LTC Physician Information Tool Kit Series

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Anemia in Long Term Care

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A C K N O W L E D G E M E N T S

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INTRODUCTION

According to U.S. Bureau of the Census data, the number of people age 65 and over is expected to rise to approximately 80 million in 2050 from 30 million in 1990.[1] The fastest growing segment of this population, people over age 85, is expected to increase fivefold by 2050.[1] With this increase in the elderly population, a rise in age-related health conditions may be expected.

Although anemia often occurs in older people, it is not considered a "normal'' consequence of aging.

Anemia is associated with increased disability, decreased physical performance, decreased muscle strength, increased risk of cardiovascular events, impaired quality of life, increased risk of falls, and increased mortality. The condition is common in long-term care patients, but it is often unrecognized, undiagnosed, and untreated. Recent research suggests that anemia, even in frail, older patients, is potentially treatable.

DEFINITION

Anemia, the most common abnormality of the blood,[2] is a deficiency in the concentration of hemoglobin (Hb)-containing red blood cells (RBCs). The World Health Organization's (WHO's) criteria for anemia are an Hb level of less than 13 g/dL in men and less than 12 g/dL in women.[1]

SIGNS AND SYMPTOMS

As RBCs containing oxygen-carrying Hb decrease, the body has to work much harder, resulting in signs and symptoms that are usually insidious and are frequently nonspecific and asymptomatic. Symptoms of mild anemia may include increased heart rate, palpitations and shortness of breath on exertion, and mild fatigue; severe anemia may cause symptoms such as palpitations and shortness of breath at rest, severe fatigue, and exercise intolerance. Other symptoms may include dizziness, fainting, angina, irritability, insomnia, muscle weakness, headache, decreased concentration, insomnia, pale skin, conjunctival pallor, and impaired wound healing. Symptoms of other conditions, such as congestive heart failure, angina, or cognitive impairment, may also worsen when anemia is present.

CAUSES OF ANEMIA IN THE ELDERLY

Studies have shown that Hb levels in healthy elderly people between ages 60 and 98 do not change significantly.[1] Anemia in the elderly population may be attributed to different etiologies; it may be caused by disease, the underlying treatment of disease, or both.

Anemia may be caused by nutritional deficiencies (iron, vitamin B_{12}, or folate), blood loss (such as that from gastrointestinal ulcers, diverticular disease, colon cancer, or colonic angiodysplasia), chronic inflammatory disease or malignant disease, and unknown causes. Based on the results from the third National Health and Nutrition Examination Survey (NHANES III), Guralnik and colleagues reported the distribution of types of anemia in older anemic people in the United States as follows:[3]

– Approximately one-third of all anemias are deficiencies of iron, vitamin B_{12}, or folate and blood loss; half of this group consists of iron deficiency anemia.
– Anemia of chronic inflammation or chronic kidney disease, or both: approximately one-third of all anemia.
– Unexplained anemia: approximately one-third of all anemia.

Deficiencies of Iron, Vitamin B_{12}, or Folate

Iron deficiency anemia may result from inadequate dietary intake or absorption of iron, but most adults with iron deficiency have gastrointestinal blood loss.[3] It is important to determine the cause of blood loss because it may be a marker of underlying disease. Iron deficiency anemia may be diagnosed on the basis of low serum ferritin levels, high total iron-binding capacity (TIBC) and transferrin levels, low transferrin saturation, high concentration of free transferrin receptor, and the absence of bone marrow iron stores.[1]

The prevalence of vitamin B_{12} deficiency is unknown, but the incidence appears to increase with age.[4] Vitamin B_{12} deficiency is rarely caused by inadequate nutrient intake; in most cases it is caused by decreased digestion and release of vitamin B_{12} from food for absorption resulting from increased gastric pH and reduced gastrin production.[1] Pernicious anemia, gastrectomy, small bowel disorders, bacterial overgrowth, and atrophy of gastric cells that produce intrinsic factor may cause decreased digestion and uptake of vitamin B_{12} from food. These conditions increase with age.[5] Prolonged use of acid-suppression therapy, which is becoming common, may also cause malabsorption and depletion of B_{12} stores.[4]

