University of Tennessee, Knoxville

TRACE: Tennessee Research and Creative Exchange

Faculty Publications and Other Works -- Nursing

Nursing

January 2002

Differentiation and treatment of anemia in HIV disease

Kenneth D. Phillips
University of South Carolina, kphill22@utk.edu

M Groer

Follow this and additional works at: https://trace.tennessee.edu/utk_nurspubs

Part of the Critical Care Nursing Commons

Recommended Citation

Phillips, K. D., & Groër, M. (2002). Differentiation and treatment of anemia in HIV disease. *Journal of the Association of Nurses in AIDS Care*, 13(3), 47-72.

This Article is brought to you for free and open access by the Nursing at TRACE: Tennessee Research and Creative Exchange. It has been accepted for inclusion in Faculty Publications and Other Works -- Nursing by an authorized administrator of TRACE: Tennessee Research and Creative Exchange. For more information, please contact trace@utk.edu.

Continuing Education Offering Instructions

Differentiation and Treatment of Anemia in HIV Disease

Goal: The goal of this continuing education offering is to update nurses on HIV-related anemia and be able to properly diagnose and treat HIV-infected individuals suffering from anemia in order to improve quality of life.

Objectives: Upon completion of this offering, the reader will be able to

1. Define the most common type of anemia in HIV disease;
2. List the three major categories of anemia;
3. Understand the pathophysiology of anemia and laboratory tests; and
4. Properly diagnose and treat HIV-related anemia.

How to Earn Continuing Education Credit:

1. Read the article titled "Differentiation and Treatment of Anemia in HIV Disease."
2. Complete the test.
3. Send the answer form with your $10 processing fee (ANAC members) or $15 (non-ANAC members) check or money order payable to Association of Nurses in AIDS Care (ANAC) or with credit card information (MasterCard or Visa ONLY) to ANAC, 80 S. Summit Street, 500 Courtyard Square, Akron, OH 44308, or fax form and credit card information to (330) 762-5813.
4. Answer forms must be postmarked by June 30, 2003. Certificates indicating successful completion of this offering will bear the date your answer form is received at ANAC in Ohio.
5. Answer forms may be photocopied.
6. To earn 1.5 contact hours of continuing education credit, you must achieve a score of 75% (12 of 15 correct). If you do not pass the test, you may take it again at no additional charge.
7. The test results will be sent to you within 4 weeks of our receipt of your answer form. If you have any questions about the continuing education, please call (800) 260-6780.
8. The Association of Nurses in AIDS Care is accredited as a provider of continuing education in nursing through the Virginia Nurses Association, which is accredited as an approver of continuing education in nursing by the American Nurses Credentialing Center's Commission on Accreditation.

Copyright © 2002 Association of Nurses in AIDS Care

CONTINUING EDUCATION OFFERING

Differentiation and Treatment of Anemia in HIV Disease

Kenneth D. Phillips, PhD, RN
Maureen Groer, PhD, RN, FAAN

Anemia is a frequent complication of HIV disease that contributes to decreased quality of life and increased morbidity and mortality. The three major categories of anemia in HIV disease are anemia due to impaired red blood cell production, anemia due to increased red blood cell destruction, and anemia due to increased red blood cell loss. Although anemia of chronic illness is the most common type of anemia in HIV disease, other classifications of anemia may be encountered. Understanding the pathophysiology of anemia and laboratory tests that are frequently used to establish the differential diagnosis of anemia helps to ensure that HIV-infected individuals will receive appropriate treatment.

Key words: *anemia, HIV/AIDS, nutritional anemia, hemolytic anemia, blood loss anemia*

Hematologic abnormalities are among the most common pathophysiological processes in HIV/AIDS. Of these, anemia is thought to be the most common hematologic abnormality (Coyle, 1997). Anemia refers to a reduction in the number of circulating red blood cells, insufficient amount of hemoglobin, or a decreased hematocrit. Anemia, uncommon in early HIV disease, is increasingly more prevalent as HIV disease progresses (Arevalo et al., 1997; Doweiko, 1993; Spivak, Barnes, Fuchs, & Quinn, 1989; Zon, Arkin, & Groopman, 1987).

Anemia is a serious complication of HIV/AIDS that is associated with increased morbidity, faster progression to AIDS, decreased survival time, and increased mortality (Moore, Keruly, & Chaisson, 1998; Spivak et al., 1989; Sullivan et al., 1998). HIV-infected individuals who are severely anemic experience debilitating symptoms, functional impairment, decreased sense of well-being, and a poorer quality of life (Cella, Mo, & Peterman, 1996). For these reasons, it is imperative that nurses in AIDS care be well prepared to manage HIV-related anemia. Pathophysiology provides the scientific basis for understanding HIV-related anemia. Pathophysiology, the study of the pathogenesis, etiology, clinical manifestations, diagnosis, complications, and treatment of specific diseases, provides a scientific basis for the management of HIV-related anemia. The purpose of this article is to provide advanced-practice nurses with a knowledge base for the differential diagnosis and treatment of the most common types of anemia experienced by HIV-infected individuals.

Kenneth D. Phillips, PhD, RN, is an associate professor in the College of Nursing at the University of South Carolina. Maureen Groer, PhD, RN, FAAN, is a professor and associate dean for research in the College of Nursing at the University of Tennessee.

JOURNAL OF THE ASSOCIATION OF NURSES IN AIDS CARE, Vol. 13, No. 3, May/June 2002, 47-72
Copyright © 2002 Association of Nurses in AIDS Care

Prevalence, Morbidity, and Mortality of HIV-Related Anemia

As many as 66% to 85% of persons who have progressed to AIDS have some degree of anemia (Ganser, 1988; Hambleton, 1996; Scadden, Zon, & Groopman, 1989). Zon and Groopman (1988) reported that 8% of HIV-infected individuals who were asymptomatic, 20% who were symptomatic, and 71% who had progressed to AIDS were anemic. Spivak et al. (1989) reported that anemia occurred in 18% of HIV-infected individuals who were asymptomatic, 50% who were symptomatic, and 75% who had progressed to AIDS. Despite advances in the treatment of HIV infection, the prevalence of anemia in HIV disease has remained relatively constant (Mocroft et al., 1999; Sullivan et al., 1998).

Anemia is more common among HIV-infected women than HIV-infected men (Means, 1997). This may be due in part to the fact that, in general, anemia is more prevalent in women than men. Menses, pregnancy, and lactation are times when women are more at risk for anemia. Men are capable of storing greater amounts of iron, approximately 1000 mg of iron, whereas women are able to store only 300 to 500 mg (Leclair, 1997).

Anemia is an independent predictive marker for disease progression and death in HIV-infected patients (Mocroft et al., 1999; Rabeneck, Hartigan, Huang, Soucheck, & Wray, 1997; Spino, Kahn, Dolin, & Phair, 1997). Controlling for CD4 cell count and viral load, Mocroft et al. (1999) found that the latest hemoglobin value was a strong independent prognostic marker for death. Likewise, successful treatment of anemia is associated with a reduction in the risk of HIV-related death (Moore et al., 1998).

Overview of Normal Erythropoiesis

Hematopoiesis refers to the production and development of erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets). The tissues of the hematopoietic system consist of the bone marrow, liver, spleen, lymph nodes, and thymus gland. These tissues are responsible for the production, maturation, and destruction of blood cells. In infancy and early childhood, hematopoiesis occurs in all bones; however, in adults, it occurs primarily in the red bone marrow of the pelvic bones, vertebrae, skull, ribs, sternum, and the proximal ends of the femur. During periods of severe anemia, the fatty bone marrow, liver, and spleen can participate in hematopoiesis in a process known as extramedullary hematopoiesis (Gallicchio, 1992).

All blood cells (erythrocytes, leukocytes, and platelets) are derived from progenitor cells called pluripotent stem cells located in the red bone marrow. Although relatively few in number (less than 0.01% of the nucleated cells are in the bone marrow), they produce all the blood cells an individual will ever have across the life span. The pluripotent stem cells express the CD34 surface protein marker and are negative for CD38. Upon stimulation by growth factors, colony-stimulating factors, and interleukins, the pluripotential stem cells give rise to myeloid stem cells that differentiate into erythrocytes, leukocytes, or platelets or lymphoid stem cells that become T- or B-lymphocytes (Bell & Hughes, 1997; Sacher & McPherson, 2000) (see Figure 1).

Erythropoiesis refers to the production and development of erythrocytes. There are at least four cytokines (hormone-like growth factors) that stimulate proliferation, differentiation, and activation of erythrocytes. These cytokines are erythropoietin, interleukin-3, granulocyte-monocyte colony-stimulating factor, and monocyte-macrophage colony-stimulating factor (Bell & Hughes, 1997; Sacher & McPherson, 2000) (see Figure 1).

The primary cytokine responsible for erythropoiesis is erythropoietin. Although insignificant amounts are produced elsewhere in the body, erythropoietin is produced in greatest quantities by cells in the kidneys. The primary stimulus for the synthesis and release of erythropoietin is hypoxia (decreased oxygen in the tissues). Hypoxia may result from declining numbers of red blood cells, low hemoglobin levels, chronic obstructive disease, or inspiring air that contains less than 21% oxygen. Hypoxia stimulates the production and release of erythropoietin into the circulation. Erythropoietin travels in the circulation to its target tissue, the bone marrow, where it stimulates the differentiation of pluripotent stem cells into

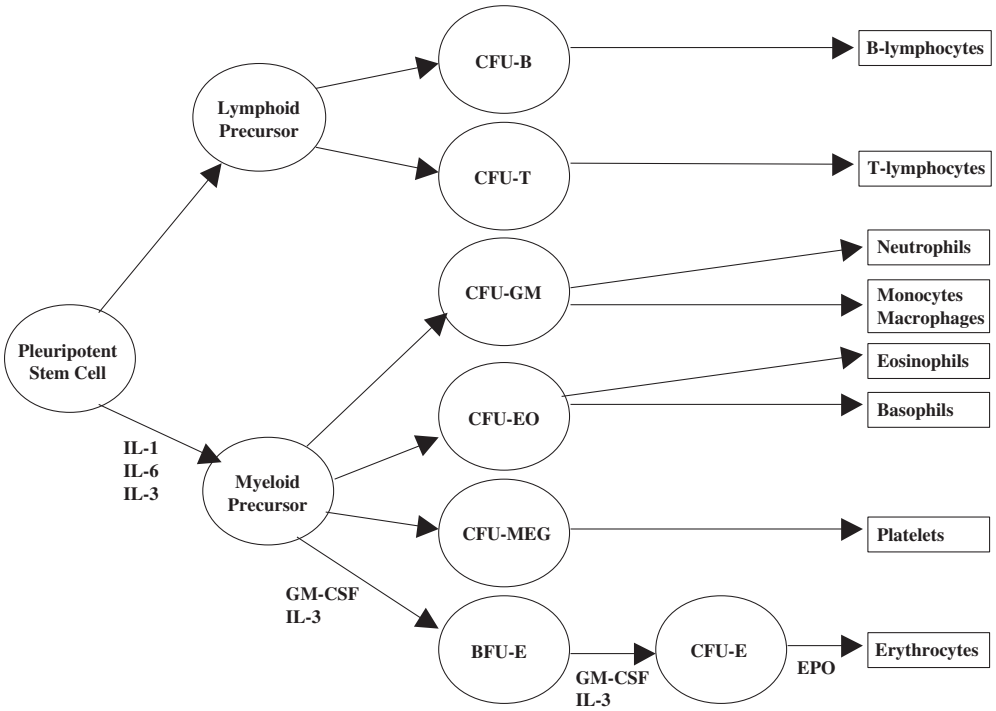

Figure 1. Stages of Hematopoiesis (GM-CSF = granulocyte-monocyte-macrophage colony-stimulating factor, CFU-B = colony-forming unit-B lymphocyte, CFU-T = colony-forming unit-T lymphocyte, CFU-GM = colony-forming unit-granulocyte-monocyte, CFU-EO = colony-forming unit-eosinophil, CFU-MEG = colony-forming unit-megakaryocyte, BFU-E = burst-forming unit-erythroid, CFU-E = colony-forming unit-erythroid, EPO = erythropoietin)

erythrocytes (Bell & Hughes, 1997; Sacher & McPherson, 2000) (see Figure 1).

