

# Anemia

A HIDDEN EPIDEMIC



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First convened in November 2000, the National Anemia Action Council (NAAC) is a multispecialty consortium comprised of nearly 30 leading physicians who are experts in identifying and treating anemia. Their specialties include hematology, nephrology, oncology, cardiology, critical care, rheumatology, gastroenterology, infectious diseases, geriatrics, and surgery.

Based on scientific evidence, NAAC has identified anemia as a public health concern that requires concerted attention and action. One of NAAC's primary objectives is to raise professional and public awareness of anemia, its consequences, and treatment options. NAAC is also dedicated to stimulating research and new therapeutic approaches to achieve better patient outcomes.

Written with the editorial input of a number of prestigious NAAC members and other anemia specialists, ***Anemia: A Hidden Epidemic*** is designed to be an in-office handbook for primary care and specialty medical practitioners who may be seeing patients with undiagnosed anemia. In addition to providing a broad overview of the condition, the monograph contains chapters on the association of anemia with: chronic kidney disease, cardiovascular disease, diabetes, cancer, HIV/AIDS, inflammatory bowel disease, hepatitis C, rheumatoid arthritis, surgery, and aging.

Visit [www.anemia.org](http://www.anemia.org), the official Web site of the National Anemia Action Council, to obtain additional copies of ***Anemia: A Hidden Epidemic*** and to access other scientific anemia information and CME materials.



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*“At least 3.4 million Americans have been diagnosed as anemic, and millions more may be undiagnosed or at increased risk of developing anemia.”*

# I Anemia

## Overview

### **Key Points**

- Anemia is often underrecognized and undertreated.
- Anemia is associated with many chronic diseases and other conditions.
- If left untreated, anemia can have serious consequences.
- Anemia can be readily managed by current therapies.



### **A Hidden Epidemic**

Traditionally, the health care community has not focused on anemia as a serious and common condition. However, findings from the National Center for Health Statistics and the recent identification of anemia as a significant public health concern by the United States Department of Health and Human Services in *Healthy People 2010*<sup>1</sup> have sounded a call for a re-examination of the impact of anemia on the health of Americans.

Based on a national household interview survey, the National Center for Health Statistics estimated in 1996 that 3.4 million Americans were living with anemia.<sup>2</sup> The actual number of individuals with the condition may be far greater, as anemia is often underdiagnosed and undertreated. Anemia's signs and symptoms may be vague, and it is present in a substantial number of patients with a variety of chronic and serious diseases. Frequently, however, anemia remains undetected because it is masked by symptoms of the diseases with which it is associated, including chronic kidney disease, cancer, diabetes, cardiovascular disease, HIV/AIDS, rheumatoid arthritis, and inflammatory bowel disease.

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) new clinical practice guideline on the classification system for chronic kidney disease (CKD) estimates that more than 19.5 million Americans have CKD.<sup>3</sup> Anemia is a common and early complication of CKD<sup>4-8</sup> and worsens as the disease progresses. The estimated 50 million Americans with hypertension<sup>9</sup> and 17 million with diabetes<sup>10</sup> are at increased risk for CKD—

and subsequently anemia.

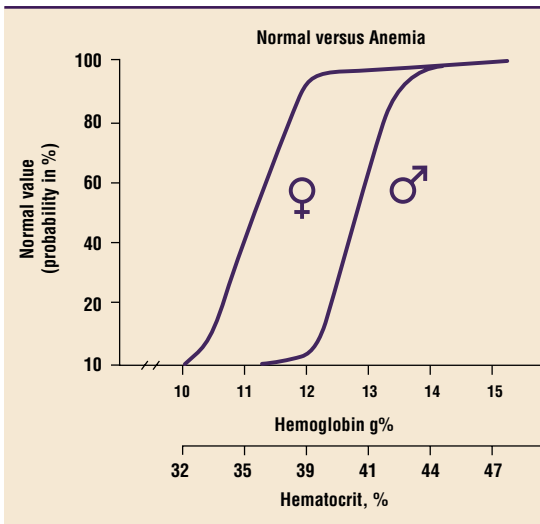
Not only is anemia a consequence of many diseases, it may also occur from the treatment of the disease itself, such as in patients with cancer, HIV/AIDS, and hepatitis C. Candidates for surgery may be anemic due to underlying disease or become so due to blood loss during the perioperative period. Anemia also occurs more frequently among the elderly, and its prevalence in this group is expected to increase as baby-boomers become senior citizens.

At least 3.4 million Americans have been diagnosed as anemic, and millions more may be undiagnosed or at increased risk of developing anemia. Anemia is a hidden epidemic in this nation, and a condition that can have serious consequences if left untreated. However, it is also a condition that can be readily managed by current therapies.

### **Anemia Defined**

Anemia is defined as a reduction in the number of circulating red blood cells, the hemoglobin concentration, or the volume of packed red cells (hematocrit) in the blood. In the laboratory, anemia is identified when a patient's hemoglobin (Hb)/hematocrit (Hct) values fall below the lower end of a normal range of values for age- and sex-matched subjects. The likelihood and severity of anemia is based on the patient's deviation from normal values. Women in their childbearing years normally have a lower Hb value by about 1 gm/dL than men of the same age, likely due to hormonal influences. After menopause, the gender difference virtually disappears.