Signs and symptoms of vitamin B_{12} deficiency are not always present; evaluation of serum B_{12} levels may be performed in all elderly patients, and those whose levels are less than 350 pg/mL may require further testing.[5] Several studies have shown that use of B_{12} level as a sole marker for B_{12} deficiency may lead to missed diagnoses. Elevated levels of methylmalonic acid and homocysteine may be early markers for vitamin B_{12} deficiency and may be a much more sensitive diagnostic clue than serum B_{12} levels.

Folate deficiency usually is the result of inadequate dietary intake, but it may also be caused by other conditions such as alcoholism, liver disease, malabsorption, or medications. It may be detected by examining the serum folate level, serum homocysteine level, and methylmalonic acid level. (If the methylmalonic acid level is also elevated, it is important to determine whether the anemia is secondary to vitamin B_{12} deficiency.)

Treatment-Related Anemia

Anemia may occur either as a direct result of disease or as a side effect of treatment of the disease. In cancer patients, anemia may be caused (or worsened) by the myelosuppressive effects of chemotherapy or radiation therapy or by the destruction of RBCs during surgery. Cazolla reported that certain chemotherapy agents can blunt erythropoietin production, causing prolonged anemia.[6]

Anemia of Chronic Inflammation

Anemia of chronic inflammation (ACI) was traditionally referred to as anemia of chronic disease (ACD) and included any anemia without a known cause in people with chronic diseases.[3] This new term is more precise and reflects current concepts in anemia pathogenesis.[3] ACI has been correlated with elevated inflammatory cytokines, which have been implicated in the development of anemia by stimulating the production of hepcidin, which in turn causes reduced intestinal iron absorption and decreased release of iron.[3] The inability to replace RBCs normally is associated with diseases such as cancer and arthritis and other inflammatory conditions. The severity of the anemia is closely related to the severity of the underlying disease. Diseases associated with ACI include acute infections, chronic infections, chronic inflammatory disorders, malignancies, chronic kidney disease, and hypothyroidism.

Unknown Causes of Anemia (UA)

It is not always possible to identify a cause for anemia among the elderly. Inadequate workups sometimes hinder recognition of common causes such as ACI. Artz and colleagues suggested that nursing home residents with unknown causes of anemia have a blunted endogenous erythropoietin response.[7] Stressors such as shortened RBC survival, occult blood loss, and nutrient deficiencies may contribute to diminished marrow erythropoiesis.[7] Cytokine level alterations associated with aging may cause inhibition of erythopoiesis.[7] Increased cytokines are sometimes found in elderly people who have no discernible chronic disease or inflammation. These circulating cytokines may either decrease production of erythropoietin or impair response to endogenous erythropoietin, resulting in anemia.[8] Aging is associated with increased concentration of cytokines such as serum IL-6;9 according to Ershler, this association may suggest an "anemia of aging."[8] If proven, the finding would represent a departure from the current belief that aging itself is not associated with anemia.

PREVALENCE OF ANEMIA IN THE ELDERLY

The Third National Health and Nutrition Examination Survey (NHANES III) provides a comprehensive database for determining prevalence of anemia in the U.S. population.[3] The study revealed that in the community-dwelling population, 11.0 percent of men and 10.2 percent of women age 65 and older were anemic according to the WHO definitions of anemia. Among those 85 and older, 26.1 percent of men and 20.1 percent of women were anemic,[3] almost a doubling in the prevalence of anemia over people in 75-to-84 age group. Additionally, substantial differences exist in the prevalence of anemia by race; prevalence of anemia is 3 times greater among non-Hispanic blacks than among any other ethnic group.[3]

NHANES III found a greater prevalence of anemia in men than in women. However, the WHO defines anemia differently for men and women. Because low Hb levels are more common in younger women (due to menstrual blood loss), a Hb level of 12 g/dL may be a suboptimal criterion for "normal" for postmenopausal women.[10] If the same definition of anemia is used for both men and women (Hb of less than 13 g/dL), the prevalence of anemia in women age 65 and older is 32.5 percent, compared with 11.0 percent in men.[3]