Erythrocytes are biconcave disks approximately 7 to 8 μm in diameter. Their biconcave shape maximizes the red blood cell's surface area and ability to carry oxygen for gas exchange. Unlike most other cells in the body, mature erythrocytes do not contain cell organelles; therefore, they are unable to synthesize proteins, including enzymes. Energy, in the form of adenosine triphosphate (ATP), is produced by the conversion of glucose to lactate in the Embden-Meyerhof metabolic pathway. Each erythrocyte contains approximately 300 molecules of hemoglobin enmeshed within the cell membrane (Bell & Hughes, 1997; Sacher & McPherson, 2000).

The life span of the average erythrocyte is approximately 120 days. As erythrocytes age, their intracellular enzymes decrease and their metabolism begins to slow. At about day 120, intracellular metabolism becomes insufficient to maintain the integrity of the red blood cell. The red blood cell plasma membrane becomes osmotically fragile, and hemolysis begins. Normally, about 1% of circulating red blood cells die and are removed by the reticuloendothelial system each day (Sacher & McPherson, 2000). At this rate of erythrocyte destruction, healthy adults must produce more than 2,400,000 new erythrocytes per second just to maintain a steady state. At senescence, the spleen breaks down erythrocytes and the reticuloendothelial cells degrade hemoglobin into heme and globin, which are then recycled.

Hemoglobin, the major constituent of erythrocytes, is responsible for carrying oxygen to the tissues. Normal adult hemoglobin has four major constituents: globin, protoporphyrin, iron, and 2,3-diphosphoglycerate (2,3-DPG). Globin chains are polypeptide chains that are synthesized by the developing red blood cells. Protoporphyrin is synthesized

by the developing red blood cells. Heme is formed when protoporphyrin combines with ferrous iron. Chemical bonding of heme with globin results in the formation of hemoglobin. Hemoglobin carries oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. Iron is responsible for the characteristic bright red color of oxygenated blood and dark red color of deoxygenated blood (Ludvigsen, 1992).

For adequate oxygenation to take place, oxygen must attach to hemoglobin in the lungs and detach from hemoglobin when it reaches the tissues, where it can enter the cells and be used for metabolism. At the alveolar-capillary membrane, hemoglobin must have a high affinity for oxygen, and at the capillary membrane of other tissues, hemoglobin must have a low affinity for oxygen. Three factors influence this process: body temperature, serum carbon dioxide concentration, and the level of 2,3-DPG contained by red blood cells. High body temperatures, high carbon dioxide levels, and elevated 2,3-DPG decrease hemoglobin's affinity for oxygen, making it easier for oxygen to dissociate from hemoglobin when it reaches the tissues. Anemic patients can increase the concentration of 2,3-DPG in erythrocytes by the nonoxidative metabolism of the Embden-Meyerhof pathway (Harmening, 1997; Ludvigsen, 1992).

In adults, only three types of hemoglobin exist under physiologic conditions: hemoglobin A_1 (HbA_1; two α and two β chains), hemoglobin A_2 (HbA_2; two α and two δ chains), and hemoglobin F (HbF; two α and two γ chains). Adult hemoglobin (HbA1) is the predominant type of hemoglobin during adulthood (96%-98%). Although fetal hemoglobin (HbF) is the predominant type of hemoglobin during fetal life, it only accounts for about 0.5% to 0.8% of the hemoglobin during adult life. Hemoglobin A_2 accounts for 1.5% to 3.0% of the hemoglobin in normal adults (Harmening, 1997; Ludvigsen, 1992).

Laboratory Tests of Erythrocyte Structure and Function

To correctly diagnose and treat anemia, knowledge of several laboratory tests is required. The following is a brief discussion of the laboratory tests used to establish a diagnosis of anemia. The normal values and interpretation of these laboratory tests are presented in Table 1.

Erythrocytes

Red blood cell count. The red blood cell count is the total number of red blood cells in a cubic millimeter of blood measured in millions of cells/mm^3. A low red blood cell count indicates anemia. A higher than normal red blood cell count indicates an overproduction of red blood cell, known as polycythemia. Although polycythemia can be a hemoproliferative disorder (polycythemia vera), secondary polycythemia (due to chronic hypoxemia) is the most common type of polycythemia. The red blood cell count is normally higher in men than in women. Overhydration can falsely lower the red blood cell count, whereas dehydration has the opposite effect (Fischbach, 1996; Sacher & McPherson, 2000).

Hemoglobin. The amount of hemoglobin attached to red blood cells is measured in milligrams per deciliter (mg/dL). A low hemoglobin indicates anemia. Hemoglobin is normally higher in men than in women (Fischbach, 1996; Sacher & McPherson, 2000).

Hematocrit. Hematocrit is the percentage of whole blood that is made up of red blood cells. Red blood cells make up 97% of the cells in whole blood. White blood cells and platelets account for the other 3% of blood cells. When whole blood is centrifuged, it separates into two layers, blood cells and plasma. Blood cells normally make up slightly less than half of the volume of whole blood (Fischbach, 1996; Sacher & McPherson, 2000).

Reticulocyte count. The reticulocyte count is the number of immature red blood cells that have been released from the bone marrow into the circulation. It requires approximately 4 or 5 days for reticulocytes to become mature red blood cells after being released into the circulation. The reticulocyte count indicates how well the bone marrow is functioning and how well

Table 1. Normal Values and Interpretation of Laboratory Tests for Anemia

Test	Normal Value	Interpretation
Red blood cell count	Men: 4.6%-6.2% $\times 10^6$ Women: 4.2%-5.4% $\times 10^6$	Low value indicative of anemia
Hemoglobin	Men: 14-18 g/dL Women: 12-16 g/dL	Low value indicative of anemia
Hematocrit	Men: 40%-54% Women: 38%-47%	Low value indicative of anemia
Mean corpuscular volume	80-98 fL	Low value indicative of microcytosis High value indicative of macrocytosis
Mean corpuscular hemoglobin	26-32 fL	Low value indicative of hypochromia High value indicative of hyperchromia
Mean corpuscular hemoglobin concentration	32-36 fL	Low value indicative of hypochromia High value indicative of hyperchromia
Reticulocyte count	0.5%-2.5%	Low value indicative of decreased production of erythrocytes in the bone marrow. High value indicates increased production of erythrocytes in the bone marrow
Red cell distribution width	11.6%-14.6%	High value indicates greater variation in the size of red blood cells (anisocytosis).
Serum iron	50-150 µg/dL	Low value indicates iron deficiency.
Serum transferrin saturation	20%-45%	Low value indicates iron deficiency.
Serum ferritin	12-300 µg/L	Low value indicates iron deficiency.
Total iron-binding capacity	240-360 µg/dL	High value indicates iron deficiency.
Free erythrocyte protoporphyrin	15-18 µg/L	High value indicates iron deficiency.
Serum vitamin B_{12} level	200-900 pg/mL	Low value indicates vitamin B_{12} deficiency.
Serum folic acid level	3-20 ng/mL	Low value indicates folic acid deficiency.
Red blood cell folic acid level	165-600 ng/mL	Low value indicates folic acid deficiency.
Direct Coombs' test	Negative	A positive direct Coombs' test indicates the presence of an antibody on red blood cells and is useful for investigating hemolysis.
Indirect Coombs' test	Negative	A positive indirect Coombs' test detects antibodies in the serum against red blood cells and is useful for investigating the etiology of acquired hemolytic anemia.
Shilling's test	15%-40% of the 0.5-µg dose	Low value indicates decreased absorption of vitamin B_{12} is abnormal.
	5%-40% of the 1.0-µg dose	If the administration of intrinsic factor with vitamin B_{12} corrects the malabsorption, it is likely pernicious anemia.
Total bilirubin	0.1-1.0 mg/dL	Sum of the direct and indirect bilirubin
Serum bilirubin (direct)	0.1-0.3 mg/dL	High value may indicate biliary obstruction.
Serum bilirubin (indirect)	0.2-0.8 mg/dL	High value may indicate hemolysis. High value may indicate that the liver is not able to conjugate bilirubin.

SOURCE: Fischbach (1996) and Sacher and McPherson (2000).

it is responding to erythropoietin. Therefore, the reticulocyte count is low in bone marrow failure or when erythropoiesis is insufficient (Fischbach, 1996; Sacher & McPherson, 2000).

Erythrocyte Indices

Mean corpuscular volume. The mean corpuscular volume refers to the relative volume (size) of red blood

cells. When the mean corpuscular volume is low, red blood cells are microcytic (smaller than normal). A high mean corpuscular volume indicates that the red blood cells are macrocytic (larger than normal) (Fischbach, 1996; Sacher & McPherson, 2000).

Mean corpuscular hemoglobin. The mean corpuscular hemoglobin is a measure of the average amount of hemoglobin in red blood cells. If the mean corpuscular hemoglobin is low, red blood cells are hypochromic. Hypochromic red blood cells have a central area of pallor greater than 3 μm. If the mean corpuscular hemoglobin is high, red blood cells are hyperchromic. Hyperchromic cells stain gray-blue in color and are usually larger than normal red blood cells (Ciesla, 1997).

Mean corpuscular hemoglobin concentration. The mean corpuscular hemoglobin concentration refers to the average concentration of hemoglobin in a single red blood cell. When the mean corpuscular hemoglobin concentration is high, red blood cells are hyperchromic. When the mean corpuscular hemoglobin concentration is low, the red blood cells are hypochromic (Fischbach, 1996; Sacher & McPherson, 2000).