The three major categories of anemia are hypoproliferative, maturation defects,



**Figure 1-1** The amount of deviation from age- and sex-matched normal subjects indicates the probability and severity of anemia. Reprinted with permission from *Harrison's Textbook of Internal Medicine*.<sup>11</sup>

and hemolysis/blood loss. The most common anemia in the United States is hypoproliferative anemia, which includes iron deficiency, chronic kidney disease (CKD), and the inflammation-associated

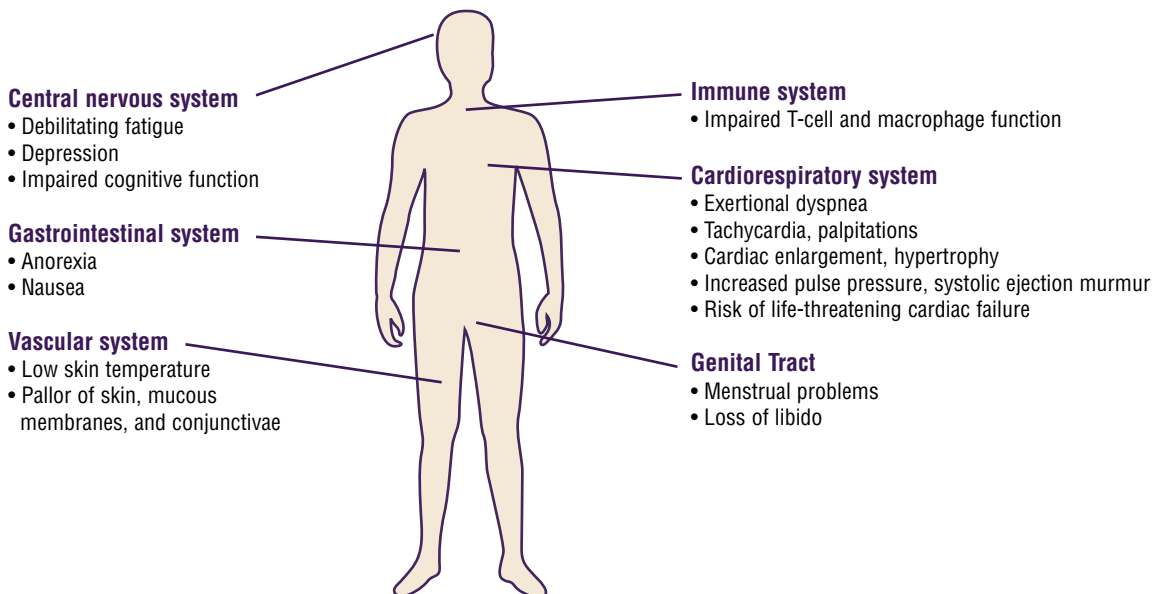
anemia of chronic disease, which is found in patients with chronic conditions, such as rheumatoid arthritis, inflammatory bowel disease, HIV/AIDS, and cancer. Anemia may be acquired (eg, through blood loss, inflammation, and malignancy) or inherited (eg, by patients with sickle cell disease, thalassemia, and other hemoglobinopathies).

**The Burden of Anemia**

Because anemia affects the delivery of oxygen to all of the body's organs, its signs and symptoms are varied.

**Impaired Quality of Life**

It is generally accepted that the symptoms of anemia adversely affect quality of life (QOL), even when anemia is mild. In end-stage renal disease (ESRD), severe impairment of QOL may occur in as many as 31% of patients.<sup>13</sup> Several factors contribute to poor QOL in these patients, including low Hb or Hct.



**Figure 1-2** Symptoms and signs occur when the oxygen carrying capacity of the blood is unable to meet the oxygen requirements of body tissues. Adapted and reprinted with permission from *Semin Oncol*.<sup>12</sup>

Anemia in patients with cancer contributes to fatigue and may reduce patients' ability to function normally, thus reducing QOL.<sup>12,14,15</sup> The corollary to this is that the correction of anemia is associated with improved QOL. In fact, improved Hb and Hct values are associated with better scores on QOL assessments in a variety of disease states, including CKD,<sup>13,16,17</sup> inflammatory bowel disease,<sup>18</sup> rheumatoid arthritis,<sup>16,19</sup> cancer,<sup>20,21</sup> and HIV/AIDS.<sup>22-24</sup>

### ***Increased Cardiovascular Morbidity***

Anemia is associated with significant cardiovascular morbidity and mortality. Compensatory hemodynamic changes that occur in anemia lead to increased cardiac output and blood flow, resulting in a variety of cardiovascular consequences.<sup>25,26</sup> Decreased oxygenation of the heart muscle combined with increased cardiac workload may result in symptoms such as angina<sup>27,28</sup> and palpitations,<sup>29</sup> and, over time, result in cardiac enlargement and congestive heart failure.<sup>30,31</sup>

The relationship between anemia and cardiovascular disease has been the topic of much research in CKD, both in pre-dialysis patients and those with ESRD on dialysis. This is partly because of the increased cardiovascular morbidity in CKD patients and the increased cardiovascular-associated mortality observed in dialysis patients. For example, left ventricular hypertrophy is associated with a 50% decrease in 4-year survival in ESRD.<sup>32</sup> Similarly, dialysis patients with low Hct (<33%) have a significantly higher risk of cardiac death than patients with higher Hct ( $\geq 33\%$  to  $< 36\%$ ) at 1 year (RR, 1.74; 95% CI, 1.66-1.83).<sup>33</sup> In cancer

patients, cardiovascular symptoms and signs of anemia include tachycardia, palpitations, cardiac enlargement, increased pulse pressure, systolic ejection murmur, and risk of cardiac failure.<sup>34</sup>