Ershler reported that a National Geriatrics Research Consortium survey found anemia (as defined by the WHO criteria of less than 13 g/dL for men and less than 12 g/dL for women) in approximately 50 percent of residents of long-term care facilities.[8] Besa reported that the prevalence of anemia in the population age 65 and older varies greatly depending on whether the individuals live in community or long-term care facilities; less anemia is observed in those who live at home or in residential care homes than in those who reside at chronic- or acute-care facilities.[11]

DISEASES AND CONDITIONS ASSOCIATED WITH ANEMIA IN THE LONG-TERM CARE SETTING

Anemia is associated with diseases and conditions such as chronic kidney disease, cardiovascular disease, and diabetes, which are prevalent in the long-term care setting. These comorbidities are discussed in more detail below.

Chronic Kidney Disease

The National Kidney Foundation defines chronic kidney disease (CKD) as either kidney damage for 3 or more months characterized by structural or functional abnormalities of the kidney, with or without decreased glomerular filtration rate (GFR); or as GFR of less than 60mL/min/1.73 m2 for 3 months or more, with or without kidney damage.[12] CKD is associated with poor health outcomes, including progression of kidney failure, complications related to decreased kidney function, and the development of cardiovascular disease, as well as increased health care costs.[13] CKD is present in more than 20 million adults in the United States, and millions more are at risk for developing the disease[13] The prevalence of CKD is greatest in patients over age 65 and in those with diabetes or hypertension.[13] As the number of patients with diabetes and hypertension increases, the number of patients with CKD is also expected to increase. The elderly are at especially high risk for CKD due to the normal decline in renal function with aging and the high prevalence of diabetes and hypertension in this age group.[14]

Renal anemia is one of the most common complications of CKD. Anemia develops early in patients with CKD because the diseased kidneys are unable to produce adequate quantities of erythropoietin in response to hypoxia. Renal anemia is a contributor to the extremely high cardiovascular mortality seen in CKD patients.[14]

Cardiovascular Disease

Anemia may worsen cardiac function because the hemodynamic mechanisms that interact to compensate for anemia may increase cardiac output, which may result in the development of left ventricular hypertrophy (LVH). Each 1 g/dL decrease in Hb is associated with a 6 percent increase in LVH risk.[15] This risk for LVH is of the same magnitude as a 10 mmHg increase in systolic blood pressure. LVH is another important contributor to cardiovascular morbidity and mortality.[16]

Severe anemia can lead to congestive heart failure (CHF) even in the absence of underlying cardiovascular disorders.[15] When underlying cardiovascular disorders are present, anemia can lead to additional cardiovascular complications.[15] Silverberg reported that anemia is common in patients with CHF and is present in about one-third of patients with CHF.[17] He also found that anemia worsens with the

severity of CHF.[17] Other investigators have observed that patients with CHF who are anemic have higher rates of hospital readmission and mortality than CHF patients who are not anemic.[18]

Silverberg has recently proposed the term "cardio-renal anemia syndrome (CRA)" to illustrate the complex relationships between CKD, CHF, and anemia. Both CKD and CHF may cause anemia, which in turn can worsen CHF. Both anemia and CHF can further damage the kidneys, leading to worsening of anemia and CHF. This vicious cycle can result in progression of all three conditions.[17]

Diabetes

Diabetes is the leading cause of CKD in the United States. In the Prevalence of Anemia in Early Renal Insufficiency (PAERI) study, a large-scale survey, the prevalence of anemia was highest in CKD patients who also had a medical history of diabetes.[19] In this study, more than 50 percent of diabetic CKD patients had anemia, defined as a Hb of 12 g/dL or less.[19] Anemia in patients with CKD due to diabetes develops earlier and is more severe than in patients with nondiabetic renal disease.[20] Even a modest degree of anemia is associated with an increased risk for the development of end-stage renal disease in Type 2 diabetes patients with nephropathy.[21]