Red blood cell distribution width. The red blood cell distribution width indicates the degree of variation in size of the red blood cells. If the red blood cell distribution width is out of normal range, anisocytosis is present (Glassman, 1997). A normal red blood cell distribution width in the presence of macrocytosis (increased mean corpuscular volume) suggests round macrocytosis that is seen in conditions such as alcohol abuse, liver disease, or acute hemolytic anemia. An increased red blood cell distribution width in the presence of macrocytosis suggests oval macrocytosis that is seen in conditions such as aplastic anemia, vitamin B_{12} deficiency, or folic acid deficiency (Teferri, 2001).

Iron Metabolism

Serum iron. Serum iron is a measurement of the amount of iron in the serum. A low serum iron level may indicate iron deficiency. A high serum iron level may indicate iron poisoning. Serum iron levels must be evaluated in context with serum transferrin, serum transferrin saturation, and serum ferritin (Leclair, 1997).

Serum transferrin. Serum transferrin is a measurement of the amount of transferrin, a globulin in the blood that is responsible for binding and transferring iron. Transferrin increases in iron deficiency anemia and decreases in chronic illness and hypoproteinemia (Fischbach, 1996; Sacher & McPherson, 2000).

Serum transferrin saturation. Serum transferrin saturation is a calculation that indicates how much iron is available for hemoglobin synthesis. It is obtained using the following formula: serum transferrin saturation = serum iron level × 100% total iron-binding capacity. Serum transferrin saturation should be at least 20% to ensure that there is enough iron present to meet the requirements of hemoglobin synthesis (Fischbach, 1996; Sacher & McPherson, 2000).

Serum ferritin. Serum ferritin is an iron-phosphate-protein complex. Iron is stored in the body as ferritin. Ferritin is made by the intestinal mucosa when iron combines with a protein known as apoferritin. Ferritin is stored primarily in the reticuloendothelial cells of the liver, spleen, and bone marrow. Serum ferritin is more sensitive than either serum iron or total iron-binding capacity for diagnosing iron deficiency or overload (Fischbach, 1996; Sacher & McPherson, 2000).

Total iron-binding capacity. Total iron-binding capacity is the additional amount of iron that transferrin can bind. In iron deficiency anemia, there is more transferrin available to transfer iron in the serum than there is iron (Fischbach, 1996; Sacher & McPherson, 2000).

Laboratory Tests Used to Detect Vitamin Deficiencies

Serum folic acid level. Serum folic acid level is the amount of folic acid present in the serum. Serum folic acid levels fluctuate in response to dietary intake of folic acid. Folic acid deficiency may be due to inadequate intake (i.e., diet that lacks fresh vegetables or

chronic illness), increased usage (i.e., pregnancy and lactation), and certain drugs (i.e., many anti-neoplastic agents and anti-malarials). Increased folic acid levels may be seen in pernicious anemia, in vegetarian diets, and following blood transfusions (Fischbach, 1996; Sacher & McPherson, 2000).

Red blood cell folic acid level. Red blood cell folic acid level is the amount of folic acid present in the red blood cells. Because red blood cell folic acid levels do not fluctuate as greatly in response to dietary intake of folic acid, many believe that red blood cell folic acid level more accurately reflects tissue stores of folic acid (Fischbach, 1996; Sacher & McPherson, 2000).

Serum vitamin B_{12}. Serum vitamin B_{12} is the amount of cyanocobalamin and hydrocobalamin present in the serum. A low vitamin B_{12} level may indicate either pernicious anemia or malabsorption of vitamin B_{12}. In the United States, inadequate dietary intake is rarely the cause of Vitamin B_{12} deficiency (Fischbach, 1996; Sacher & McPherson, 2000).

Serum or urine methylmalonic acid. In equivocal cases of B_{12} deficiency, increased amounts of methylmalonic acid in the serum or urine gives added evidence that B_{12} is being poorly absorbed. B_{12} is necessary for the conversion of methylmalonic acid to succinic acid; therefore, in B_{12} deficiency increased levels of methylmalonic acid accumulate in the serum or the urine. Vitamin B_{12} is required for the conversion of methylmalonic acid to acetyl coenzyme A (Teferri, 2001).

Plasma homocystine. Both vitamin B_{12} and folate are necessary for the conversion of homocystine to methionine. Therefore, homocystine levels will be elevated in vitamin B_{12} deficiency and folate deficiency (Taghizadeh, 1997).

Schilling's test. Schilling's test is a specific test used to diagnose vitamin B_{12} deficiency. The purpose of Schilling's test is to measure the body's ability to secrete biologically active intrinsic factor and to absorb vitamin B_{12}. The individual must fast for 12 hours before Schilling's test and 3 hours after the test. Schilling's test requires a cooperative patient who can successfully maintain a 24-hour urine specimen. Schilling's test consists of two stages.

In the first stage, the patient is given 0.5 mg to 2.0 µg of radioactive vitamin B_{12}. Following the oral dose, the individual is given an intramuscular injection of 1000 µg unlabeled vitamin B_{12} to fully saturate the liver and other sites that bind vitamin B_{12}. A 24-hour urine specimen is collected. Normally, more than 7% of the radioactive vitamin B_{12} should be excreted in the 24-hour urine sample. If the test is normal at this point, the test is concluded (Fischbach, 1996; Ludvigsen, 1992). If less than 7% of the radioactively labeled vitamin B_{12} is excreted, the patient undergoes the second stage of the test.

If less than 7% of the radioactively labeled vitamin B_{12} is excreted, two interpretations are suggested. First, there may be an absence of intrinsic factor. Second, there may be malabsorption in the ileum. If the results are abnormally low, the test is repeated in 3 to 4 days to differentiate between these two possibilities. This time, the individual is given intrinsic factor and radioactively labeled vitamin B_{12}. If the urinary excretion of radioactive vitamin B_{12} rises to normal levels, it suggests an absence of intrinsic factor (pernicious anemia). If the urinary secretion fails to rise to normal, malabsorption is considered the etiology of the vitamin B_{12} deficiency (Fischbach, 1996; Ludvigsen, 1992).

Laboratory Tests Used to Diagnose Hemolysis

Serum bilirubin. Serum bilirubin is a test that is beneficial in the diagnosis of hemolytic anemia. There are two forms of bilirubin: direct bilirubin (conjugated) and indirect bilirubin (unconjugated). Indirect bilirubin is the unbound fat-soluble form of bilirubin that results from the break down of hemoglobin. Indirect bilirubin circulates freely in the blood. When the direct bilirubin circulates through the liver it is bound to a protein produced by the liver and becomes water-soluble. Conjugated bilirubin makes up a large part of bile. The gastrointestinal tract excretes bile. A normal bilirubin indicates normal liver function and appropriate hemolysis of senescent cells. A high indirect bilirubin in the presence of jaundice suggests hemolytic anemia or liver disease (i.e., hepatitis) that prevents the conjugation of bilirubin. A high direct bilirubin in the

Table 2. Classification of Anemia Based on Red Blood Cell Size

Decreased Mean Corpuscular Volume	Normal Mean Corpuscular Volume	Elevated Mean Corpuscular Volume
Iron deficiency anemia	Anemia of chronic illness	Acute hemolytic anemia
Thalassemia	Early iron deficiency anemia	Zidovudine or other drug-induced anemia
Anemia of chronic illness	Hemolytic anemia	Vitamin B_{12} deficiency anemia
	Aplastic anemia	Folate deficiency anemia
	Drug-induced bone marrow suppression	

presence of jaundice suggests obstruction of the common bile duct or hepatic ducts (Fischbach, 1996; Sacher & McPherson, 2000).

Coombs' test. The Coombs' test helps to differentiate the types of hemolytic anemia. The direct Coombs' test is a measure of the amount of antibodies attached to the surface of red blood cells. The indirect Coombs' test is a measure of the amount of antibodies against red blood cells present in the serum. A positive direct Coombs' test most often indicates antibody-mediated hemolytic anemia and less commonly may occur after a transfusion reaction or the administration of drugs. A negative direct Coombs' test does not rule out nonautoimmune hemolytic anemia (Fischbach, 1996; Sacher & McPherson, 2000).

Pathophysiology of HIV-Related Anemia

Anemia is defined in men as a hematocrit less than 42% (hemoglobin < 14 g/dL) and in women as a hematocrit less than 37% (hemoglobin < 12 g/dL) (Sacher & McPherson, 2000). Many classification systems for anemia exist. One useful classification system is based on erythrocyte size as determined by the mean corpuscular volume. Using this system, there are three broad classifications of anemia: normocytic anemia (red blood cells are normal in size), microcytic anemia (red blood cells are smaller than normal), and macrocytic anemia (red blood cells are larger than normal). Etiologies for each type of anemia are presented in Table 2.

The three major causes of anemia in HIV disease are decreased red blood cell production, increased red blood cell destruction, and blood loss (see Table 3). The clinical spectrum of anemia varies from mild to very severe. The National Cancer Institute (1977) has developed a grading scale for the severity of anemia (see Table 4). The symptoms of anemia depend on the severity. Because the oxygen-carrying capacity of red blood cells is reduced, the symptoms of anemia are due to tissue hypoxia. The cardinal symptoms of anemia are dizziness, weakness, fatigue, and headache. Other symptoms of anemia are listed in Table 5.

Anemia Due to Impaired Red Blood Cell Formation

Anemia of Chronic Illness

The most common type of anemia seen in HIV infection is the anemia of chronic illness. In the anemia of chronic illness, erythropoiesis is impaired and reticulocyte response is suppressed. HIV infection increases the body's requirement to produce erythrocytes while at the same time decreasing the body's ability to produce these cells (Scadden et al., 1989; Zon & Groopman, 1988).

Pathophysiology

The major cause of anemia in HIV disease is impaired erythropoiesis (Coyle, 1997; Mitsuyasu, 1999). Intrinsic immune mechanisms, opportunistic infections, opportunistic malignancies, medications, and malabsorption of vitamins, trace elements, and other nutrients may contribute independently or synergistically to impaired erythropoiesis. The anemia of chronic illness associated with HIV disease is typically associated with low serum erythropoietin levels (Spivak et al., 1989).