Correction of anemia has been associated with significant improvements in cardiovascular morbidity and mortality. In patients with heart failure, the correction of mild anemia to a Hb level of 12.5 g/dL is associated with functional improvement, increased left ventricular ejection fraction, improved exercise capacity, and a decline in hospitalizations.<sup>29,35,36</sup> In patients with CKD, partial correction of anemia is associated with improvements in left ventricular mass index,<sup>37-41</sup> myocardial ischemia, and exercise duration.<sup>42</sup>

### ***Hindered Cognitive Function***

Researchers have shown a relationship between Hct and cognitive function. In patients with ischemic cerebrovascular disease, Hct correction to the normal range (40% to 45%) was shown to improve cerebral oxygen delivery.<sup>43</sup> Similarly, in dialysis patients, Hct correction to normal was shown to improve neurophysiologic parameters indicative of cognitive function and memory.<sup>44</sup> Even partial correction of anemia in CKD patients (to Hct of 36% to 36.5%) has been shown to improve cognitive function, including sustained attention and memory.<sup>45,46</sup>

The Hct values necessary to maintain optimal cognitive function, however, remain to be defined. For example, in dialysis patients, maximal oxygenation of the cerebral hemisphere was estimated to occur at a Hct of 35.2%, but the optimal level varied with the region of the brain explored (eg, a Hct

of 33% provided maximal oxygen delivery in the occipital region, whereas a Hct of 45% was needed in the frontal region).<sup>47</sup>

### ***Increased Hospitalization and Mortality Risk***

In patients with CKD, anemia has been shown to correlate directly with the risk of hospitalization. In a recent study of more than 66,000 dialysis patients, those with Hct of 33% to <39% were found to have lower hospitalization rates than patients with Hct <33%.<sup>33</sup> Findings of another study indicated that dialysis patients with Hct <30% had the highest risk of hospitalization, while those with Hct levels of 33% to 36% had the lowest hospitalization risk.<sup>48</sup> Both fewer hospitalizations per year and shorter hospital stays were observed for new dialysis patients treated with recombinant human erythropoietin (epoetin) than for their untreated peers.<sup>49</sup>

Anemia in dialysis patients is also associated with increased mortality, with higher 1-year mortality risk in patients with lower Hct.<sup>31,33</sup> Similarly, 3-year mortality in dialysis patients increases with decreasing Hct, with the highest mortality at Hct <30%.<sup>51</sup> Observational studies in dialysis patients show reductions in mortality with correction of anemia to Hct 33% to 36%.<sup>52</sup>

Such a relationship also has been noted between anemia and survival in cancer patients. In a systematic review of 60 published studies, researchers reported that the presence of anemia was associated with an overall 65% increased relative risk of death, although the relative risk varied by cancer type.<sup>53</sup>

Results of a recent retrospective study of nearly 79,000 acute myocardial infarction patients  $\geq 65$  years indicated that a lower Hct at admission was associated with a higher 30-day mortality rate. Short-term mortality rates were lowered in patients with a Hct of  $\leq 30\%$  at admission who were given blood transfusions to correct anemia.<sup>54</sup>

### **Diagnosing Anemia**

Since anemia is a sign of a wide range of underlying disorders, and, in itself, is associated with morbidity and even an increased risk of mortality, it is critical that the underlying pathophysiologic mechanism be identified for any given patient. The hypoproliferative anemias may be associated with inadequate erythroid marrow stimulation by erythropoietin for red blood cell production and with inadequate iron availability for Hb synthesis. Because it is the most common cause of anemia, iron deficiency must be ruled out in the evaluation of any anemic patient.

Anemia is almost always discovered through abnormal laboratory screening test results. It is unusual for patients to present with anemia so advanced that the clinical manifestations (eg, pallor, palpitations, weakness, etc.) predominate. With acute anemia, the only real considerations are blood loss or hemolysis.

An anemia work-up should include a routine complete blood count (CBC) with reticulocyte count (corrected for the Hct) and three red cell indices: mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC).

## Anemia Labs

### Reticulocyte Count

The reticulocyte count estimates the rate of red cell production. An elevated reticulocyte count generally indicates that the marrow is responding to endogenous erythropoietin stimulation. The reticulocyte count must be corrected for the degree of anemia in order to have a valid estimate of the rate of red cell production. A normal reticulocyte count in the presence of anemia suggests impaired erythropoietin production or an impaired response to erythropoietin by the erythroid marrow.

An elevated reticulocyte count and slightly increased MCV suggest a hemolytic process. An elevated MCV can reflect a very high reticulocyte production or a nuclear maturation defect (eg, vitamin B<sub>12</sub> or folic acid deficiency).

### Iron Supply Parameters

The serum iron level and percent transferrin saturation reflect the iron available for Hb synthesis. When the serum iron falls (true iron deficiency or acute inflammation), Hb synthesis is impaired and microcytic, hypochromic red cells are produced. The serum ferritin reflects total body iron stores and is decreased in iron deficiency, but normal or increased in states of acute or chronic inflammation. This is a useful laboratory test to distinguish between true iron deficiency and chronic inflammatory states.

