Anemia

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Plan of lecture

- **Anemia**: etiology and pathogenesis;
- **Anemia**: diagnosis;
- **Anemia**: treatment.

Anemia [1M]

Basis of anemia data was Medscape (Author : **Joseph E Maakaron, MD** Research Fellow, Department of Internal Medicine, Division of Hematology/Oncology, American University of Beirut Medical Center, Lebanon; Coauthor(s): **Ali T Taher, MD, PhD, FRCP** Professor of Medicine, Associate Chair of Research, Department of Internal Medicine, Division of Hematology/Oncology, Director of Research, NK Basile Cancer Center, American University of Beirut Medical Center, Lebanon; **Marcel E Conrad, MD** Distinguished Professor of Medicine (Retired), University of South Alabama College of Medicine; Chief Editor: **Emmanuel C Besa, MD** Professor Emeritus, Department of Medicine, Division of Hematologic Malignancies and Hematopoietic Stem Cell Transplantation, Kimmel Cancer Center, Jefferson Medical College of Thomas Jefferson University ; - **Medscape: https://emedicine.medscape.com/article/198475-overview [1M])**

Practice Essentials

Anemia is strictly defined as a decrease in red blood cell (RBC) mass. The function of the RBC is to deliver oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs. This is accomplished by using hemoglobin (Hb), a tetramer protein composed of heme and globin. In anemia, a decrease in the number of RBCs transporting oxygen and carbon dioxide impairs the body's ability for gas exchange. [1] The decrease may result from blood loss, increased destruction of RBCs (hemolysis), or decreased production of RBCs.

Anemia, like a fever, is a sign that requires investigation to determine the underlying etiology. Often, practicing physicians overlook mild anemia. This is similar to failing to seek the etiology of a fever. The purpose of this article is to provide a method of determining the etiology of an anemia.

Anemia [1M]

Methods for measuring RBC mass are time consuming and expensive and usually require transfusion of radiolabeled erythrocytes. Thus, in practice, anemia is usually discovered and quantified by measurement of the RBC count, Hb concentration, and hematocrit (Hct). These values should be interpreted cautiously, because they are concentrations affected by changes in plasma volume. For example, dehydration elevates these values, and increased plasma volume in pregnancy can diminish them without affecting the RBC mass.

Complications

The most serious complications of severe anemia arise from tissue hypoxia. Shock, hypotension, or coronary and pulmonary insufficiency can occur.

Anemia [1M]

This is more common in older individuals with underlying pulmonary and cardiovascular disease.

Pathophysiology

Erythrocyte life cycle

Erythroid precursors develop in bone marrow at rates usually determined by the requirement for sufficient circulating Hb to oxygenate tissues adequately. Erythroid precursors differentiate sequentially from stem cells to progenitor cells to erythroblasts to normoblasts in a process requiring growth factors and cytokines.[2] This process of differentiation requires several days. Normally, erythroid precursors are released into circulation as reticulocytes.

Reticulocytes are so called because of the reticular meshwork of rRNA they harbor. They remain in the circulation for approximately 1 day before they mature into erythrocytes, after the digestion of RNA by reticuloendothelial cells. The mature erythrocyte remains in circulation for about 120 days before being engulfed and destroyed by phagocytic cells of the reticuloendothelial system.

Anemia [1M]

Erythrocytes are highly deformable and increase their diameter from 7 μm to 13 μm when they traverse capillaries with a 3-μm diameter. They possess a negative charge on their surface, which may serve to discourage phagocytosis. Because erythrocytes have no nucleus, they lack a Krebs cycle and rely on glycolysis via the Embden-Meyerhof and pentose pathways for energy. Many enzymes required by the aerobic and anaerobic glycolytic pathways decrease within the cell as it ages.

Anemia [1M]

In addition, the aging cell has a decrease in potassium concentration and an increase in sodium concentration. These factors contribute to the demise of the erythrocyte at the end of its 120-day lifespan.