A rise in the level of the inflammatory cytokines (interleukin-1, interleukin-6, tumor necrosis factor,

Table 3. Three Major Causes of HIV-Related Anemia

Classification	Type	Etiological Factor
Impaired production of erythrocytes	Anemia of chronic illness	Opportunistic infections of bone marrow
		Parvovirus B19
		Mycobacterium avium complex
		Histoplasma capsulatum
		Cryptococcus neoformans
		Coccidiodes immitis
		Cytomegalovirus
		Pneumocystis carinii
		Medications
		Zidovudine
		Ganciclovir
		Trimethoprim-sulfamethoxazole
		Dapsone
		Sulfadiazine
		Pyrimethamine
		Amphotericin B
		5-flucytosine
		Antineoplastics
		Interferon-α
		Cidofovir
	Iron Deficiency Anemia	Inadequate intake of iron
		Iron-deficient diet
		Inadequate absorption of iron
		Achlorhydria
		Decreased absorptive area
		Excess loss of iron
		Menorrhagia
		Gastrointestinal bleeding
		Increased physiologic demand for iron
		Pregnancy
		Lactation
		Increased growth in infancy and childhood
	Vitamin B_{12} deficiency anemia	Decreased absorption of vitamin B_{12}
		Intrinsic factor deficiency
		Gastrectomy
		Certain drugs
		Consumption by small-bowel bacteria
		Consumption by fish tapeworms
		Decreased absorptive area in the ileum
	Folate deficiency anemia	Inadequate intake of folate
		Alcoholism
		Starvation
		Increased requirements
		Pregnancy
		Lactation
		Infancy
		Drugs
		Zidovudine
		Trimethoprim
		Methotrexate
		Trimetrexate
		Cycloserine

(continued)

Table 3. continued

Classification	Type	Etiological Factor
Increased destruction of erythrocytes	Antibody-mediated hemolytic anemia	
	Sickle cell anemia	A hereditary disorder in which the gene responsible for coding for hemoglobin substitutes valine for glutamic acid in the NH_2 terminal of the β chain
	Hereditary spherocytosis	A hereditary disorder caused by an intrinsic defect in the red blood cell membrane
	Glucose-6-phosphate dehydrogenase deficiency	Hereditary disorder caused by a deficiency of glucose-6-phosphate, which is an enzyme that is key in the Embden-Meyerhof metabolic pathway; antioxidants, infection, or fever can precipitate a hemolytic crisis
Increased loss of erythrocytes	Acute blood loss	Hemophilia Gastrointestinal bleeding Menstruation
	Chronic blood loss	Gastrointestinal bleeding Menstruation

and interferon) marks the progression of HIV disease. Likewise, the degree of anemia worsens as the serum levels of these inflammatory cytokines rise in HIV-infected individuals. These cytokines have been shown to inhibit erythropoiesis in vitro. Tumor necrosis factor-α has been shown to inhibit erythropoiesis in vitro. Interferon-γ has been shown to suppress the formation of the erythroid colony-forming units (Spivak et al., 1989).

Several opportunistic organisms have been shown to infiltrate the bone marrow and disrupt erythropoiesis. The most common infectious agents associated with HIV-related anemia include *Mycobacterium avium* complex, *Mycobacterium tuberculosis*, *Histoplasma*, *Cryptococcus*, *Coccidiodes*, *Pneumocystis carinii*, and *Leishmania* (Hambleton, 1996). In immunosuppressed individuals, *M. avium* complex may produce a widely disseminated infection involving the blood, bone marrow, and other tissues. *M. avium* infection has been highly implicated as a cause of HIV-related anemia. Anemia due to *M. avium* is usually isolated to a reduction in red blood cells. Anemia resulting from other organisms is frequently associated with pancytopenia (Hambleton, 1996). Another organism strongly associated with HIV-related anemia is *Parvovirus B19* infection (Hambleton, 1996).

Several drugs used to combat HIV and its complications may contribute to the anemia that is seen in HIV disease (Aboulafia, 1997). Zidovudine is a reverse transcriptase inhibitor that is most commonly associated with anemia in HIV disease (Northfelt, 1999). Zidovudine inhibits the development of erythrocytes, lymphocytes, and platelets (Walker et al., 1988). In the early clinical trials, 34% of the patients receiving zidovudine demonstrated a statistically significant reduction in hemoglobin after 6 weeks of therapy (Richman et al., 1987). Now that zidovudine is being administered at lower doses in combination with other antiretrovirals, the incidence of severe anemia has declined (Collier et al., 1990; Eron et al., 1995; Volberding et al., 1990). Anemia related to zidovudine therapy often subsides when the drug is withdrawn. Other reverse transcriptase inhibitors may be less myelosuppressive than zidovudine and should be considered for anemic patients.

Zidovudine increases the mean corpuscular volume of red blood cells. Thus, mean corpuscular volume is often used as a measure of adherence to zidovudine therapy. Other drugs that increase the mean corpuscular volume are trimethoprim/sulfamethoxazole and dapsone (Northfelt, 1999).

In the anemia of chronic illness, the red blood cells are usually normochromic (normal mean corpuscular

Table 4. National Cancer Institute's Anemia Grading Scale

Grade	Hemoglobin Level (g/dL)
I mild	10.0 to normal
II moderate	8.0 to 9.9
III severe	6.5 to 7.9
IV very severe	< 6.5

SOURCE: National Cancer Institute (1977).

Table 5. Signs and Symptoms of Anemia

Fatigue
Muscle weakness
Shortness of breath
Headache
Lightheadedness
Feeling faint
Tachypnea
Tachycardia
Hypotension

hemoglobin and mean corpuscular hemoglobin concentration) and normocytic (normal mean corpuscular volume). However, microcytic, hypochromic red blood cells are sometimes seen in the anemia of chronic illness. Anisocytosis is frequently observed (increased red blood cell distribution width). Disruption of iron metabolism is manifested by low serum iron, total iron-binding capacity, and transferrin saturation with an elevated serum ferritin level (Linker, 2001).

Low serum erythropoietin levels are associated with HIV-related anemia. In a cohort study that included HIV-infected individuals at all stages of the illness, researchers in Greece identified antibodies to erythropoietin. Circulating autoantibodies to erythropoietin significantly predicted anemia and were significantly associated with higher erythropoietin levels (Sipsas et al., 1999).

Treatment

The first step in the treatment of HIV-related anemia is to identify the underlying etiology of the anemia. Review the medications, especially the antiretrovirals, currently being taken. All assessment data, especially cardiovascular, respiratory, and skin data, should be considered when initiating therapy for HIV-related anemia. Therapy should be based not solely on the individual's hemoglobin level but also on the physical assessment data. Consider substituting another drug for one that is myelosuppressive. For instance, it is often possible to substitute another nucleoside analog reverse transcriptase inhibitor for zidovudine.

Opportunistic infections. Constant vigilance in the treatment of opportunistic infections is required. In particular, prevention and treatment is required for the following organisms known to be associated with HIV-related anemia: *M. avium* complex, *M. tuberculosis*, *Histoplasma*, *Cryptococcus*, *Coccidiodes*, *P. carinii*, *Leishmania*, and *P. B19*.

Recombinant erythropoietin. Erythropoietin alfa, a recombinant, biosynthetic form of erythropoietin, is synthesized using recombinant DNA technology. Recombinant erythropoietin stimulates two progenitors of erythrocytes, the burst-forming units and the colony-forming units. The safety and efficacy of recombinant erythropoietin for treating anemia have been demonstrated (Henry et al., 1992). The initial dosage of epoietin alfa is 100 to 300 units/kg subcutaneously or intravenously three times per week. The maintenance dose is individually titrated to keep the hematocrit between 36% and 40%. The response to erythropoietin alfa depends on the endogenous serum erythropoietin level prior to treatment. A good response to erythropoietin is usually observed in individuals with a serum erythropoietin less than 500 μU/mL (American Hospital Formulary Service, 2001). Little response to erythropoietin therapy is observed in individuals with a serum erythropoietin greater than 500 μU/mL (American Hospital Formulary Service, 2001).

Red cell transfusions. Red cell transfusions are used with caution in HIV disease because blood transfusions have been shown to be immunosuppressive, to increase HIV replication, to accelerate disease progression, to decrease the survival time in HIV disease,

and to transmit a number of blood-borne pathogens (Groopman, 1997). Proteins on the surface of white blood cells in transfused blood are known to be immunosuppressive. Following transfusion, HIV-infected blood recipients have decreased CD4:CD8 ratios (Kaplan, Sarnaik, Gitlin, & Lusher, 1984), natural killer cell activity (Kaplan et al., 1984), lymphocyte blastogenesis (Waymack et al., 1986), and cell-mediated recall of antigens (Tartter, Heimann, & Aufses, 1986; Schot & Schuurman, 1986). Transfusions induce cellular immune activation, and this activation appears to increase HIV viral replication (Margolick, Volkman, Folks, & Fauci, 1987; Mudido et al., 1996).

Iron Deficiency Anemia

Pathophysiology

Worldwide, iron deficiency is the most common type of anemia. Deficient intake of iron, malabsorption of iron, increased requirement of iron, and blood loss most commonly cause iron deficiency. Although deficient iron intake is uncommon in adults, it should be considered as a cause of iron deficiency for all HIV-infected infants, children, adolescents, and adults. Malabsorption may result from inflammatory changes of the gastrointestinal mucosa. Acute and chronic blood loss can result from conditions such as Kaposi's sarcoma, excessive menstruation, or gastrointestinal bleeding. Increased demands for iron are experienced during infancy, adolescence, pregnancy, and lactation.

In the United States, the average diet provides approximately 10 to 15 mg of iron per day. Normally, 1 mg of iron is absorbed primarily across the mucosal cells of the duodenum and upper jejunum. Iron is transported in the blood by transferrin. In the blood, iron combines with apoferritin, a protein present in the blood, and becomes ferritin, the storage form of iron. Likewise, 1 mg of iron is lost per day through fecal or urinary excretion. Women who experience menorrhagia (excessive menstrual bleeding at the time of menstruation) may lose as much as 3 to 4 mg of iron per day (Leclair, 1997; Sacher & McPherson, 2000).

In iron deficiency anemia, pica is frequently experienced, but the patient often fails to report unusual cravings for ice, starch, clay, or other substances. Signs of severe iron deficiency anemia include glossitis (inflamed tongue), cheilitis (fissures in the corner of the mouth), koilonychia (thin concave nails with raised edges sometimes called spoon nails), blue sclera, and dysphagia due to the formation of esophageal webs (Leclair, 1997; Sacher & McPherson, 2000).

In early iron deficiency anemia, a decrease in serum ferritin may be observed. As iron deficiency anemia progresses, the red blood cells become hypochromic (decreased mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration) and microcytic (decreased mean corpuscular volume). The red blood cell count may be normal during early iron deficiency. As iron stores deplete, serum transferrin usually increases. Typically, the amount of transferrin saturated with iron (transferrin saturation) decreases to less than 10% (Teferri, 2001).

Treatment

Iron supplementation can be administered orally or parenterally. The oral route is preferred because parenteral iron supplementation is associated with increased risk of anaphylaxis. Ferrous sulfate is often the oral iron preparation of choice because this form of iron is less expensive and more readily absorbed. Ferrous gluconate and ferrous fumarate are other common iron preparations that may be administered orally. Oral administration of iron may produce constipation, diarrhea, dark stools, and/or epigastric pain (American Hospital Formulary Service, 2001) (see Table 6).