### Red Cell Indices

The red cell indices reflect the state of red cell production. Anemia with normal red cell indices is almost always hypoproliferative in nature. Microcytic red cells can be seen with true iron deficiency as well as chronic severe inflammation. In the latter, the inflammatory process impairs iron release from storage sites, resulting in a low serum iron value, despite normal or increased iron stores. Macrocytic red cells are most commonly seen with the nuclear maturation disorders, such as vitamin B<sub>12</sub> or folic acid deficiency.

Table 1-1 **Assessing Blood Status**

Laboratory Test	Reference Range*
<b>Hb</b>	
• Males	14.0 g/dL – 17.4 g/dL
• Females	12.3 g/dL – 15.3 g/dL
<b>Hct</b>	
• Males	41.5% - 50.4%
• Females	36.0% - 45.0%
MCV	80 fL – 96 fL
MCH	27.5 pg/cell - 33.2 pg/cell
MCHC	33.4 g/dL - 35.5 g/dL
Reticulocytes	0.5% - 2.5%

\*All values from *Wintröbe's Clinical Hematology*.<sup>55</sup>

In addition, measurements of iron supply [serum iron, total iron binding capacity (TIBC), percent transferrin saturation (TSAT), and serum ferritin] and a careful evaluation of the peripheral blood smear are necessary.

Table 1-2 **Assessing Iron Status**

Laboratory Test	Reference Range*
Serum iron	60 µg/dL – 150 µg/dL
TIBC	250 µg/dL – 435 µg/dL
<b>TSAT</b>	
• Males	20% - 50%
• Females	15% - 50%
<b>Serum ferritin</b>	
• Males	20 ng/mL – 250 ng/mL
• Females	10 ng/mL – 120 ng/mL

\*Serum iron and TIBC values from *Wintröbe's Clinical Hematology*.<sup>55</sup> TSAT and serum ferritin values from *Tietz Textbook of Clinical Chemistry*.<sup>56</sup>

Marked alterations (either increased or decreased) in the red cell indices almost always reflect a maturation defect or iron deficiency. Iron deficiency is revealed by a low serum iron, low percent transferrin saturation, and low serum ferritin. A microcytic anemia in the presence of normal iron values

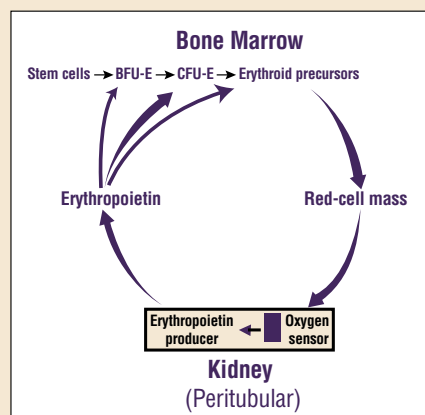
## Erythropoiesis

Hematopoiesis is the process by which the formed elements of the blood are regulated through a series of steps, beginning with the pluripotent stem cell. Once stem cells are committed to specific differentiated cell lineages, hematopoietic precursor cells come under increasing regulation by growth factors and hormones. The physiologic regulator of red cell (erythrocyte) production is the glycoprotein hormone erythropoietin, of which >90% is made in the kidney.

The machinery responsible for red cell production (erythropoiesis) resides in the bone marrow. The erythropoietin molecule interacts and binds to specific receptors on the surface of marrow erythroid progenitor cells, inducing them to proliferate and mature. The key to erythropoietin production is the availability of oxygen, which is transported to tissues in a form bound to the Hb molecule contained within the red cells.

The fundamental stimulus for erythropoietin production is oxygen availability to the kidney. Impaired oxygen delivery to the kidney is caused by a decrease in the number of circulating red cells (anemia), impaired oxygen loading of the red cell Hb or, rarely, impaired flow of red cells to the kidney because of renal artery stenosis.

Erythropoietin not only is responsible for the day-to-day regulation of erythropoiesis, but it also responds dramatically to increase red cell production in the face of an inadequate oxygen supply, thereby meeting tissue oxygen needs. When the Hb concentration falls below 10 g/dL to 12 g/dL, and if kidney function is normal, plasma erythropoietin levels rise logarithmically in inverse proportion to the level of Hb. Under the stimulus of erythropoietin, red blood cell production can increase four- to fivefold within 1 to 2 weeks. However, this can occur only in the presence of adequate substrates, most particularly iron. In order for this feedback system to function properly, there must be normal renal production of erythropoietin, a functioning erythroid marrow, and an adequate supply of substrates for Hb synthesis. A defect in any of these key components can lead to anemia.<sup>58</sup>



**Figure 1-4.** Inadequate oxygen delivery to the kidney stimulates erythropoietin production. BFU-E= Burst-forming units-erythroid; CFU-E= Colony forming units-erythroid. Adapted and reprinted with permission from *N Eng J Med*.<sup>59</sup>

