hypersplenism, autoimmune hemolysis, renal dysfunction, and other conditions.

**What are the causes and risks of anemia in the LTC population?**

Although anemia is common in the elderly population and its prevalence increases with age, it is not an inevitable consequence of aging. In approximately 80 percent of elderly patients diagnosed with anemia, an underlying cause for hemoglobin values of less than 12 g/dL is identified—most commonly iron deficiency and chronic disease (CKD, infections, malignancies, and chronic inflammatory disorders).

Other causes are gastrointestinal bleeding, myelodysplastic syndromes, vitamin B12 deficiency, and folate deficiency. Blood loss from surgery, injuries, and gastrointestinal and genitourinary bleeding increases risk but is more common in hospitalized patients. Multiple factors often contribute to the problem in the LTC population, among whom multiple co-morbidities are common. However, in about 20% of elderly population who are anemic, no cause is found.

There are multiple definitions for anemia (see Figure 3). Although these definitions are useful for diagnostic purposes and clinical studies, they should not be thought of as a “magic” number that reveals an absolute high and low risk of adverse outcomes in elderly anemic patients.

**Figure 3**

<table>
<thead>
<tr>
<th>Definitions of Anemia</th>
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<tr>
<td><strong>World Health Organization (WHO)</strong></td>
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<td>Women: Hgb &lt; 12 g/dL</td>
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<td>Men: Hgb &lt; 13 g/dL</td>
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<tr>
<td><strong>National Kidney Foundation</strong></td>
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<tr>
<td>Recommends further evaluation of CKD patients if Hgb is &lt; 12 g/dL</td>
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The Women’s Health and Aging Study, a cohort study of community-dwelling women 65 years of age and older, revealed that hemoglobin values below 13 g/dL are an independent risk factor for mortality and disability. Moreover, two recent studies concluded that higher hemoglobin measurements, up to approximately 14 g/dL, are associated with improved overall health measures, and concentrations only slightly below the WHO threshold level may be correlated with worse outcomes in the elderly.

**How is anemia diagnosed in the LTC population?**

A careful history and physical examination coupled with a laboratory evaluation (complete blood count with reticulocyte count, tests of hepatic and renal function, serum ferritin, vitamin B12 level, stools for occult blood) frequently provide enough information to determine the cause of anemia in an elderly patient. Microcytosis and reduced serum ferritin values—both signs of iron deficiency—are somewhat less likely to be present in older people; anemia due to iron deficiency can be masked by elevations due to the presence of other co-morbidities. Pernicious anemia (which affects approximately 2% of the population older than 60 years) can be missed because of the absence of macrocytosis or clinical signs. Measurement of vitamin B12 levels is therefore important in anemic LTC patients. The evaluation of anemia in patients with CKD is discussed further below.

**What is the relationship between anemia and CKD in older people?**

Chronic kidney disease (CKD) is defined by the National Institutes of Health’s National Kidney Disease Education Program (NKDEP) as a persistent and usually progressive reduction in glomerular filtration rate (GFR less than 60 mL/min/1.73 m²), and/or albuminuria (more than 30 mg of urinary albumin per gram of urinary creatinine). This definition is consistent with the National Kidney Foundation’s definition of CKD. According to the NKDEP, in adults the best equation for estimating GFR from serum creatinine is the Modification of Diet in Renal Disease (MDRD) equation. However, it is important to note inaccuracies due to the non-steady state of serum creatinine. In addition, older patients often have co-morbidities causing malnutrition, and may be prescribed medications that can interfere with the measurement of serum creatinine. A calculator for GFR based on both the MDRD and Cockcroft-Gault equations is available on the internet at www.nephron.com.

CKD is prevalent in the U.S., affecting close to 19 million people, with the greatest prevalence in those over age 65 and those with diabetes or hypertension. Clinically significant declines in kidney function have been reported in LTC populations. For example, a recent Canadian study found almost 40 percent of residents in LTC facilities had a GFR < 60 mL/min/1.73m². Anemia increases in prevalence and severity as renal function deteriorates, adding to the morbidity and mortality of CKD. Anemia can develop relatively early in the course of CKD. A health maintenance organization study of 1,658 CKD patients found 73% had serum creatinine values of less that 1.0 mg/dL, but higher gender-specific norms—and in 28% of these mild CKD cases, anemia was noted.

As kidney function declines, the likelihood of anemia associated with a poor endogenous EPO response increases. Awareness of the adverse consequences of untreated anemia of CKD has increased and national guidelines have been developed by the National Kidney Foundation (see Figure 4) to disseminate diagnosis, workup and treatment standards for anemia associated with CKD.

Early detection and treatment of anemia associated with CKD may significantly improve the quality of life of elderly patients, and may also slow the progress of cardiovascular disease and decrease hospitalizations and mortality in this population.
What is the impact of anemia, CKD, and cardiovascular disease in the LTC population?

Cardiovascular disease, also common in the LTC population, as well as CKD, may be complicated individually by anemia. This triad of disorders may be the best reason to treat anemia of CKD in the elderly. Such compounding of multiple co-morbidities is in fact common in the LTC population.