Parenteral iron therapy using iron dextran should only be used when the patient is unable to tolerate any oral iron preparation or when malabsorption is the etiology of iron deficiency. Iron dextran can be given intramuscularly or as an intravenous infusion over 4 to 6 hours. Severe anaphylactic reactions have been observed following parenteral iron therapy. Anaphylactic reactions most often occur within minutes of onset of administration. Anaphylaxis is characterized by respiratory difficulty (wheezing, bronchospasm, rigor, dyspnea, and cyanosis), tachycardia, and hypotension. Because respiratory and/or cardiac arrest are possible, parenteral iron therapy should only be administered by persons who are able to deliver resuscitative measures, if needed (American Hospital Formulary Service, 2001).

Table 6. Medications Commonly Used for Treating Anemia

Classification	Generic Name	Route	Usual Therapeutic Dosage	Nursing Considerations
Anti-anemia drugs	Epoietin alfa	Subcutaneously Intravenously	100-300 units/kg 3 times weekly	The target hematocrit range is 36%-40%. Treatment with epoietin alfa is usually indicated for patients with endogenous erythropoietin levels ≤500 mU/mL.
Oral iron preparations	Ferrous sulfate	Orally	Large dose for adults: 50-100 mg of elemental iron orally three times daily	All oral iron preparations should be taken 2 hours before or 1 hour after a meal.
	Ferrous gluconate		Smaller dose for adults: 60-120 mg of elemental iron orally daily in two or three divided doses	Vitamin C increases the absorption of iron from the gastrointestinal tract.
	Ferrous fumarate		Pediatric dose: 3-6 mg/kg of elemental iron daily in two or three divided doses	Reticulocytosis usually begins by the 10th day and indicates effective therapy.
Parenteral iron preparation	Iron dextran	Intramuscularly	The dosage is calculated using a formula that takes body weight and desired and observed hemoglobin levels into consideration	Iron dextran is used for iron deficiency when oral iron replacement is unfeasible or ineffective.
		Intravenously		Iron dextran is not recommended for children under 4 months of age. The most common adverse reaction of iron dextran is anaphylaxis. A test dose should be given prior to initiating iron dextran therapy. The test dose for an adult is 25 mg of iron dextran. The test dose for a child weighing 10 to 20 kg is 15 mg of iron dextran. The test dose for a child weighing <10 kg is 10 mg of iron dextran. Must be given by the Z-track method if given intramuscularly Reticulocytosis usually begins by the fourth day after administration and indicates effective therapy.
Vitamins	Folic acid	Orally	Initial dose: 5 mg/day for 4 months	Folic acid is commonly administered to prevent folic acid deficiency.

The following formula is used to calculate the total dosage of iron dextran that is required for iron deficiency anemia (the weight is lean body weight rather than total body weight):

Total dose of iron dextran in mL = $[0.0476 \times \text{weight} \times (\text{hemoglobin}_{\text{normal}} - \text{hemoglobin}_{\text{measured}})] + 1$ mL per 5 kg of weight (up to a maximum of 14 mL) (American Hospital Formulary Service, 2001, p. 1364).

The following formula is used to calculate the total dosage of iron dextran that is required for iron replacement secondary to blood loss:

Total dose of iron dextran in mL = $0.02 \times$ blood loss in mL $\times$ hematocrit (expressed as a decimal fraction) (American Hospital Formulary Service, 2001, p. 1364).

Reticulocytosis indicates that iron supplementation is effective. Reticulocytosis should appear within 10

days following the initiation of therapy. Following the appearance of reticulocytosis, the hemoglobin is expected to rise 0.1 to 0.2 g per deciliter if iron deficiency is the etiology of the anemia (Sacher & McPherson, 2000).

Vitamin B_{12} Deficiency Anemia

Pathophysiology

Vitamin B_{12} is required for folate metabolism. Therefore, vitamin B_{12} deficiency also leads to defective DNA synthesis. There are two forms of vitamin B_{12}, cyanocobalamin and hydroxycobalamin, which are synthesized by microorganisms ubiquitous in nature. Humans obtain vitamin B_{12} from eating meat. The average American diet provides 5 to 30 µg of vitamin B_{12}; however, only 1 to 5 µg are absorbed. The liver stores from 3000 to 5000 µg of vitamin B_{12}, enough to meet the requirements for about 6 months. For that reason, dietary deficiency of vitamin B_{12} is rarely ever the cause of vitamin B_{12} deficiency in this country (Sacher & McPherson, 2000).

Malabsorption due to a lack of intrinsic factor is the most common cause of vitamin B_{12} deficiency. Vitamin B_{12} deficiency due to a lack of intrinsic factor is called pernicious anemia. Intrinsic factor, a substance produced by parietal cells in the stomach, is responsible for the absorption of vitamin B_{12} in the terminal ileum. Intrinsic factor binds to vitamin B_{12} and to receptor sites in the lumen of the terminal ileum. This binding process promotes the absorption of vitamin B_{12}. Partial or total gastrectomy may lead to decreased production of intrinsic factor and decreased absorption of vitamin B_{12}. Inflammatory changes to the ileal wall secondary to HIV disease may lead to decreased absorption of B_{12}. Because intestinal bacteria use the vitamin B_{12} present in the intestinal lumen, another cause of vitamin B_{12} deficiency is bacterial overgrowth. Bacterial overgrowth often follows aggressive antibiotic therapy and may increase the amount of vitamin B_{12} that is used (Sacher & McPherson, 2000).

In addition to the general symptoms of anemia, the person with vitamin B_{12} deficiency may present with gastrointestinal symptoms such as a sore mouth, a beefy or atrophic tongue (glossitis), or diarrhea. In addition, neurologic signs due to peripheral neuropathy (i.e., impaired gait, paresthesia, and decreased vibratory sense in the extremities) may be seen. Neurologic signs may also include decreased ability to think and reason and personality change (Sacher & McPherson, 2000).

Serum vitamin B_{12} level. Serum vitamin B_{12} level is a simple and relatively inexpensive test to confirm vitamin B_{12} deficiency. A low value indicates vitamin B_{12} deficiency (Sacher & McPherson, 2000).

Treatment

Cyanocobalamin (vitamin B_{12}). Although cyanocobalamin may be given orally in large doses, it is poorly absorbed from the gastrointestinal tract in the absence of intrinsic factor. Cyanocobalamin may also be given nasally. The preferred route is subcutaneously or intramuscularly. For pernicious anemia, lifelong vitamin B_{12} therapy is required (Sacher & McPherson, 2000).

Folate Deficiency Anemia

Pathophysiology

Folic acid is necessary for thymidine synthesis. Thymidine is an amino acid that is found in DNA but is absent in RNA. Thus, folate deficiency impairs the synthesis of DNA in the developing red blood cells.

The most likely cause of folic acid deficiency anemia in the general population is inadequate dietary intake. Foods that are rich in folate include asparagus, black-eyed peas, lettuce, spinach, collards, broccoli, liver, yeast, and mushrooms. Overcooking vegetables in water decreases the amount of folate they contain. A number of drugs that are used in the treatment of HIV disease antagonize the use of folate. These include trimethoprim, methotrexate, and trimetrexate. A drug that decreases the absorption of folic acid is the antitubercular drug cycloserine. *Giardial* infestation may impair the absorption of folic acid. Pregnancy increases the amount of folate that is needed. There is strong evidence that folic acid deficiency leads to neural tube deficits in the developing fetus. All women of reproductive age should begin folate therapy prior to becoming pregnant (Sacher & McPherson, 2000).

The signs and symptoms of folic acid deficiency anemia are the same as for vitamin B_{12} deficiency anemia. Neurological signs and symptoms may not be present (Teferri, 2001).

Folate deficiency anemia is manifested by a low serum folic acid level (< 3 ng/mL) and a low red blood cell folic acid level (< 165 ng/mL). An effective response to folic acid therapy is indicated by a prompt and pronounced increase in the number of circulating reticulocytes (Sacher & McPherson, 2000).

Treatment

Except for cases in which malabsorption is the basis for folic acid deficiency, a daily dose of folic acid 1 to 2 mg by mouth is sufficient. In cases where folic acid deficiency is due to malabsorption, a daily parenteral dose of 1 to 2 mg folic acid may be administered (American Hospital Formulary Service, 2001).

Anemia Due to Increased Red Blood Cell Destruction

Hemolysis refers to the destruction of red blood cells. Rapid and early destruction of red blood cells leads to hemolytic anemia. When the red blood cells are destroyed, they release free hemoglobin into the circulation. Through a series of steps, hemoglobin is broken down into bilirubin in the blood. This soluble form of bilirubin is referred to as unconjugated or indirect bilirubin. Glucuronic acid, a substance found in liver cells, acts on bilirubin to conjugate it to an insoluble form of bilirubin (direct bilirubin) that can be excreted as bile through the gastrointestinal system. In hemolytic anemia, there is more indirect bilirubin in the blood than can be conjugated by the hepatocytes, leading to hyperbilirubinemia.

Antibody-Mediated Hemolytic Anemia

Pathophysiology

Frequently, HIV-infected individuals present with hypergammaglobulinemia (excessive gamma globulin in the blood). A positive direct Coombs' test, indicating the attachment of immunoglobulins to the red blood cell membrane, is generally seen in non-AIDS-related antibody-mediated hemolytic anemia. Although approximately 20% to 40% of HIV-infected individuals have a positive direct Coombs' test (Telen, Roberts, & Bartlett, 1990), the incidence of AIDS-related antibody-mediated hemolytic anemia is rare (Coyle, 1997). HIV-infected individuals who experience antibody-mediated hemolytic anemia become severely anemic and often require numerous transfusions (Saif, 2001). Other signs of AIDS-related antibody-mediated hemolytic anemia include a low serum haptoglobin, microspherocytes on the peripheral blood smear, splenomegaly, increased indirect bilirubin, and hyperplasia of the red blood cell precursors in the bone marrow. A characteristic finding of antibody-mediated hemolytic anemia is reticulocytosis; however, reticulocytosis is noticeably absent in AIDS-related antibody-mediated hemolytic anemia (Coyle, 1997).

Treatment

Treatment of AIDS-related antibody-mediated hemolytic anemia includes glucocorticoids, intravenous gammaglobulin, and splenectomy (Coyle, 1997).

Hereditary Spherocytosis

Pathophysiology

Normal red blood cell membranes comprise 10 major and 200 minor proteins. Six proteins, spectrin, ankyrin, adducin, band 4.1, band 3, and band 4.2, form the cytoskeleton of red blood cells and help maintain their normal biconcave shape. In hereditary spherocytosis, one or more of these proteins are defective. Spectrin is the protein that is most often defective. This defect decreases the surface area of the red blood cell membrane and allows the cell to become spherical in shape, to swell more than normal, and to become osmotically fragile. Together, these factors decrease the survival time of the spherocytes (Zail & Coetzer, 1997).