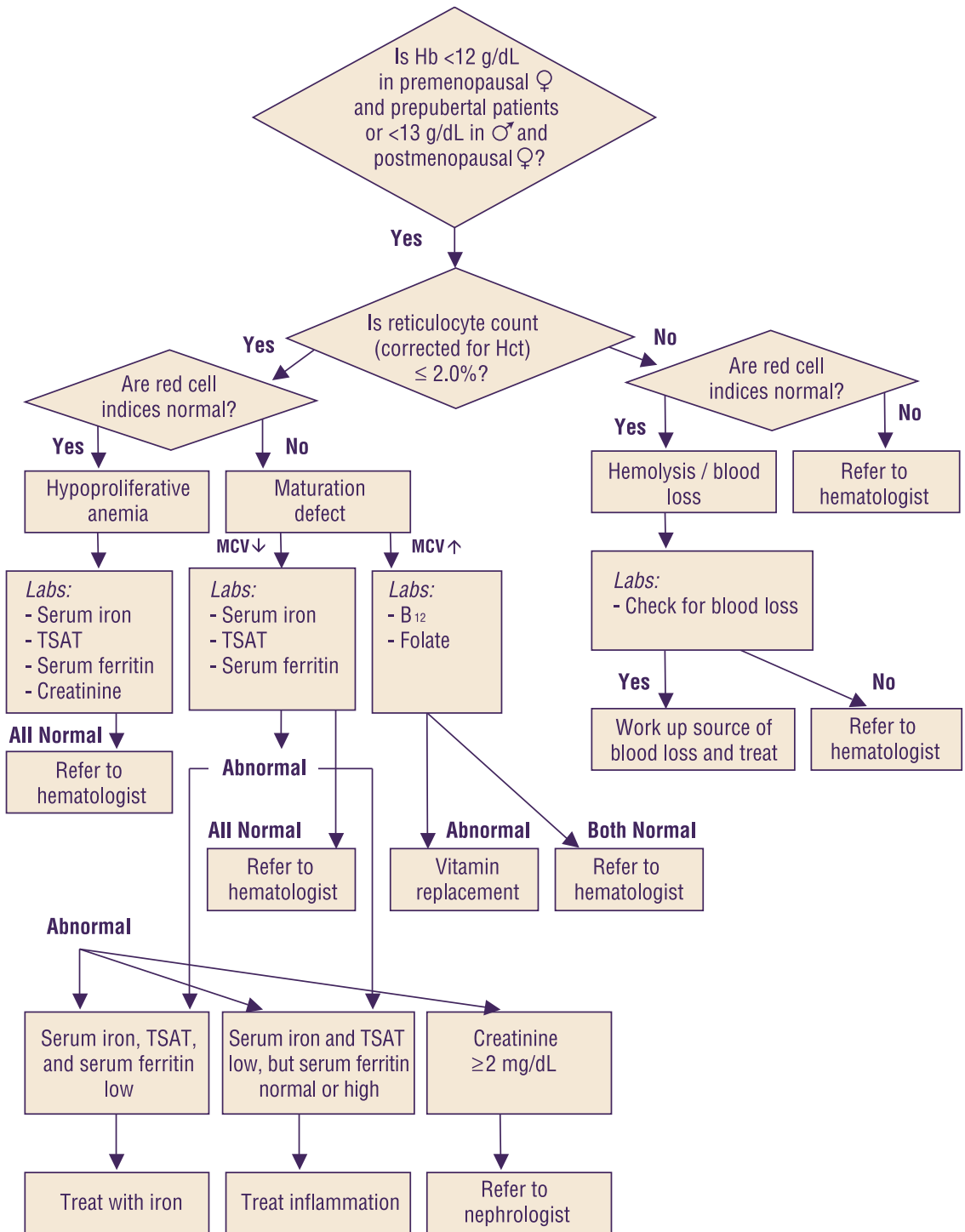


Figure 1-3. Overview of anemia diagnostic work-up using WHO anemia definitions.

suggests a defect (most commonly inherited) in Hb synthesis.

The algorithm in Figure 1-3 provides an overview of a diagnostic work-up for anemia. The World Health Organization defines anemia as Hb <12g/dL for premenopausal women and prepubertal patients, and Hb <13g/dL for men and postmenopausal women.<sup>57</sup> Because Hb/Hct values below the normal age- and sex-adjusted values represent probabilities of anemia, they are more easily interpreted when they are compared to patients' historic values.

### **Anemia Management**

A correct diagnosis of the cause is key to managing anemia. Once the cause is determined, the approach is to implement the appropriate treatment to correct the anemia. In most medical practices, the identification of iron deficiency should be foremost, since it may be associated with occult bleeding or other serious conditions, and it can be quickly and easily treated with iron supplementation. Other less common but reversible anemias include vitamin B<sub>12</sub> and folate deficiency, and some cases of anemia associated with inflammation. Each of these requires a slightly different therapeutic approach.

Iron deficiency in adult males and postmenopausal females must be considered due to chronic blood loss until proven otherwise. There are a variety of oral and parenteral iron preparations to choose from in treating iron deficiency. For most uncomplicated cases, an oral iron preparation will suffice. A total elemental iron dose of 200 mg/day will gradually reverse the iron deficiency anemia. Oral iron should be continued for

some months after the reversal of the anemia in order to replenish body iron stores. A convenient rule of thumb is to continue iron replacement for 6 months after correction of the anemia. If oral iron is not absorbed well, or if the patient cannot tolerate the side effects of oral iron treatment, parenteral iron may be given.

For the other anemias, the same principles apply. Vitamin B<sub>12</sub> deficiency must be corrected with parenteral B<sub>12</sub> injections. Folate deficiency is generally due to poor dietary intake of the vitamin, and the deficiency state is generally rapidly reversed with improved nutrition.