IMPACT OF ANEMIA IN THE LONG-TERM CARE POPULATION

Anemia is common in the long-term care population. As many patients in this population live to age 85 or older, age-related health conditions and anemia associated with those conditions are expected to increase. Even mild anemia is linked to physical decline in this group and may cause worsening disability, poor health, decreased muscle strength, functional dependence, cognitive abnormalities, falls, and reduced quality of life. Additionally, anemia in this population is a risk factor for hospitalization and mortality. In the Established Populations for Epidemiologic Studies of the Elderly (EPESE), anemic patients were more likely to die, to be hospitalized, and to spend more days in the hospital than nonanemic patients.[22] Chaves and colleagues evaluated the costs and resource utilization of anemic patients and found them to be higher than those of nonanemic patients. Anemic patients incurred annual mean costs that were approximately twice that of nonanemic patients, and they had more physician encounters, hospital admissions, and longer hospital stays.[23] Untreated anemia can increase the risk of conditions such as CHF, myocardial infarction, and dementia, thus increasing the demand for medical care in the long-term care setting and increasing the cost and utilization of health care resources.

QUALITY ASSURANCE PROGRAM FOR ANEMIA RECOGNITION AND MANAGEMENT

Anemia is not always listed as a diagnosis in patient medical records. A study by Ania and colleagues that used a Mayo Clinic laboratory database found that the diagnosis of anemia was documented in the medical records of only one-fourth of patients with moderate to severe anemia (Hb ≤11g/dL).[24]

Careful documentation is important in anemia management: A treatment plan should be developed, and the presence of anemia should be listed on the patient's

problem list so other providers are aware of the diagnosis. Anemia management documentation should include all disciplines and should focus on assessment, diagnosis of clinical problems, development and implementation of the care plan, evaluation of the Hb/hematocrit (Hct) response to treatment, and revision of the care plan as needed.[25]

When direct-care nursing staff notice any of the signs and symptoms of anemia as described above or in the "Be an Anemia Detective'' tool (Appendix 1), or the Minimum Data Set (MDS) nursing assessment coordinator notices that many of the items in the "Anemia Detective MDS Tool'' (Appendix 2) are checked, two quality assurance (QA) measures might be instituted: (1) to look at the patient's last Hb level in the medical record and (2) to speak to the attending physician about obtaining new blood work and then evaluating the anemia based on the results.

Because anemia is underrecognized in the elderly, the medical director or director of nursing may request a chart audit to see how many patients are anemic. After this information is collected, patient-specific audits may be conducted. Such an audit could include assessing whether the anemic patient has fallen recently, has experienced a decrease in any level of function, or has shown any symptoms of anemia. Hb/Hct levels may be obtained for such patients.

As part of a good QA program, it is important to educate care staff about the signs, symptoms, and consequences of anemia. Often, the symptoms of anemia are mistaken for other conditions. For example, a patient who is becoming weak and is declining physically due to anemia may be referred for a physical or occupational therapy evaluation. This evaluation would not be helpful, but unfortunately, such referrals commonly occur. The nursing staff needs to learn to become alert for signs and symptoms of anemia and know when to involve the attending physician or other health care provider to initiate an evaluation.

A QA program should be developed that considers the steps of the care process as follows:

1. Recognition: identifying the presence of signs and symptoms of anemia (History of anemia? Risks of anemia? Hb level below normal?).
2. Assessment: clarifying the nature, causes, and impact of anemia on the patient.
3. Treatment: selecting and providing appropriate interventions for the patient (Treatment options based on underlying cause).
4. Monitoring: reviewing the course of anemia as the basis for deciding to continue, change, or stop interventions.