Response to anemia

- The physiologic response to anemia varies according to acuity and the type of insult. Gradual onset may allow for compensatory mechanisms to take place. With anemia due to acute blood loss, a reduction in oxygen-carrying capacity occurs along with a decrease in intravascular volume, with resultant hypoxia and hypovolemia. Hypovolemia leads to hypotension, which is detected by stretch receptors in the carotid bulb, aortic arch, heart, and lungs. These receptors transmit impulses along afferent fibers of the vagus and glossopharyngeal nerves to the medulla oblongata, cerebral cortex, and pituitary gland.

- In the medulla, sympathetic outflow is enhanced, while parasympathetic activity is diminished.

Anemia [1M]

Increased sympathetic outflow leads to norepinephrine release from sympathetic nerve endings and discharge of epinephrine and norepinephrine from the adrenal medulla. Sympathetic connection to the hypothalamic nuclei increases antidiuretic hormone (ADH) secretion from the pituitary gland. [3] ADH increases free water reabsorption in the distal collecting tubules. In response to decreased renal perfusion, juxtaglomerular cells in the afferent arterioles release renin into the renal circulation, leading to increased angiotensin I, which is converted by angiotensin-converting enzyme (ACE) to angiotensin II.

Angiotensin II has a potent pressor effect on arteriolar smooth muscle. Angiotensin II also stimulates the zona glomerulosa of the adrenal cortex to produce aldosterone. Aldosterone increases sodium reabsorption from the proximal tubules of the kidney, thus increasing intravascular volume. The primary effect of the sympathetic nervous system is to maintain perfusion to the tissues by increasing systemic vascular resistance (SVR). The augmented venous tone increases the preload and, hence, the end-diastolic volume, which increases stroke volume.

Anemia [1M]

Therefore, stroke volume, heart rate, and SVR all are maximized by the sympathetic nervous system. Oxygen delivery is enhanced by the increased blood flow.

In states of hypovolemic hypoxia, the increased venous tone due to sympathetic discharge is thought to dominate the vasodilator effects of hypoxia. Counterregulatory hormones (eg, glucagon, epinephrine, cortisol) are thought to shift intracellular water to the intravascular space, perhaps because of the resultant hyperglycemia. This contribution to the intravascular volume has not been clearly elucidated.

Etiology

- Basically, only three causes of anemia exist: blood loss, increased destruction of RBCs (hemolysis), and decreased production of RBCs. Each of these causes includes a number of disorders that require specific and appropriate therapy. Genetic etiologies include the following:
- Hemoglobinopathies
- Starvation and generalized malnutrition

Anemia [1M]

- Thalassemias
- Enzyme abnormalities of the glycolytic pathways
- Defects of the RBC cytoskeleton
- Congenital dyserythropoietic anemia
- Rh null disease
- Hereditary xerocytosis
- Abetalipoproteinemia
- Fanconi anemia

Nutritional etiologies include the following:

- Iron deficiency
- Vitamin B-12 deficiency
- Folate deficiency

Anemia [1M]

Physical etiologies include the following:

- Trauma
- Burns
- Frostbite
- Prosthetic valves and surfaces

Chronic disease and malignant etiologies include the following:

- Renal disease
- Hepatic disease
- Chronic infections
- Neoplasia
- Collagen vascular diseases

Infectious etiologies include the following:

- Viral - Hepatitis, infectious mononucleosis, cytomegalovirus
- Bacterial - Clostridia, gram-negative sepsis
- Protozoal - Malaria, leishmaniasis, toxoplasmosis

Anemia [1M]

Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome may be a cause of anemia. Hereditary spherocytosis either may present as a severe hemolytic anemia or may be asymptomatic with compensated hemolysis. Similarly, glucose-6-phosphate dehydrogenase (G-6-PD) deficiency may manifest as chronic hemolytic anemia or exist without anemia until the patient receives an oxidant medication. Immunologic etiologies for anemia may include antibody-mediated abnormalities. In the emergency department (ED), acute hemorrhage is by far the most common etiology for anemia.