Chronic inflammatory states are more complex, depending on the underlying inflammatory process.

One of the most common and chronic hypoproliferative anemias is the anemia of CKD. This is a hormone deficiency state, in which the diseased kidney is incapable of meeting the endogenous erythropoietin needs of the patient. As a result of erythropoietin deficiency, the moderately shortened lifespan of the circulating red cells, and the obligatory blood loss that accompanies dialysis, CKD patients can experience profound, debilitating anemia. Such patients have benefited greatly from the availability of epoetin alfa, a recombinant human erythropoietin.

Epoetin alfa is a 165-amino-acid glycoprotein manufactured by recombinant DNA technology and is identical in structure and biological activity to native erythropoietin. Originally approved by the Food and Drug Administration (FDA) for the treatment of anemia in CKD patients on dialysis, epoetin alfa is currently indicated for treating anemia in CKD patients

whether on dialysis or not, in cancer patients on chemotherapy, and in zidovudine-treated HIV-infected patients. It is also approved for reducing allogeneic blood transfusions in anemic patients undergoing elective, noncardiac, nonvascular surgery.<sup>60</sup>

Epoetin beta and epoetin omega are other forms of recombinant human erythropoietin used outside of the United States. Because European researchers sometimes include data on epoetin beta, epoetin in this monograph refers to epoetin alfa and epoetin beta.

For more than a decade, epoetin has been used successfully to manage the anemia of patients with CKD or cancer-related anemia. Epoetin therapy has dramatically reduced the need for transfusions in these patient groups, has led to an improvement in QOL for those who have responded, and has decreased anemia-associated morbidity.<sup>61</sup> Epoetin has also been shown to be of benefit in managing anemia in patients with HIV/AIDS,<sup>22-24</sup> inflammatory bowel disease,<sup>18</sup> and rheumatoid arthritis.<sup>16,62</sup> The anemia of the elderly and those undergoing surgery<sup>63,64</sup> has also been responsive to therapy with epoetin. In some cases, epoetin is given with supplemental iron, a strategy that has been of proven value for a variety of patients, including patients with ESRD on dialysis, patients with rheumatoid arthritis, and some surgical patients.

Epoetin, however, has a relatively short circulating half-life and, consequently, it is usually administered several times a week or at least weekly. Most

recently, a novel erythropoiesis-stimulating protein (NESP) has been developed that addresses some of the inconvenience of frequent epoetin dosing. Engineered specifically for increased biological activity, darbepoetin alfa has the same number of amino acids as epoetin alfa, but they have been molecularly modified to add two additional N-linked glycosylation sites to the molecule, bringing the total number to five, instead of the usual three. This results in a threefold increase in terminal elimination half-life (23.5 hours vs. 8.5 hours). As a result, darbepoetin alfa allows less frequent dosing than epoetin alfa and is well tolerated. Darbepoetin alfa was approved by the FDA in 2001 for the treatment of patients with the anemia of CKD whether on dialysis or not.<sup>65</sup> Study findings to date have shown the medication also to be of benefit in patients with nonmyeloid hematological malignancies or solid tumors.<sup>66,67</sup> Darbepoetin alfa is currently undergoing FDA review for use in the treatment of anemia in cancer patients receiving chemotherapy.

Replacement therapy, whether it is iron or epoetin, takes time to correct the anemia. Thus, if the anemia is severe and the patient is symptomatic, transfusion therapy with packed red blood cells is an option. Although the safety of blood transfusions has been brought to an extremely high level, exposure to red cell transfusions still carries a measurable risk of allosensitization, and in some patient groups, such as those with HIV/AIDS and cancer, it can have an adverse effect on mortality.