A case in point: recent research has shown that anemia associated with CKD is a risk factor for increased morbidity and mortality due to cardiovascular events in a diverse adult population. In addition, anemia and abnormal renal function have been associated with an increased risk of death in patients who undergo percutaneous coronary interventions. Another recent study of 436 high-functioning community-dwelling women between the ages of 70 and 80 participating in the Women’s Health and Aging Studies I and II found that mildly low and even low-normal hemoglobin concentrations were associated independently with increased frailty. This risk was synergistically modified and increased in women with CVD. It remains unproven whether this association is causal.

The impact of even mild anemia in patients with CHF can be significant. In a retrospective study of 142 CHF patients with anemia, 40% of the patients were also diagnosed with CKD. Epoetin and intravenous iron were administered once weekly to achieve target hemoglobin values of 12.5 g/dL. The final mean hematocrit reached in this group was 35.9%. Over a period of about 7.2 months, the left ventricular ejection fraction (LVEF) increased significantly (from 27.7% to 35.4%). Of particular interest to the LTC community was a significantly decreased rate of hospitalization – the number of hospitalizations per patients was reduced more than 10 fold. In addition, the RENALL trial demonstrated that a hemoglobin value of approximately 11 g/dL was associated with a four times greater risk of End Stage Renal Disease (ESRD) than normal hemoglobin defined as >13.6g/dl.

How do we optimally treat anemia in the LTC population, based on what we know now?

Therapeutic strategies for anemia include:

- Identifying and treating any underlying disorder (e.g. vitamin B12 deficiency, acute or chronic blood loss)
- Iron
- Erythropoietic agents
- Blood transfusions

A brief note about blood transfusions: the decision to transfuse elderly anemic patients, especially those undergoing surgery, is not always clearly defined and the issue has seen sparked debate and controversy. In the ABC (anemia and blood transfusions in the critically ill) study involving 3,534 patients in 146 western European ICUs, 54% of patients were transfused because of an inadequate hemoglobin concentration, and transfusions increased with age. The results of the study suggest a deleterious effect of blood transfusion on surgical outcomes. Each patient should be
assessed individually with the clinical decision to transfuse based on the individual's condition, age, and oxygenation parameters with indexes of tissue hypoxia, as well as traditional measurements of hemoglobin and hematocrit.

Drug treatments for anemia are outlined in Figure 5.

Supplementation with iron is used for the treatment of iron deficiency anemia. The usual recommended dose is 50 to 100 mg of elemental iron three times a day. If side effects such as constipation and/or compliance are problematic, a lower dose of elemental iron, such as a single 325-mg tablet of iron sulfate can be tried, although it is often inadequate to replace iron stores, especially during initial management. Patients with iron deficiency who fail to respond to these strategies can be given intravenous (IV) iron replacement. IV iron sucrose (Venofer®) can be administered safely in pre-dialytic patients with anemia without the risk of adverse reactions associated with iron dextran products.

Vitamin B12 deficiency is treated by administration of parenteral or oral vitamin B12 supplementation. The intramuscular dose is 1,000 µg, usually given daily for one week, then weekly for one month and monthly. Daily oral therapy (1,000 to 2,000 µg of vitamin B12) has been shown to be as effective as intramuscular injections.

Human recombinant erythropoietin (epoetin alfa), introduced in 1989, has significantly impacted the treatment of anemia associated with CKD. Today, two erythropoiesis-stimulating proteins (ESPs) are available for anemia associated with CKD - epoetin alfa and darbepoetin alfa. Standard dosing for these drugs are based on weight (but units differ for each ESP). All patients on ESP treatment should receive concomitant iron therapy in order to replenish iron stores that are used in the process of erythropoiesis.

Are ESPs safe and efficacious in the elderly LTC population?

Several studies have addressed this question and concluded there were no significant differences in safety and efficacy for older patients when compared to younger cohorts. An important aspect of ESP therapy is monitoring the hemoglobin response, initially once per week to make sure hemoglobin is not increasing too quickly. Dosage should be reduced by 25% if the hemoglobin rises by more than 1 g/dL over a course of 2 weeks. On the other hand, if hemoglobin has not risen by more than 1 g/dL after 4 weeks, the dose should be increased by 25% in order to reach a target hemoglobin value in the range of 11 to 12 g/dL.

Emerging issues regarding pure red blood cell aplasia in patients receiving ESP therapy: in late November 2005 both companies that market ESPs, Amgen and Ortho Biotech, sent letters to health professionals warning of pure red blood cell aplasia, associated with darbepoetin alfa (Aranesp®), epoetin alfa (Epogen® Procrit®). Pure red blood cell aplasia is an anti-erythropoietin-antibody-mediated severe anemia and red blood cell aplasia. The prevalence of anti-erythropoietin-antibodies has been reported at 3% in cancer patients and 4% in patients with CKD (with a product manufactured in Europe (Eprex). Anti-erythropoietin antibodies neutralize the hematopoietic factor rendering it ineffective and producing a severe anemia.