Hereditary spherocytosis is the most prevalent form of inherited hemolytic anemia in Caucasians (Zail & Coetzer, 1997). It is usually transmitted by an autosomal dominant inheritance pattern (75%); however, it may also be transmitted by an autosomal

recessive pattern (25%). Due to chronically elevated serum bilirubin levels, many individuals with hereditary spherocytosis often develop pigment gallstones. The most common pattern for hereditary sphero-cytosis is chronic mild hemolytic anemia. Approximately 10% of individuals with hereditary spherocytosis may experience a severe hemolytic episode requiring transfusion. Rarely, aplastic crises complicate hereditary spherocytosis. The most common cause of such crises is *P. B19* infection (Zail & Coetzer, 1997).

The patient with hereditary spherocytosis may present with jaundice, anemia, and splenomegaly from birth to adulthood. The hallmark of hereditary spherocytosis is the presence of spherocytes on the peripheral blood smear. Red blood cells from individuals with hereditary spherocytosis have increased osmotic fragility and undergo more rapid autohemolysis when allowed to incubate in a test tube for 48 hours at body temperature. Electrophoresis is used to determine which structural protein is defective (Teferri, 2001).

Treatment

Splenectomy is beneficial for most patients. The life span of red blood cells returns to near normal levels (120 days) following splenectomy. Following splenectomy, the individual becomes more susceptible to bacterial infections and may require prophylactic antibiotics. Life-threatening sepsis may occur following a splenectomy (Linker, 2001; Teferri, 2001).

Glucose-6-Phosphate Dehydrogenase Deficiency

Pathophysiology

Red blood cells contain no nuclei. Glucose-6-phosphate dehydrogenase (G6PD) is a protein required for aerobic glycolysis. In red blood cells, G6PD catalyzes the conversion of glucose to glutathione. Glutathione prevents hemoglobin from becoming denatured. In the presence of glutathione deficiency, oxidative destruction of the globin chains of hemoglobin occurs, and the red blood cell membrane becomes damaged. Most individuals with G6PD deficiency are asymptomatic most of the time and often reach adulthood before learning that they have G6PD deficiency. Certain drugs that are used in the treatment of HIV and other conditions, such as malaria, are known to induce hemolysis is G6PD-deficient individuals. Fava beans often trigger hemolysis (Sacher & McPherson, 2000). These drugs are summarized in Table 6.

G6PD deficiency is one of the most prevalent genetic disorders known. G6PD deficiency is transmitted by an X-linked recessive pattern of inheritance. G6PD deficiency is expressed in men who inherit the gene from their mothers who are carriers. G6PD deficiency is expressed in women only when both X chromosomes contain the gene (homozygous). G6PD deficiency is more common in African Americans, Asians, and people of Mediterranean descent (Sacher & McPherson, 2000; Sim, McCarron, & Glassman, 1997).

The individual may become jaundiced, and his or her urine may become tea colored. Hemoglobin and hematocrit levels decrease. Heinz bodies (precipitated hemoglobin) appear on the peripheral blood smear. Serum bilirubin levels increase and haptoglobin levels decrease. Addition of certain drugs may result in the formation of Heinz bodies in an in vitro blood sample. Other tests that can be used to confirm the diagnosis of G6PD deficiency are the methemoglobin reduction test (sensitive), the ascorbate-cyanide test (not specific), the fluorescent spot test (sensitive and specific), and the specific G6PD assay (sensitive and specific) (Sacher & McPherson, 2000; Sim et al., 1997).

Treatment

Prevention remains the best treatment for G6PD deficiency hemolytic anemia. Avoid oxidant drugs that may precipitate a hemolytic crisis.

Anemia Due to Increased Blood Loss

Chronic Blood Loss Anemia

Pathophysiology

Chronic blood loss occurs in AIDS and contributes to the high incidence of anemia in this population. It is

Table 7. Stages of Acute Blood Loss

Clinical Sign	Stage I Initial	Stage II Compensatory	Stage III Progressive	Stage IV Final
Blood loss	< 750 mL	750-1500 mL	1500-2000 mL	> 2000 mL
Percentage blood volume	< 15%	15%-30%	30%-40%	> 40%
Heart rate	Mildly elevated	Moderately elevated	Severely elevated	Very severely elevated
Blood pressure	Normal	Normal	Moderately decreased	Severely decreased
Respirations	Mildly elevated	Moderately elevated	Severely elevated	Very severely elevated
Urine output	Normal	Mildly decreased	Moderately decreased	Severely decreased
Skin	Cool, pink	Cold, pale	Cold, pale, moist	Cold, mottled, moist
Thirst	Mildly elevated	Moderately elevated	Severely elevated	Very severely elevated

important to note that the anemia of HIV disease is often multifactorial, and therefore much less blood loss may precipitate symptoms. Early in chronic blood loss, the red blood cell morphology is normal. As chronic blood loss continues, the red blood cells become hypochromic and microcytic, indicating an inability of the bone marrow to adequately replace the erythrocytes that are being lost through chronic bleeding. The origin of chronic bleeding is most commonly in the gastrointestinal tract. Abnormal uterine bleeding due to reproductive tract malignancies is another possibility in female patients. Hemorrhagic cystitis due to infection may also be the etiology of chronic bleeding (Ghez, Oksenhendler, Scieux, & Lassoued, 2000). Within the gastrointestinal tract, cytomegalovirus (CMV) is the most common cause, although blood loss from gastrointestinal lymphoma or Kaposi's sarcoma may also contribute.

When blood loss occurs very slowly, patients adapt and are often asymptomatic until the hemoglobin and hematocrit become very low. The patient with AIDS may be weakened by a number of other pathophysiological processes, however, and may become symptomatic earlier than a well person who develops chronic blood loss. Chronic blood loss causes pallor, fatigue, shortness of breath, light-headedness, dizziness, weakness, palpitations, and tinnitus. The pulse pressure (systolic blood pressure minus the diastolic blood pressure) widens due to peripheral vasodilation, and a systolic ejection murmur may be noticeable. These are physiological adaptations ensuring that tissue oxygenation is maintained for as long as possible. The oxyhemoglobin dissociation curve shifts to allow more oxygen to leave the hemoglobin molecule and diffuse into the tissues.

Treatment

Treatment of chronic blood loss is directed at ascertaining the etiology and appropriately treating it to achieve hemostasis, whenever possible. Transfusions may be required to return the hemoglobin and hematocrit to normal values. Increasing dietary iron sources is usually recommended, although iron can irritate the gastric mucosa and should be used carefully in the patient with AIDS-related gastrointestinal diseases.

Acute Blood Loss Anemia

Pathophysiology

The individual with HIV disease is at risk for both acute and chronic blood loss mainly through gastrointestinal bleeding, with upper gastrointestinal bleeding occurring more commonly than lower. Because of underlying thrombocytopenia, the risk of bleeding from any lesions increases dramatically in the person with AIDS (Chalasani & Wilcox, 1999). Upper gastrointestinal bleeding is most often associated with non-HIV-related factors, such as peptic ulcer disease and gastritis, whereas lower gastrointestinal bleeding is more commonly associated with HIV. A number of opportunistic infections can cause erosions and ulcerations of the gastrointestinal mucosa. The most prevalent infection is with CMV, which is the most common viral pathogen in patients with AIDS. CMV infection

Table 8. Major Types of Anemia in HIV Disease

Etiology	Type	Hemoglobin	Hematocrit	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Mean Corpuscular Hemoglobin Concentration	Reticulocytes	Red Blood Cell Distribution Width	Other Findings
Impaired production of erythrocytes	Anemia of chronic illness	↓	↓	→↓	→↓	→↓	→	→↑	Serum iron ↓ Serum transferrin ↓ Serum ferritin ↓ Total iron-binding capacity ↓
	Aplastic anemia	↓	↓	→↑	→	→	↓	→↑	Pancytopenia Platelets < 20,000 cells/mm^3 Retics < 40,000 cells/mm^3
	Iron deficiency anemia	↓	↓	↓	↓	↓	→↑↓	↑	Serum iron ↓ Serum ferritin ↓ Transferrin saturation ↓
	Vitamin B_{12} deficiency anemia	↓	↓	↑	→	→	↓	↑	Anisocytosis present Ovalocytes present Indirect bilirubin ↑ Serum iron ↑ Serum vitamin B_{12} level ↓ Red blood cell vitamin B_{12} level ↓ Schilling's test abnormal (< 2%)
	Folate deficiency anemia	↓	↓	↑	→	→	↓	↑	Anisocytosis present Ovalocytes present Indirect bilirubin ↑ Serum iron ↑ Serum folate ↓ Red blood cell folate ↓
Increased destruction of erythrocytes	Hereditary spherocytosis	↓	↓	→↑	→	→	↑	↑	Indirect bilirubin ↑ Lactic dehydrogenase ↑ Spherocytes present Osmotic fragility test positive Coombs' test negative
	Glucose-6-phosphate dehydrogenase deficiency anemia	↓	↓	→↑	→	→	↑	↑	Hemoglobinemia Hemoglobinuria Indirect bilirubin ↑ Heinz bodies present
	Sickle cell disease	↓	↓	→↑	→	→	↑	↑	Anisocytosis present Target cells present Sickled cells present Indirect bilirubin ↑ Sickledex test positive
Increased loss of erythrocytes	Chronic blood loss	↓	↓	→↑	→	→	↑	→	See text
	Acute blood loss	↓	↓	→↑	→	→	↑	→	See text and Table 7

NOTE: ↓ = decrease, ↑ = increase, → = no change.