# References



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## ANEMIA OVERVIEW

### References

1. US Department of Health and Human Services. *Healthy People 2010: Understanding and Improving Health*. Washington, DC: US Government Printing Office, November 2000.
2. National Center for Health Statistics. FASTATS-Anemia. *National Center for Health Statistics*. Available at: <http://www.cdc.gov/nchs/fastats/anemia.htm>. Accessed July 10, 2001.
3. National Kidney Foundation Disease. NKF-K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. *Am J Kidney Dis*. 2002;39:S1-S266.
4. US Renal Data System. *USRDS 1999 Annual Data Report*. Bethesda, MD: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 1999.
5. Kausz AT, Khan SS, Abichandani R, et al. Management of patients with chronic renal insufficiency in the Northeastern United States. *J Am Soc Nephrol*. 2001;12:1501-1507.
6. Kazmi WH, Kausz AT, Khan S, et al. Anemia: an early complication of chronic renal insufficiency. *Am J Kidney Dis*. 2001;38:803-812.
7. Radtke HW, Claussner A, Erbes PM, et al. Serum erythropoietin concentration in chronic renal failure: relationship to degree of anemia and excretory renal function. *Blood*. 1979;54:877-884.
8. Obrador GT, Ruthazer R, Arora P, et al. Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. *J Am Soc Nephrol*. 1999;10:1793-1800.
9. Joint National Committee on Prevention Detection, Evaluation, and Treatment of High Blood Pressure. *The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure*. Bethesda, MD: National Institutes of Health; 1993.
10. US Department of Health and Human Services. HHS, ADA warn Americans of "pre-diabetes," encourage people to take healthy steps to reduce risks. March 27, 2002. Available at: <http://www.hhs.gov/news/press/2002pres/20020327.html>. Accessed April 10, 2002.
11. Braunwald E, Fauci AS, Kasper DS, et al. *Harrison's Principles of Internal Medicine*. New York, NY: The McGraw-Hill Companies; 2001;349.
12. Ludwig H, Fritz E. Anemia in cancer patients. *Semin Oncol*. 1998;25(suppl 7):2-6.
13. Valderrabano F. Quality of life benefits of early anaemia treatment. *Nephrol Dial Transplant*. 2000;15(suppl 3):23-28.
14. Cella D. Factors influencing quality of life in cancer patients: anemia and fatigue. *Semin Oncol*. 1998;25:43-46.
15. Curt GA. Impact of fatigue on quality of life in oncology patients. *Semin Hematol*. 2000;37:14-17.
16. Fantini F, Gattinara M, Gerloni V, et al. Severe anemia associated with active systemic-onset juvenile rheumatoid arthritis successfully treated with recombinant human erythropoietin: a pilot study. *Arthritis Rheum*. 1992;35:724-726.
17. McMahon LP, Mason K, Skinner SL, et al. Effects of haemoglobin normalization on quality of life and cardiovascular parameters in end-stage renal failure. *Nephrol Dial Transplant*. 2000;15:1425-1430.
18. Gasché C, Dejaco C, Waldhoer T, et al. Intravenous iron and erythropoietin for anemia associated with Crohn disease: a randomized, controlled trial. *Ann Intern Med*. 1997;126:782-787.
19. Peeters HR, Jongen-Lavrencic M, Bakker CH, et al. Recombinant human erythropoietin improves health-related quality of life in patients with rheumatoid arthritis and anaemia of chronic disease: utility measures correlate strongly with disease activity measures. *Rheumatol Int*. 1999;18:201-206.
20. Sweeney PJ, Nicolae D, Ignacio L, et al. Effect of subcutaneous recombinant human erythropoietin in cancer patients receiving radiotherapy: final report of a randomized, open-labelled, phase II trial. *Br J Cancer*. 1998;77:1996-2002.
21. Leitgeb C, Pecherstorfer M, Fritz E, et al. Quality of life in chronic anemia of cancer during treatment with recombinant human erythropoietin. *Cancer*. 1994;73:2535-2542.
22. Abrams DI, Steinhart C, Frascino R. Epoetin alfa therapy for anaemia in HIV-infected patients: impact on quality of life. *Int J STD AIDS*. 2000;11:659-665.

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## ANEMIA OVERVIEW

### References

23. Revicki DA, Brown RE, Henry DH, et al. Recombinant human erythropoietin and health-related quality of life of AIDS patients with anemia. *J Acquir Immune Defic Syndr*. 1994;7:474-484.
24. Henry DH, Beall GN, Benson CA, et al. Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy: overview of four clinical trials. *Ann Intern Med*. 1992;117:739-748.
25. Eckardt KU. Cardiovascular consequences of renal anaemia and erythropoietin therapy. *Nephrol Dial Transplant*. 1999;14:1317-1323.
26. London G. Pathophysiology of cardiovascular damage in the early renal population. *Nephrol Dial Transplant*. 2001;16(suppl 2):3-6.
27. Hoffbrand AV, Pettie J. *Essential Hematology*. 3rd ed. Oxford, UK: Blackwell Science, Inc.; 1993.
28. Mackie MJ, Ludlam CA. Diseases of the blood. In: Edwards CRW, ed. *Davidson's Principles and Practice of Medicine*. Philadelphia, PA: Churchill; 1995:775-842.
29. Silverberg DS, Wexler D, Sheps D, et al. The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. *J Am Coll Cardiol*. 2001;37:1775-1780.
30. Levin A, Thompson CR, Ethier J, et al. Left ventricular mass index increase in early renal disease: impact of decline in hemoglobin. *Am J Kidney Dis*. 1999;34:125-134.
31. Foley RN, Parfrey PS, Harnett JD, et al. Cardiovascular disease and mortality in ESRD. *J Nephrol*. 1998;11:239-245.
32. Silberberg JS, Barre PE, Prichard SS, et al. Impact of left ventricular hypertrophy on survival in end-stage renal disease. *Kidney Int*. 1989;36:286-290.
33. Collins AJ, Li S, St Peter W, et al. Death, hospitalization, and economic associations among incident hemodialysis patients with hematocrit values of 36 to 39%. *J Am Soc Nephrol*. 2001;12:2465-2473.
34. Ludwig H, Strasser K. Symptomatology of anemia. *Semin Oncol*. 2001;28(suppl 8):7-14.
35. Silverberg DS, Wexler D, Blum M, et al. The use of subcutaneous erythropoietin and intravenous iron for the treatment of the anemia of severe, resistant congestive heart failure improves cardiac and renal function and functional cardiac class, and markedly reduces hospitalizations. *J Am Coll Cardiol*. 2000;35:1737-1744.
36. Mancini D, Katz S, LaManca J. Erythropoietin improves exercise capacity in patients with heart failure. Vol 104(suppl II): *Circulation*; 2001.
37. Hayashi T, Suzuki A, Shoji T, et al. Cardiovascular effect of normalizing the hematocrit level during erythropoietin therapy in predialysis patients with chronic renal failure. *Am J Kidney Dis*. 2000;35:250-256.
38. Lopez-Gomez JM. Effects of partial correction of anemia on left ventricular structure and function: Proc American Society of Nephrology 33rd annual meeting; 2000.
39. Silberberg J, Racine N, Barre P, et al. Regression of left ventricular hypertrophy in dialysis patients following correction of anemia with recombinant human erythropoietin. *Can J Cardiol*. 1990;6:1-4.
40. Zehnder C, Zuber M, Sulzer M, et al. Influence of long-term amelioration of anemia and blood pressure control on left ventricular hypertrophy in hemodialyzed patients. *Nephron*. 1992;61:21-25.
41. Pascual J, Teruel JL, Moya JL, et al. Regression of left ventricular hypertrophy after partial correction of anemia with erythropoietin in patients on hemodialysis: a prospective study. *Clin Nephrol*. 1991;35:280-287.
42. Wizemann V, Kaufmann J, Kramer W. Effect of erythropoietin on ischemia tolerance in anemic hemodialysis patients with confirmed coronary artery disease. *Nephron*. 1992;62:161-165.
43. Kusunoki M, Kimura K, Nakamura M, et al. Effects of hematocrit variations on cerebral blood flow and oxygen transport in ischemic cerebrovascular disease. *J Cereb Blood Flow Metab*. 1981;1:413-417.