Determining which patients should undergo evaluation is based on clinical judgment and must be individualized on the basis of life expectancies, goals of care, and the etiology and severity of the anemia. If the patient has a reasonable life expectancy and is willing to undergo blood draws, then a work-up is probably justified. However, if a patient is minimally symptomatic and has very limited life expectancy, then a full evaluation might not be warranted. Treatment of symptomatic anemia, apart from investigating its cause, may be considered in even very

“end-stage’’ patients if palliation is the goal of care. When the anemia is caused by nutritional deficiencies, treatment may be easy accomplished with supplementation. In making decisions, it is important to consider that treatment of anemia is associated with improvement in quality of life in the studies cited previously.

The patient history and physical examination may suggest laboratory tests to identify the type of anemia, the underlying causes, and the possible treatment options. Laboratory evaluation includes a complete blood count (CBC), which includes Hb/Hct, mean corpuscular volume (MCV), RBC, reticulocyte count, serum ferritin, serum iron, transferrin saturation, and B_{12} and folate.

ANEMIA MANAGEMENT

Role of the Medical Director

Most medical directors of long-term care facilities also serve as patients’ primary care physician, so the issue of anemia should be addressed from those two perspectives. Medical directors have a responsibility to focus on the processes of care for a population of people. They realize that good care needs a team approach and that care processes are not entirely physician based. Physicians are not the only caregivers who under-appreciate the role of anemia in negative health outcomes, so medical directors have an important role in educating and discussing this issue with the entire health care team. The “Anemia Detective’’ tool (Appendix 1) may be helpful to that end. Standardizing processes for anemia detection, routinely calculating GFR, and monitoring outcomes all should be considered in order to "raise the bar" for anemia management.

When caring for older patients, it is important to remember that recent studies clearly show that health care providers under-recognize and under-appreciate anemia. Practitioners and licensed staff should realize that they cannot keep writing “anemia’’ on a patient’s medical problem list without looking more critically at the condition’s cause and the probable negative effects it is having on the patient’s care goals. As discussed above, many illnesses can contribute to causing anemia; although it is necessary to manage those diseases optimally, treatment options for anemia exist beyond transfusions for the most urgent cases.

Renal insufficiency as a cause of impaired erythropoietin release and, ultimately anemia, is something that providers likely need to consider more thoughtfully. A patient does not need to have renal failure or be on dialysis for renal insufficiency to be a relevant problem. In fact, given that blood urea nitrogen (BUN) and creatinine are not highly sensitive markers of renal function in early renal insufficiency, routinely measuring or calculating GFR or creatinine clearance in anemic patients may help practitioners consider whether renal insufficiency is a contributing factor.

More work remains to be done in anemia research, especially in frail, older patients. The AMDA Foundation (see http://www.amdafoundation.org/) might play a role in supporting studies that look at the functional outcomes of treating anemia in patients with multiple chronic illnesses. Will treating the Hb value reduce the higher risk of hospitalization, functional decline, and mortality in someone who will continue to deal with CHF or rheumatoid arthritis? Studies that help answer this question more definitively for the frail elderly population should continue.

Treatment of Deficiencies of Iron, Vitamin B_{12}, or Folate

Treatment of iron deficiency anemia is determined by the underlying cause and the severity of the anemia. Severe, symptomatic iron deficiency anemia may require blood transfusion. The underlying cause of the iron deficiency should be evaluated and treated in most patients. Replacement iron therapy can include oral iron (300 mg elemental iron/day) or parenteral iron.[26] Iron supplementation therapy is recommended only when both the serum ferritin and Hb are low. Consideration should be given to investigating potential sources of blood loss as part of the workup in addition to treating the anemia.

If vitamin B_{12} deficiency is detected, the treatment is replacement therapy. Vitamin B_{12} replacements are generally given to patients with vitamin B_{12} levels below 300 pg/mL. Because the cause of deficiency is usually malabsorption, parenteral treatment as intramuscular cyanocobalamin on a monthly basis is recommended. Oral crystalline B_{12} also can be given daily, although compliance can be a concern.[27]

If folate deficiency is detected, replacement therapy is indicated. Daily oral or injected folic acid supplementation and dietary changes may be recommended to ensure adequate folate intake.[27] Decreased alcohol intake may also be recommended.