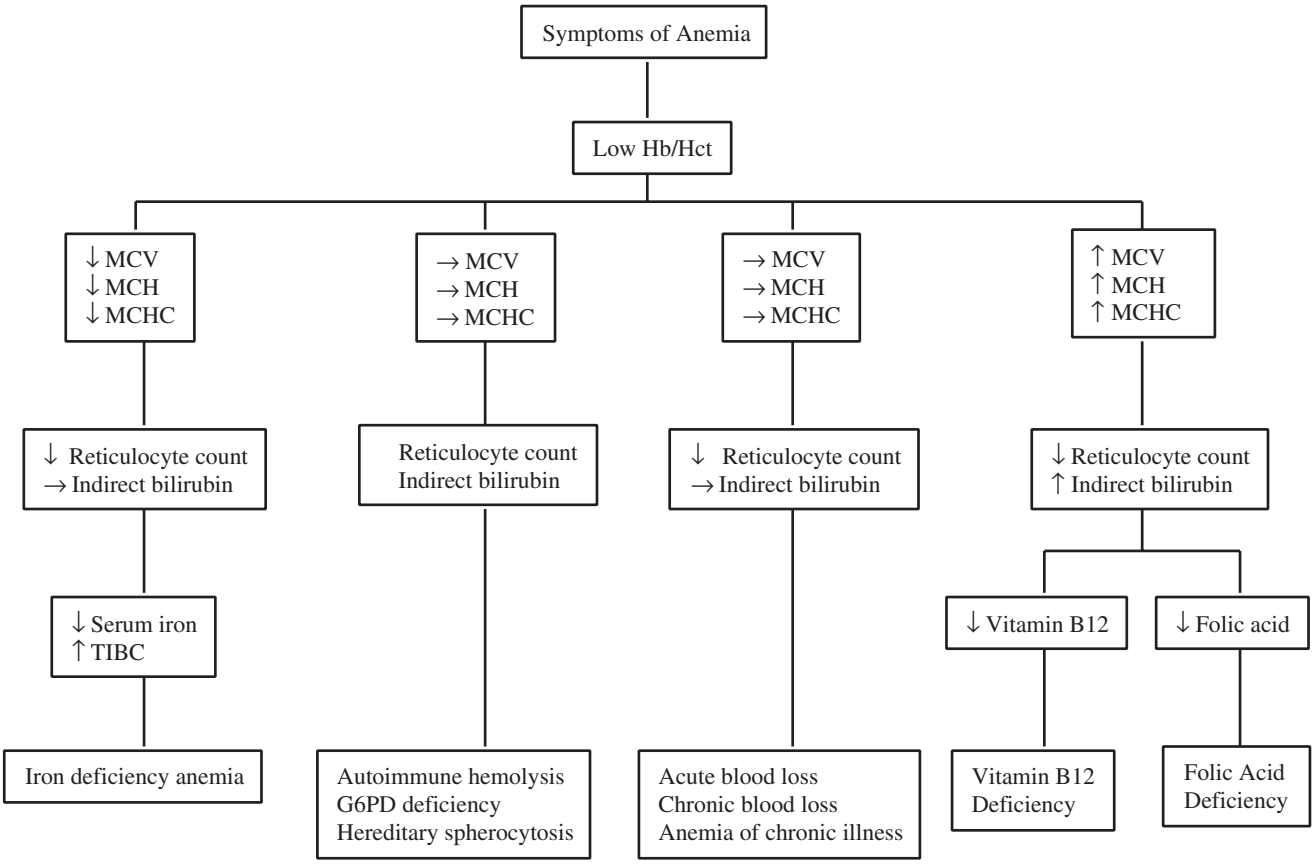

Figure 2. Differential Diagnosis of HIV-Related Anemia (TIBC = total iron-binding capacity)

of the gastrointestinal tract causes inflammatory changes that lead to focal thrombosis, occlusion, ischemia, and mucosal ulceration (Poles & Dieterich, 1996). The friable, damaged mucosa bleeds easily, and ulcerative lesions may even perforate through the muscularis mucosa. There are several sites of CMV infection, but the esophagus and colon are the most common. Esophageal involvement can occasionally present as upper gastrointestinal bleeding, whereas CMV colitis leads to hematochezia, diarrhea, cramping, and abdominal pain. Other causes of colitis in AIDS include *Cryptosporidium*, *Shigella*, *Salmonella*, *Campylobacter*, and *Clostridium difficile*. Anorectal ulcerations and fissures are an additional, fairly common cause of bleeding in patients with AIDS and can be due to CMV, Chlamydia, Treponema, herpes simplex virus, and HIV (Poles & Dieterich, 1996).

Human immunodeficiency virus infection may be associated with bacterial and fungal lesions in other organs, which may ultimately lead to bleeding. Subarachnoid hemorrhage due to cerebral arteriopathy has been reported in AIDS (Mazzoni, Chiriboga, Millar, & Rogers, 2000). Massive bleeding into the peritoneum can also occur.

Acute blood loss occurs during hemorrhage, usually from the gastrointestinal tract or the uterus. In hemophiliacs, bleeding may result from external or internal injury. Hemorrhage into body cavities and joint spaces should be considered. An acute event may also be superimposed on a situation of chronic blood loss. The volume of blood loss over time determines the symptoms, which are related to hypovolemia with consequent sympathetic nervous system activation. Depending on the amount of blood loss and the

physical condition of the patient, hemorrhage may be fatal if shock develops. Signs and symptoms of hemorrhagic shock include tachycardia, tachypnea, pallor, cold, clammy skin, decreased urine formation, dry mucous membranes, and weight loss. The anemia that develops following acute blood loss is normocytic (see Table 7).

Treatment

The debilitated patient with AIDS who suffers hemorrhagic blood loss will require heroic lifesaving efforts and transfusions to recover volume and oxygen-carrying capacity in most cases. The volume of blood, and the loss of cells, will be replaced over time if the patient recovers from the massive bleeding, although it may take 3 to 6 weeks for full recovery.

Differentiation of Anemia

The differentiation of anemia begins with a complete history and physical examination. A complete blood cell count is the next step in the differentiation. Red blood cell size, determined by the mean corpuscular volume, helps to broadly classify anemia for differential diagnosis. Following the complete blood cell count, a peripheral blood smear may provide useful information. Common findings for each type of anemia are presented in Table 8. Figure 2 provides a flow chart to help with decision making.

References

Aboulafia, D. M. (1997). Use of hematopoietic hormones for bone marrow defects in AIDS. *Oncology*, *11*, 1827-1834, 1839, 1843-1844.

American Hospital Formulary Service. (2001). *AHFS drug information 2001*. Bethesda, MD: American Society of Health System Pharmacists.

Arevalo, V. A., Mateo, R. F., Sanchez, P. M., Alonso, C. G., Perez-Arellano, J. L., & Fuertes, M. A. (1997). Iron metabolism in patient infected by human immunodeficiency virus type I. *Sangre*, *42*, 345-349.

Bell, M. S., & Hughes, V. (1997). Hematopoiesis: Morphology of human blood and marrow cells. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 3-39). Philadelphia: F. A. Davis.

Cella, D., Mo, F., & Peterman, A. (1996). Anemia, fatigue, and quality of life in people with cancer and HIV infection. *Blood*, *88*(Suppl. 1), 146a.

Chalasani, N., & Wilcox, C. M. (1999). Gastrointestinal hemorrhage in patients with AIDS. *AIDS Patient Care & STDS*, *13*, 343-346.

Ciesla, B. E. (1997). Morphological changes associated with disease. In D. M. Harmening (Ed.), *Clinical hematology and fundamental hemostasis* (pp. 80-94). Philadelphia: F. A. Davis.

Collier, A. C., Bozzette, S., Coombs, R. W., Causey, D. M., Schoenfeld, D. A., Spector, S. A., et al. (1990). A pilot study of low-dose zidovudine in human immunodeficiency virus infection. *New England Journal of Medicine*, *232*, 1015-1021.

Coyle, T. E. (1997). Hematologic complications of human immunodeficiency virus infection and acquired immunodeficiency syndrome. *Medical Clinics of North America*, *81*, 449-470.

Doweiko, J. P. (1993). Hematologic aspects of HIV infection. *AIDS*, *7*, 753-757.

Eron, J. J., Benoit, S. L., Jemsek, J., MacArthur, R. D., Santana, J., Quinn, J. B., et al. (1995). Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *New England Journal of Medicine*, *333*, 1662-1669.

Fischbach, F. (1996). *A manual of laboratory and diagnostic tests* (5th ed.). Philadelphia: J. B. Lippincott.

Gallicchio, V. S. (1992). Hematopoiesis and review of genetics. In C. A. Lotspeich-Steininger, E. A. Steine-Martin, & J. A. Koepke (Eds.), *Clinical hematology: Principles, procedures, and correlations* (pp. 46-56). Philadelphia: J. B. Lippincott.

Ganser, A. (1988). Abnormalities of hematopoiesis in the acquired immunodeficiency syndrome. *Blut*, *56*(2), 49-53.

Ghez, D., Oksenhendler, E., Scieux, C., & Lassoued, K. (2000). Haemorrhagic cystitis associated with adenovirus in a patient with AIDS treated for a non-Hodgkin's lymphoma. *American Journal of Hematology*, *63*(1), 32-34.

Glassman, A. B. (1997). Anemia: Diagnosis and clinical considerations. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 71-79). Philadelphia: F. A. Davis.

Groopman, J. E. (1997). Impact of transfusion on viral load in human immunodeficiency virus infection. *Seminars in Hematology*, *34*(3, suppl. 2), 27-33.

Hambleton, J. (1996). Hematologic complications of HIV infection. *Oncology*, *10*, 671-680.

Harmening, D. M. (1997). The red blood cell: Structure and function. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 54-70). Philadelphia: F. A. Davis.

Henry, D. H., Beall, G. N., Benson, C. A., Carey, J., Cone, L. A., Eron, L. J., et al. (1992). Recombinant human erythropoietin in the treatment of anemia associated with human immunodeficiency virus (HIV) infection and zidovudine therapy. *Annals of Internal Medicine*, *117*, 739-748.

Kaplan, J., Sarnaik, S., Gitlin, J., & Lusher, J. (1984). Diminished helper/suppressor lymphocyte ratios and natural killer activity in recipients of repeated blood transfusions. *Blood*, *64*, 308-310.

Leclair, S. J. (1997). Iron metabolism and hypochromic anemias. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 97-115). Philadelphia: F. A. Davis.

Linker, C. A. (2001). Blood. In L. M. Tierney, Jr., S. J. McPhee, & M. A. Papadakis (Eds.), *Current medical diagnosis and treatment* (40th ed., pp. 505-557). New York: Lange Medical Books/McGraw-Hill.

Ludvigsen, F. B. (1992). Hemoglobin synthesis and function. In C. A. Lotspeich-Steininger, E. A. Stiene-Martin, & J. A. Koepke (Eds.), *Clinical hematology: Principles, procedures, and correlations* (pp. 72-87). Philadelphia: J. B. Lippincott.

Margolick, J. B., Volkman, D. J., Folks, T. M., & Fauci, A. S. (1987). Amplification of HTLV-III/LAV infection by antigen-induced activation of T cells and direct suppression by virus of lymphocyte blastogenic responses. *Journal of Immunology*, *138*, 1719-1723.

Mazzoni, P., Chiriboga, C. A., Millar, W. S., & Rogers, A. (2000). Intracerebral aneurysms in human immunodeficiency virus infection: Case report and literature review. *Pediatric Neurology*, *23*, 252-255.

Means, R. T., Jr. (1997). Cytokines and anaemia in human immunodeficiency virus infection. *Cytokines, Cellular and Molecular Therapy*, *3*, 179-186.

Mitsuyasu, R. T. (1999). Hematologic disease. In R. Dolin, H. Masur, & M. Saag (Eds.), *AIDS therapy* (pp. 666-679). New York: Churchill Livingstone.

Mocroft, A., Kirk, O., Barton, S. E., Dietrich, M., Proenca, R., Colebunders, R., et al. (1999). Anaemia is an independent predictive marker for clinical prognosis in HIV-infected patients from across Europe. *AIDS*, *13*, 950.

Moore, R. D., Keruly, J. C., & Chaisson, R. E. (1998). Anemia and survival in HIV infection. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology*, *19*(1), 29-33.