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## ANEMIA OVERVIEW

### References

44. Pickett JL, Theberge DC, Brown WS, et al. Normalizing hematocrit in dialysis patients improves brain function. *Am J Kidney Dis*. 1999;33:1122-1130.
45. Marsh JT, Brown WS, Wolcott D, et al. Recombinant human erythropoietin treatment improves brain and cognitive function of anemic dialysis patients. *Kidney Int*. 1991;39:155-163.
46. Revicki DA, Brown RE, Feeny DH, et al. Health-related quality of life associated with recombinant human erythropoietin therapy for predialysis chronic renal disease patients. *Am J Kidney Dis*. 1995;25:548-554.
47. Hirakata H, Kanai H, Fukuda K, et al. Optimal hematocrit for the maximum oxygen delivery to the brain with recombinant human erythropoietin in hemodialysis patients. *Clin Nephrol*. 2000;53:354-361.
48. Xia H, Ebben J, Ma JZ, et al. Hematocrit levels and hospitalization risks in hemodialysis patients. *J Am Soc Nephrol*. 1999;10:1309-1316.
49. Churchill DN, Muirhead N, Goldstein M, et al. Effect of recombinant human erythropoietin on hospitalization of hemodialysis patients. *Clin Nephrol*. 1995;43:184-188.
50. Ma JZ, Ebben J, Xia H, et al. Hematocrit level and associated mortality in hemodialysis patients. *J Am Soc Nephrol*. 1999;10:610-619.
51. United States Renal Data System. *USRDS 2001 Annual Data Report*. Bethesda: National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health; 2001.
52. Eknoyan G. The importance of early treatment of the anaemia of chronic kidney disease. *Nephrol Dial Transplant*. 2001;16(suppl 5):45-49.
53. Caro JJ, Salas M, Ward A, et al. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. *Cancer*. 2001;91:2214-2221.
54. Wu WC, Rathore SS, Wang Y, et al. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. 2001;345:1230-1236.
55. Lee GR, Foerster J, Lukens J, et al. *Wintrube's Clinical Hematology*. 10<sup>th</sup> ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1999;2,4.
56. Burtis CA, Ashwood ER, Tietz NW. *Tietz Textbook of Clinical Chemistry*. 3rd ed. Philadelphia, PA: W. B. Saunders Company; 1999;1813.
57. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst*. 1999;91:1616-1634.
58. Adamson JW. Iron deficiency and other hypoproliferative anemias. In: Braunwald E, Fauci AS, Kasper DS, et al., eds. *Harrison's Principles of Internal Medicine*. 15<sup>th</sup> ed. New York, NY: McGraw-Hill; 2001:660-666.
59. Erslev AJ. Erythropoietin. *N Engl J Med*. 1991;324:1339-1334.
60. Amgen Inc. EPOGEN (epoetin alfa) package insert, Thousand Oaks, CA: Amgen Inc.; 2000.
61. Nissenson AR. Epoetin and cognitive function. *Am J Kidney Dis*. 1992;20(suppl 1):21-24.
62. Peeters HR, Jongen-Lavrencic M, Raja AN, et al. Course and characteristics of anaemia in patients with rheumatoid arthritis of recent onset. *Ann Rheum Dis*. 1996;55:162-168.
63. Helm RE, Gold JP, Rosengart TK, et al. Erythropoietin in cardiac surgery. *J Card Surg*. 1993;8:579-606.
64. Trovarelli T, Kahn B, Vernon S. Transfusion-free surgery is a treatment plan for all patients. *AORN J*. 1998;68:773-778, 780-774.
65. Amgen Inc. ARANESP (darbepoetin alfa) package insert, Thousand Oaks, CA: Amgen Inc.; 2001.
66. Smith RE, Jr., Jaiyesimi IA, Meza LA, et al. Novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia of chronic disease associated with cancer. *Br J Cancer*. 2001;84(suppl 1):24-30.
67. Glaspy J, Jadeja JS, Justice G, et al. A dose-finding and safety study of novel erythropoiesis stimulating protein (NESP) for the treatment of anaemia in patients receiving multicycle chemotherapy. *Br J Cancer*. 2001;84(suppl 1):17-23.