What has yet to be reported is the true risk of developing pure red cell aplasia in elderly patients and whether or not the potential is time or dose dependent. In patients developing antibody, there appears to be a greater chance of this occurring with subcutaneous injection rather than IV infusion.

As a result of this information, new recommendations are emerging. Suggested monitoring recommendations are listed in Figure 6.
Figure 6

Recommendations for Monitoring Erythropoietin Stimulating Protein ESP) Therapy

• Monitor hemoglobin weekly upon initiation of therapy with an erythropoietic stimulating protein and then monthly once stabilized at the desirable hemoglobin concentration.

• Monitor for a sudden loss of response (i.e. hemoglobin declines that can no longer be maintained at the target concentration).

• If a sudden loss of response occurs, an anemia assessment including a reticulocyte count should be recommended with a comprehensive assessment of causative factors.

• If anti-erythropoietic antibody pure red blood cell aplasia is suspected:
  • discontinue the erythropoietic stimulating protein contact the manufacturer (Amgen: 1-800-772-6436 and Ortho Biotech: 1-800-325-7504, prompt #2) to arrange for assays for binding and neutralizing the antibodies and to confirm the diagnosis.

Once antibody-mediated anemia has been confirmed, erythropoietic factors must be discontinued permanently. Due to the potential for cross-reactivity, the patient should not receive alternative erythropoietic factors (i.e. if the anemia was caused by Procrit® the patient cannot receive Aranesp® or Epogen®).

The manufacturers have reported that no clinical sequelae have resulted from antibody-mediated anemia. Alternative therapy is not available for patients that develop antibody-mediated anemia to erythropoietic stimulating proteins. Iron therapy and intermittent blood transfusions may be needed, as dictated by the severity of the underlying anemia of chronic kidney disease or chemotherapy induced anemia.

In conclusion: what do we know and what should we be doing?

• We know anemia is common in the LTC setting.

• From the data we have now, we know that anemia is associated with a number of adverse consequences such as falls and frailty, but we cannot say that anemia causes falls and frailty.

• The impact of the increasing elderly population coupled with the rise in anemia and CKD in this population heralds the need for diligence in evaluating renal function in the elderly.

• We need to recognize that anemia can occur early in the course of CKD and to think CKD when anemia is diagnosed.

• We must also recognize diagnosis can be a challenge.

• Treatment can be effective if targeted at the underlying cause of the anemia, however, we do not know if treating asymptomatic anemic elders results in benefits.

Working as a multi-disciplinary team can help overcome obstacles in the early identification and treatment of the anemia in the LTC patient population. Nursing staff can be instrumental in identifying sometimes subtle signs and symptoms. The consultant pharmacist also plays a critical role in the management of anemia associated with CKD in the LTC setting, monitoring not only pertinent laboratory values and ESP therapy, but the use of multiple therapeutic agents for anemia, other serious illness such as CKD and CVD, as well as medications for concomitant disorders often seen in the elderly population. They can also help with issues of reimbursement and timing for treatment and appropriate site for administration. Primary care clinicians must be involved in the diagnostic evaluation and targeting of treatment for anemia in LTC residents, and medical directors should be involved in developing policies and procedures that assure adequate identification and management of these common conditions.

Well-designed, prospective studies that address clinically meaningful outcomes in LTC residents with anemia and anemia associated with CKD will help all of us make better decisions. Such studies should address the optimal therapeutic regimen for patients with anemia associated with CKD and other conditions. Documentation of improvements in function, quality of life, and other outcomes with optimal diagnosis and treatment of the various forms of anemia will result in a welcome addition to our therapeutic armamentarium in the LTC population.
References


“All we can ask of our clinicians at this time is to first be aware of the hemoglobin values in each of their patients. Anemia should be on the radar screen, not just background noise. If anemia is discovered the question should be ‘what should I do about it’. One next step in the differential should be to estimate renal function and if reduced to look at the patients cardiovascular risk, especially hospitalizations. The rest of the decision making based on clinically relevant data will drive therapy.” – Eric G. Tangalos, MD, FACP, AGSF, CMD

“Important to the correction of anemia in older persons with chronic kidney disease and other causes of anemia is adequate replacement of iron stores in addition to supplementation with erythropoietic therapy. In the elderly, iron stores are difficult to replete due to the side effects of iron therapy, but nonetheless critical to the therapeutic success of the anemia regimen.” – Barbara Zarowitz, Pharm. D.

“Not all anemias need interventions - the main question or thought should always be ‘what is the overall plan of care for this patient? Would giving them a weekly injection or daily injection cause so much distress that the benefit is outweighed by the distress?’” – Debbie Gunter, G.N.P.

“From a societal perspective, the growth in the older population in LTC settings who have anemia associated with CKD as well as cardiovascular disease and other comorbidities will pose enormous challenges. Further research is critically needed to determine the impact of diagnosing and treating anemia in the LTC population on function, quality of life, other health outcomes, and the costs of care.” – William McClellan, M.D., M.P.H.