Treatment With Erythropoietic Agents

Anemia may be treated with RBC growth factors such as epoetin alfa (recombinant human erythropoietin) and darbepoetin alfa. These agents stimulate erythropoiesis by the same mechanism as endogenous erythropoietin and are FDA approved. They are not used for acute treatment of severe or life-threatening anemia.

Data from large clinical trials have shown that epoetin alfa increases Hb levels and decreases transfusion requirements in anemic cancer patients receiving chemotherapy (the results were independent of tumor response to chemotherapy and transfusion).[28] In several clinical trials, epoetin alfa has proved to be a safe and effective means of correcting the anemia associated with CKD.[29] The treatment targets are for Hb/Hct of 10–12 g/dL for hemoglobin and 33–36% for hematocrit.

Epoetin Alfa

To decrease the need for blood transfusions in patients with mild or moderate anemia, therapy with epoetin alfa should be considered. FDA-approved indications for epoetin alfa are as follows:

- Treatment of anemia in chronic renal failure or CKD in patients requiring dialysis and in patients not requiring dialysis.
- Treatment of anemia in cancer patients with nonmyeloid malignancies who are receiving chemotherapy.
- Treatment of anemia in zidovudine-treated HIV-infected patients.
- Reduction of allogeneic blood transfusions in anemic patients scheduled for elective, noncardiac, nonvascular surgery.

Epoetin alfa is not appropriate treatment for patients who require immediate correction of severe anemia and is not a substitute for emergency transfusions. Epoetin alfa is not indicated for treatment of anemia in cancer patients when the anemia is

the result of factors such as iron or folate deficiencies, hemolysis, or gastrointestinal bleeding. It is contraindicated in patients with uncontrolled hypertension, known hypersensitivity to mammalian cell–derived products, and known hypersensitivity to albumin.

Dosing of epoetin alfa differs for patients according to the condition that is being treated and the individual patient's target Hb levels. In general, the goal of therapy is to achieve an Hb level of 10–12 g/dL. Clinical judgment should be used to determine the appropriateness of initiating therapy in a patient whose Hb level is hovering near the lower limit of this range.

Treatment with epoetin alfa carries an increased risk of seizures and thrombotic events. Side effects such as hypertension, headache, nausea, vomiting, diarrhea, tachycardia, and arthralgia may occur. Because these risks may be related to higher Hb levels, it is important to carefully manage the Hb level and avoid exceeding the target level of 12 g/dL, the upper limit of the target range. Studies are currently in progress to determine the optimal dosing to balance patient factors and demand on health care services.

Darbepoetin Alfa

Therapy with darbepoetin alfa should be considered as an alternative to blood transfusion in patients who suffer from mild or moderate anemia. FDA-approved indications for darbepoetin alfa are

- treatment of anemia in cancer patients with nonmyeloid malignancies who are receiving chemotherapy and
- treatment of anemia in CKD in patients on dialysis and patients not on dialysis.

Studies are in progress to determine the optimal dosing to balance patient factors and demand on health care services.

Darbepoetin alfa is contraindicated in patients with uncontrolled hypertension and carries an increased risk of seizures and thrombotic events in all patients. It is not appropriate for patients needing immediate correction of severe anemia. Darbepoetin alfa should not be used to treat anemia caused by nutritional deficiencies or gastrointestinal bleeding. Its safety and efficacy have not been established in patients with underlying hematologic diseases such as hemolytic anemia and sickle cell anemia. The target for therapy is Hb 10–12 g/dL for both men and women; Hb should not rise too rapidly (faster than 1.0 g/dL in a 2-week period). The target Hb level should not exceed 12 g/dL.

SUMMARY

The purpose of the latest addition to the "AMDA LTC Physician Information Series'' is to raise the awareness of the incidence of anemia in the elderly and the impact it has on the elderly population. Anemia is not considered a "normal'' consequence of aging. It is associated with increased disability, decreased physical performance, decreased muscle strength, increased risk of cardiovascular events, impaired quality of life, increased risk of falls, and increased mortality. Recent research suggests that anemia, even in frail, older patients, is potentially treatable.