Drugs or chemicals commonly cause the aplastic and hypoplastic group of disorders. Certain types of these causative agents are dose related and others are idiosyncratic. Any human exposed to a sufficient dose of inorganic arsenic, benzene, radiation, or the usual chemotherapeutic agents used for treatment of neoplastic diseases develops bone marrow depression with pancytopenia.

Anemia [1M]

Conversely, among the idiosyncratic agents, only an occasional human exposed to these drugs has an untoward reaction resulting in suppression of one or more of the formed elements of bone marrow (1:100 to 1:millions). With certain types of these drugs, pancytopenia is more common, whereas with others, suppression of one cell line is usually observed. Thus, chloramphenicol may produce pancytopenia, whereas granulocytopenia is more frequently observed with toxicity to sulfonamides or antithyroid drugs.

Current evidence suggests that susceptibility to idiosyncratic reactions involves certain genetic polymorphisms involving cellular detoxifying enzymes.

Anemia [1M]

As a result, exogenous toxins that would normally be converted to nontoxic compounds are instead metabolized into reactive compounds that modify cellular proteins, which can be recognized by the immune system and trigger autoimmunity. [4]

The idiosyncratic causes of bone marrow suppression include multiple drugs in each of the categories that can be prefixed with anti- (eg, antibiotics, antimicrobials, anticonvulsants, antihistamines). The other idiosyncratic causes of known etiology are viral hepatitis and paroxysmal nocturnal hemoglobinuria. In approximately one half of patients presenting with aplastic anemia, a definite etiology cannot be established, and the anemia must be regarded as idiopathic.

Rare causes of anemia due to a hypoplastic bone marrow include familial disorders and the acquired pure red cell aplasias. The latter are characterized by a virtual absence of erythroid precursors in the bone marrow, with normal numbers of granulocytic precursors and megakaryocytes. Rare causes of diminished erythrocyte production with hyperplastic bone marrow include hereditary orotic aminoaciduria and erythremic myelosis.

A study of 2688 patients undergoing cardiac surgery in the United Kingdom from 2008-2009 found that 1463 (54.4%) met the World Health Organization definition for anemia. This prevalence was much greater than previously reported, although the reason for this association is unclear. [5]

Anemia [1M]

History

Carefully obtain a history and perform a physical examination in every patient with anemia, because the findings usually provide important clues to the underlying disorder. From the standpoint of the investigation of the anemia, asking questions in addition to those conventionally explored during a routine examination is important. Areas of inquiry found valuable are briefly described below.

Often, the duration of anemia can be established by obtaining a history of previous blood studies and, if necessary, by acquiring those records. Similarly, a history of rejection as a blood donor or prior prescription of hematinics provides clues that anemia was detected previously.

Anemia [1M]

Obtain a careful family history not only for anemia but also for jaundice, cholelithiasis, splenectomy, bleeding disorders, and abnormal hemoglobins. Carefully document the patient's occupation, hobbies, prior medical treatment, drugs (including over-the-counter medications and vitamins), and household exposures to potentially noxious agents. Patients are unlikely to volunteer exposures to tranquilizers, insecticides, paints, solvents, and hair dyes unless specifically queried.

In searching for blood loss, carefully document pregnancies, abortions, and menstrual loss. Estimates of menstrual losses are notoriously inaccurate if only routine inquiry is made.

Often, patients do not appreciate the significance of tarry stools. Changes in bowel habits can be useful in uncovering neoplasms of the colon. Hemorrhoidal blood loss is difficult to quantify, and it may be overlooked or overestimated from one patient to another. Obviously, seek a careful history of gastrointestinal complaints that may suggest gastritis, peptic ulcers, hiatal hernias, or diverticula.

Anemia [1M]

Abnormal urine color can occur in renal and hepatic disease and in hemolytic anemia.

A thorough dietary history is important in a patient who is anemic. This history must include foods that the patient eats and those that he/she avoids, as well as an estimate of their quantity. A meal-by-meal description is necessary to obtain appropriate estimates. Even then, patients frequently attempt to deceive the physician because of embarrassment regarding dietary idiosyncrasies or financial restrictions. In these circumstances, having a close and concerned family member participate in the dietary history can often be helpful, because this person is usually more objective than the patient.