Mudido, P. M., Georges, D., Dorazio, D., Yen-Lieberman, B., Bae, S., O'Brien, W. A., et al. (1996). Human immunodeficiency virus type I activation after blood transfusion. *Transfusion*, *36*, 860-865.

National Cancer Institute. (1977). *Common toxicity criteria: National Cancer Institute investigator's handbook*. Washington, DC: National Institutes of Health.

Northfelt, D. W. (1999). Hematologic aspects of HIV infection. In P. T. Cohen, M. A. Sande, & P. A. Volberding (Eds.), *The AIDS knowledge base* (pp. 505-514). Philadelphia: Williams & Wilkins.

Poles, M., & Dieterich, D. (1996). Diagnosis and management of gastrointestinal CMV disease in patients with AIDS. *Infections in Medicine*, *13*, 952-971.

Rabeneck, L., Hartigan, P. M., Huang, I. W., Soucheck, J., & Wray, N. P. (1997). Predicting outcomes in HIV-infected veterans: II. Survival after AIDS. *Journal of Clinical Pathology*, *50*, 1241-1248.

Richman, D. D., Fischl, M. A., Grieco, M. H., Gottlieb, M. S., Voldberding, P. A., Laskin, O. L., et al. (1987). The toxicity of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex: A double blind, placebo-controlled trial. *New England Journal of Medicine*, *317*, 192-197.

Sacher, R. A., & McPherson, R. A. (2000). Hematologic methods. In R. A. Sacher & R. A. McPherson (Eds.), *Widmann's clinical interpretation of laboratory tests* (pp. 31-101). Philadelphia: F. A. Davis.

Saif, M. W. (2001). HIV-associated autoiummune hemolytic anemia: An update. *AIDS Patient Care and STDs*, *15*, 217-224.

Scadden, D. T., Zon, L. I., & Groopman, J. E. (1989). Pathophysiology and management of HIV-associated hematologic disorders. *Blood*, *74*, 1455-1463.

Schot, J.D.L., & Schuurman, R.K.B. (1986). Blood transfusion suppresses cutaneous cell-mediated immunity. *Clinical Experiments in Immunology*, *65*, 336-344.

Sim, S. J., McCarron, S., & Glassman, A. B. (1997). Introduction to hemolytic anemia: Intracorpuscular defects: II. Hereditary enzyme deficiencies. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 164-172). Philadelphia: F. A. Davis.

Sipsas, N. V., Kokori, S. I., Ionnidis, J. P., Kyriaki, D., Tzioufas, A. G., & Kordossis, T. (1999). Circulating autoantibodies to erythropoietin are associated with human immunodeficiency virus type I–related anemia. *Journal of Infectious Diseases*, *180*, 2044-2047.

Spino, C., Kahn, J. O., Dolin, R., & Phair, J. P. (1997). Predictors of survival in HIV-infected persons with 50 or fewer CD4 cells/mm^3. *Journal of Acquired Immune Deficiency Syndromes*, *15*, 346-355.

Spivak, J. L., Barnes, D. C., Fuchs, E., & Quinn, T. C. (1989). Serum immunoreactive erythropoietin in HIV-infected patients. *Journal of the American Medical Association*, *261*, 3104-3107.

Sullivan, P. S., Hanson, D. L., Chu, S. Y., Jones, J. L., Ward, J. W., & Adult/Adolescent Spectrum of Disease Group. (1998). Epidemiology of anemia in human immunodeficiency virus (HIV)–infected persons: Results from the multistate adult and adolescent spectrum of HIV disease surveillance project. *Blood*, *91*, 301-308.

Taghizadeh, M. (1997). Megaloblastic anemias. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 116-134). Philadelphia: F. A. Davis.

Tartter, P. I., Heimann, T. M., & Aufses, A. H. (1986). Blood transfusions, skin test reactivity, lymphocytes in inflammatory bowel disease. *American Journal of Surgery*, *151*, 358-361.

Teferri, A. (2001). A practical approach to the diagnosis of anemia. In A. Teferri (Ed.), *Primary hematology* (pp. 3-20). Totowa, NJ: Humana Press.

Telen, M. J., Roberts, K. B., & Bartlett, J. A. (1990). HIV-associated autoimmune hemolytic anemia: Report of a case and review of the literature. *Journal of Acquired Immune Deficiency Syndromes*, *3*, 933-937.

Volberding, P. A., Lagakos, S. W., Koeh, M. A., Koch, M. A., Pettinelli, C., Myers, M. W., et al. (1990). Zidovudine in asymptomatic human immunodeficiency virus infection: A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *New England Journal of Medicine*, *323*, 941-949.

Walker, R. E., Parker, R. I., Kovacs, J. A., Masur, H., Lane, H. C., Carleton, S., et al. (1988). Anemia and erythropoiesis in patients with acquired immunodeficiency syndrome and Kaposi sarcoma treated with zidovudine. *Annals of Internal Medicine*, *108*, 372-376.

Waymack, J. P., Balakrishnan, K., McNeal, N., Gonce, S., Miskell, P., Warden, G. D., et al. (1986). Effect of blood transfusions on macrophage-lymphocyte interaction in an animal model. *Annals of Surgery*, *204*, 681-685.

Zail, S., & Coetzer, T. L. (1997). Introduction to hemolytic anemias: Intracorpuscular defects. In D. M. Harmening (Ed.), *Clinical hematology and fundamentals of hemostasis* (pp. 146-163). Philadelphia: F. A. Davis.

Zon, L. I., Arkin, C., & Groopman, J. E. (1987). Haematologic manifestations of the human immunodeficiency virus (HIV). *British Journal of Haematology*, *66*, 251-256.

Zon, L. I., & Groopman, J. E. (1988). Hematologic manifestations of the human immune deficiency virus (HIV). *Seminars in Hematology*, *25*, 208-218.

Questions

Select the best answer for the following questions:

1. The most common type of anemia in HIV disease is
   A. Iron deficiency anemia
   B. Anemia of chronic illness
   C. Folic acid deficiency anemia
   D. Vitamin B_{12} deficiency anemia
   E. Glucose-6-phosphate dehydrogenase deficiency hemolytic anemia

2. A laboratory test that indicates the percentage of blood cells in a given volume of whole blood is the
   A. Hemoglobin
   B. Hematocrit
   C. Mean corpuscular hemoglobin concentration
   D. Mean corpuscular volume

3. A mean corpuscular volume that is lower than normal indicates that the red blood cells are
   A. Microcytic (too small)
   B. Macrocytic (too large)
   C. Normocytic (normal in size)
   D. None of the above

4. Schilling's test is useful in the differential diagnosis of vitamin B_{12} deficiency. If an individual excretes _____ of the oral dose of radioactively labeled vitamin B_{12}, vitamin B_{12} deficiency is not likely.
   A. Greater than 7%
   B. Less than 3%
   C. Less than 5%
   D. Less than 7%

5. Trimethoprim, methotrexate, and trimetrexate antagonize the utilization of _____, whereas cycloserine decreases its absorption from the gastrointestinal system.
   A. Vitamin B_{12}
   B. Erythropoietin
   C. Folic acid
   D. Iron

6. Mary is a 30-year-old African American woman who is HIV-positive but asymptomatic. Her CD4+ cell count is greater than 500, and her HIV-RNA viral load is less than 50 copies/mm^3. Her chief complaint is "feeling tired all the time and excessive menstrual bleeding." Her hematological parameters indicate that she has iron deficiency anemia. Which of the following laboratory values would you not expect?
   A. Decreased mean corpuscular volume
   B. Decreased mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration
   C. Decreased total iron binding capacity
   D. Increased serum ferritin

7. Intramuscular administration of iron dextran is associated with increased risk of anaphylaxis.
   A. True
   B. False

8. The initial dose of epoietin alfa is 100 to 300 units/kg subcutaneously or intravenously three times per week. The maintenance dose is titrated to keep the hematocrit between
   A. 12% and 16%
   B. 36% and 40%
   C. 42% and 46%
   D. None of the above

9. There is strong evidence that _____ deficiency leads to neural tube deficits in the developing fetus.
   A. Folic acid deficiency
   B. Iron deficiency
   C. Vitamin B_{12} deficiency
   D. All the above

10. Vegetables such as asparagus, black eye peas, lettuce, spinach, collards, and broccoli are rich in
    A. Iron
    B. Vitamin B_{12}
    C. Erythropoietin
    D. Folic acid

11. Humans obtain vitamin B_{12} from eating vegetables.
    A. True
    B. False
12. HIV-infected men are more likely to have anemia than women.
    A. True
    B. False
13. A low red blood cell count, hemoglobin, a normal mean corpuscular volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin in association with a decreased total iron-binding capacity, transferrin saturation, and an increased serum ferritin suggests
    A. Anemia of chronic illness
    B. Iron deficiency anemia
    C. Folic acid deficiency anemia
    D. Hereditary spherocytosis
14. An elevated indirect bilirubin indicates
    A. Hepatocellular damage
    B. Iron deficiency anemia
    C. Hemolytic anemia
    D. All of the above
    E. None of the above
15. Which of the following antiretrovirals is most strongly associated with anemia in HIV disease?
    A. Didanosine
    B. Zidovudine
    C. Saquinavir
    D. None of the above

ANSWER/EVALUATION FORM

Continuing Education Credit (1.5 contact hours)
Answer Form: CE 600
Differentiation and Treatment of Anemia in HIV Disease

(Please Print Clearly or Type)

Name: _____

Address: _____

City: _____ State: _____ Zip Code: _____

Social Security # ☐☐☐–☐☐–☐☐☐☐

ANAC Member # ☐☐☐☐☐☐☐☐☐

Method of Payment ($10 for ANAC members/$15 nonmembers):

☐ Credit Card (Visa or MasterCard ONLY)

Card Number: _____ Expiration Date: ____/____

Name on Card: _____Signature: _____

☐ Check/Money Order

Payable to: Association of Nurses in AIDS Care

ANSWER FORM

1.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	[E] ☐
2.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
3.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
4.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
5.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
6.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
7.	[A] ☐	[B] ☐			
8.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
9.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
10.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
11.	[A] ☐	[B] ☐			
12.	[A] ☐	[B] ☐			
13.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	
14.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	[E] ☐
15.	[A] ☐	[B] ☐	[C] ☐	[D] ☐	

EVALUATION FORM

To evaluate this continuing education offering, please respond to each question below by checking "Yes" or "No."

	Check: Yes	No
1. Can you differentiate between the three major types of anemia?	☐	☐
2. Can you name the most common type of anemia in HIV disease?	☐	☐
3. Can you explain what a positive score on the Coombs' test indicates?	☐	☐
4. Do you understand the differences in treatment depending on the type of HIV-related anemia?	☐	☐
5. Can you describe the various signs and symptoms of anemia?	☐	☐
6. Can you identify what an increased loss of erythrocytes may indicate?	☐	☐

7. How much time did it take to complete this offering? _____

8. Additional comments: _____

_____

_____