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Internet Resources

I. KDOQI guidelines on anemia management
http://www.kidney.org/professionals/kdoqi/guidelines_updates/doqi_uptoc.html

II. GFR Calculator (or url to download MDRD/C-G for Palm or Pocket PC)
http://www.nkdep.nih.gov/healthprofessionals/tools/ and
http://www.nephron.com/mdrd/default.html

III. NCCN guidelines on cancer and treatment-related anemia
http://www.nccn.org/patients/patient_gls/_english/pdf/NCCN%20Fatigue%20Guidelines.pdf)

Appendix 1

Be an Anemia Detective

Nonspecific "Clues" That Suggest the Presence of Anemia

Instructions:

One of more of the following clues may be indicative of the presence of anemia (although no one clue indicates for sure that anemia is present). For patients with moderate to severe communication problems (e.g., language barriers, aphasia, cognitive impairment), it is important to observe and document the following nonspecific clues and, if present, seek further assessment for possible anemia.

____ Complaints of being tired all the time

____ Complaints of dizziness

____ Complaints of chest pain

____ Increase in falls

____ Inability to participate in exercises

____ Decline in function from previous level

____ Decreased activity level from before

____ Labored breathing, especially with exertion

____ Poor eating or sleeping

____ Change in behavior

____ Increased irritability

____ Increased confusion

____ Yellowish skin or eyeballs

____ Bleeding gums

____ Pale or cool skin

Be an Anemia Detective

Possible Anemia "Clues'' in the MDS 2.0

In addition to section I on the MDS, a combination of MDS "clues'' might indicate that the patient may have anemia. To assess for hidden clues, look at the patient's MDS to complete the following checklist. One or more checks could indicate the presence of anemia and should prompt further investigation. (Note that no one item by itself conclusively indicates the presence of anemia.)

____ Change in cognitive status (B6)

____ Change in sleep pattern (E1)

____ Change in mood (E3)

____ Behavioral problems (E4)

____ Decline in physical functioning (G1)

____ Functional limitations in range of motion (G4)

____ Change in ADL function (G9)

____ Disease diagnosis (I1)

____ Infections (I2)

____ Health problems (J1)

____ Falls (J4)

____ Weight changes (K3)

____ Nutritional problems (K4)

____ Skin conditions (M1) (M4)

____ Special treatments (P1)

____ Intervention programs for mood, behavior, cognitive loss (P2)

Epoetin Alfa Dosing and Administration

	Cancer Patients Receiving Chemotherapy	Chronic Renal Failure or Chronic Kidney Disease in Patients on Dialysis or Not on Dialysis	Anemic Patients Having Elective, Noncardiac, Nonvascular Surgery
Dosing	Once weekly or 3 times per week (TIW)	3 times per week (TIW)	Before surgery, day of surgery, after surgery
Hemoglobin (Hb) initiation level (or serum erythropoietin levels)		• Hb <10 g/dL. • Transferrin saturation should be at least 20%. • Ferritin should be at least 100 mg/mL. • Blood pressure (BP) should be controlled and monitored during therapy.	Hb >10 and <13 g/dL or equal to 13 g/dL
Start dose (increase no more than once a month)	150 Units(U)/kg subcutaneously (SC) TIW or 40,000 U SC weekly	50–150 U/kg intravenously (IV) or SC TIW	300 U/kg/d SC for 10 days (d) before surgery, day of surgery, and 4 d after surgery or 600 once-U/kg SC in weekly doses before (21,14, and 7 d surgery) and for 4 d after surgery
Reduce dose	**TIW dosing:** Reduce by 25% when Hb approaches 12 g/dL or Hb increases by more than 1 g/dL in a period of 2 weeks (wks). **Weekly dosing:** Reduce by 25% if Hb increases more than 1g/dL in 2 wk period.	Reduce by 25% as Hb approaches 12 g/dL or increases by more than 1 g/dL in period of 2 wks.	