Specifically question patients regarding consumption of either clay or laundry starch.

Anemia [1M]

This history will not be provided spontaneously. These substances render iron less absorbable. Changes in body weight are important with regard to dietary intake and can suggest the presence of malabsorption or an underlying wasting disease of infectious, metabolic, or neoplastic origin.

Nutritional deficiencies may be associated with unusual symptoms that can be elicited by a history. Patients with iron deficiencies frequently chew or suck ice (pagophagia). Occasionally, they complain of dysphagia, brittle fingernails, relative impotence, fatigue, and cramps in the calves on climbing stairs that are out of proportion to their anemia.

In vitamin B-12 deficiency, early graying of the hair, a burning sensation in the tongue, and a loss of proprioception are common. Suspect a loss of proprioception if the patient stumbles in the dark or must look in order to put on pants in the morning. Paresthesia or unusual sensations frequently described as pain also occur in pernicious anemia.

Anemia [1M]

Patients with folate deficiency may have a sore tongue, cheilosis, and symptoms associated with steatorrhea. Color, bulk, frequency, and odor of stools and whether the feces float or sink can be helpful in detecting malabsorption. More sensitive questions to detect steatorrhea include whether the toilet needs to be flushed more than once to rid it of stool and whether an oily substance is floating on the water surface after the first flush.

Obtain a history of fever or identify the presence of fever, because infections, neoplasms, and collagen vascular disease can cause anemia. Similarly, the occurrence of purpura, ecchymoses, and petechiae suggest the occurrence of either thrombocytopenia or other bleeding disorders; this may be an indication either that more than 1 bone marrow lineage is involved or that coagulopathy is a cause of the anemia because of bleeding.

Cold intolerance can be an important symptom of hypothyroidism or lupus erythematosus, paroxysmal cold hemoglobinuria, and certain macroglobulinemias.

Anemia [1M]

The relation of dark urine to either physical activity or time of day can be important in march hemoglobinuria and paroxysmal nocturnal hemoglobinuria.

Explore the presence or the absence of symptoms suggesting an underlying disease, such as cardiac, hepatic, and renal disease; chronic infection; endocrinopathy; or malignancy. A geographic history can also be important in establishing an etiology.

Physical Examination

Too often, the physician rushes into the physical examination without looking at the patient for an unusual habitus or appearance of underdevelopment, malnutrition, or chronic illness. These findings can be important clues to the underlying etiology of disease and provide information related to the duration of illness. The skin and mucous membranes are often bypassed, so that pallor, abnormal pigmentation, icterus, spider nevi, petechiae, purpura, angiomas, ulcerations, palmar erythema, coarseness of hair, puffiness of the face, thinning of the lateral aspects of the eyebrows, nail defects, and a usually prominent venous pattern on the abdominal wall are missed in the rush to examine the heart and the lungs.

Anemia [1M]

Examine optic fundi carefully but not at the expense of the conjunctivae and the sclerae, which can show pallor, icterus, splinter hemorrhages, petechiae, comma signs in the conjunctival vessels, or telangiectasia that can be helpful in planning additional studies.

Perform systematic examination for palpable enlargement of lymph nodes for evidence of infection or neoplasia. Bilateral edema is useful in disclosing underlying cardiac, renal, or hepatic disease, whereas unilateral edema may portend lymphatic obstruction due to a malignancy that cannot be observed or palpated.

Carefully search for hepatomegaly and splenomegaly. Their presence or absence is important, as are the size, the tenderness, the firmness, and the presence or the absence of nodules. In patients with chronic disorders, these organs are firm, nontender, and nonnodular. In patients with carcinoma, they may be hard and nodular. The patient with an acute infection usually has a palpably softer and more tender organ.

Anemia [1M]

A rectal and pelvic examination cannot be neglected, because tumor or infection of these organs can be the cause of anemia.