chart continues on following page

Epoetin Alfa Dosing and Administration

	Cancer Patients Receiving Chemotherapy	Chronic Renal Failure or Chronic Kidney Disease in Patients on Dialysis or Not on Dialysis	Anemic Patients Having Elective, Noncardiac, Nonvascular Surgery
Increase dose	**TIW dosing:** Increase dose to 300 U/kg TIW if no rise in Hb or reduction in transfusion risk after 8 wks. **Weekly dosing:** Increase dose to 60,000 U weekly if Hb not increased ≥ 1 g/dL after 4 wks of therapy (in absence of transfusion). If no response to 60,000 after 4 wks, do not increase dose.	• Increase dose if Hb does not increase by 2 g/dL after 8 wks of therapy, and Hb is below suggested target range. • Increases in dose should not be made more frequently than once a month. • Increases may be made at 4 wk intervals. • If increase in Hb < 1 g/dL over 4 wks, and iron stores are adequate, increase by approximately 25% of previous dose.	
Withhold dose	**TIW dosing:** Hb >13 until falls to 12 g/dL; restart at 25% less than previous dose **Weekly dosing:** Hb >13 until falls below 12 g/dL; restart at 25% less than previous dose	If Hb approaches 12 g/dL and continues to increase after dose reduced, then temporarily withhold dose until Hb begins to decrease and reinstate at dose approximately 25% below previous dose.	
Hb target range	10g/dL to 12g/dL	10g/dL to 12g/dL	10 g/dL to 12g/dL
Other	• Monitor Hb weekly until Hb becomes stable. • Evaluate transferrin saturation and serum ferritin before and during therapy	• Evaluate transferrin saturation (should be at least 20%) and serum ferritin (should be at least 100 ng/mL) before and during therapy • Monitor Hb twice weekly until Hb is stable.	All patients should receive adequate iron supplementation throughout therapy

Darbepoetin Alfa Dosing and Administration

	Cancer Patients Receiving Chemotherapy	Chronic Renal Failure or Chronic Kidney Disease in Patients on Dialysis or Not on Dialysis
Starting dose	2.25 mcg/kg subcutaneously (SC) weekly	0.45 mcg/kg intravenous (IV) or SC once weekly
Maintenance dose	• Doses should be titrated to not exceed a target hemoglobin (Hb) of 12 g/dL. • Dosage may be less than starting dose. Patient may need treatments only every 2 weeks (wks). Doses must be individualized to ensure Hb is maintained at the appropriate level for the patient.	• Doses should be titrated to not exceed a target hemoglobin (Hb) of 12 g/dL. • Dosage may be less than starting dose. Patient may need treatments only every 2 weeks. Doses must be individualized to ensure Hb is maintained at the appropriate level for the patient.
Reduce dose	If Hb increases by more than 1.0 g/dL in a 2 wk period or if Hb exceeds 12 g/dL, dose should be reduced by about 25%.	If Hb is increasing and approaching 12 g d/L, reduce dose by 25%. If Hb increases by more than 1.0 g/dL in a 2 wk period, decease dose by approximately 25%.
Increase dose	If there is a less than a 1.0g/dL increase in Hb after 6 wks of therapy, dose should be increased up to 4.5 mcg/kg.	• Do not increase more than once per month. • If the increase in Hb is less than 1.0 g/dL over 4 wks, and iron stores are adequate, dose may be increased by approximately 25% of previous dose.
Withhold dose	If Hb exceeds 13 g/dL, withhold dosage until Hb falls to 12 g/dL and reinitiate at dose approximately 25% below previous dose.	If Hb approaches 12 g/dL and continues to increase after dose reduced, then temporarily withhold dose until Hb begins to decrease and reinstate dose approximately 25% below previous dose.
Hb targeted level	12 g/dL	12 g/dL
Other	Monitor Hb weekly until Hb becomes stable.	Evaluate transferrin saturation (should be at least 20%) and serum ferritin (should be at least 100 ng/mL) before and during therapy.

American Medical Directors Association

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