The neurologic examination should include tests of position sense and vibratory sense, examination of the cranial nerves, and testing for tendon reflexes. The heart should not be ignored, because enlargement may provide evidence of the duration and the severity of the anemia, and murmurs may be the first evidence of a bacterial endocarditis that could explain the etiology of the anemia.

Anemia [1M]

Diagnostic Considerations

Many symptoms associated with anemia are not caused by diminished RBC mass. For example, ice chewing, calf cramps, and diminished capability to perform muscular work occur in iron deficiency anemia with a hemoglobin (Hb) level of 10-11 g/dL because of depletion of iron-containing proteins other than Hb. [12] Pernicious anemia is often detected incidentally in patients who are asymptomatic despite an Hb level as low as 6 g/dL.

Tolerance of anemia is proportional to the anemia's rate of development. Symptoms and mortality associated with rapidly developing anemia are more profound than in slowly developing anemia.

Anemia [1M]

Differential Diagnoses

- Alpha Thalassemia
- Aplastic Anemia
- Beta Thalassemia
- Hemolytic Anemia
- Iron Deficiency Anemia
- Low LDL Cholesterol (Hypobetalipoproteinemia)
- Megaloblastic Anemia
- Myelophthisic Anemia
- Pernicious Anemia
- Sickle Cell Anemia
- Spur Cell Anemia

Anemia [1M]

Approach Considerations

The first step in the diagnosis of anemia is detection with reliable, accurate tests so that important clues to underlying disease are not overlooked and patients are not subjected to unnecessary tests for and treatment of nonexistent anemia. Detection of anemia involves the adoption of arbitrary criteria.

The World Health Organization (WHO) criterion for anemia in adults is a hemoglobin (Hb) value of less than 12.5 g/dL. Children aged 6 months to 6 years are considered anemic at Hb levels less than 11 g/dL, and children aged 6-14 years are considered anemic when Hb levels are less than 12 g/dL. The disadvantage of such arbitrary criteria is that a few healthy individuals fall below the reference range, and some people with an underlying disorder fall within the reference range for Hb concentration.

Anemia [1M]

Usually, thresholds in the United States are slightly higher. Anemia is suggested in males with Hb levels less than 13.5 g/dL and in females with Hb levels less than 12.5 g/dL. Higher values are anticipated in individuals living in altitudes significantly above sea level. Conditions with an increase in plasma volume, such as during the last trimester of pregnancy, are associated with lower values without an existent anemia, because the red cell mass is normal.

Anemia [1M]

Investigation for Pathogenesis

Once the existence of anemia is established, investigate the pathogenesis. If an adequate history has been taken and a physical examination has been performed, the etiology may be obvious, and confirmatory studies and appropriate therapy can be undertaken with a minimum of investigation. If this is not the case, initiate a definite plan of investigation, considering the cost to the patient along with a determination of the etiology of the abnormality.

Often, the etiology of a patient's anemia can be determined if the red blood cells (RBCs) are altered in either size or shape or if they contain certain inclusion bodies. For example, *Plasmodium falciparum* malaria is suggested by the presence of more than one ring form in an RBC, and the infection produces pan-hemolysis of RBCs of all ages.

A rational approach to determining etiology is to begin by examining the peripheral smear and laboratory values obtained on the blood count. If the anemia is microcytic (mean corpuscular volume [MCV] < 84 fL) or macrocytic (MCV >96 fL) or if certain abnormal RBCs or white blood cells (WBCs) are observed in the blood smear, the investigative approach can be limited.

Anemia [1M]

Presently, RBC cellular indices are computer calculated and automatically placed on laboratory reports. The formulae for calculating these values follow (reference ranges are in parentheses). RBC is per million cells.

- MCV = Hct × 10/RBC (84-96 fL)
- Mean corpuscular Hb (MCH) = Hb × 10/RBC (26-36 pg)
- Mean corpuscular Hb concentration (MCHC) = Hb × 10/Hct (32-36%)

A rapid method of determining whether cellular indices are normocytic and normochromic is to multiply the RBC and Hb by 3. The RBC multiplied by 3 should equal the Hb, and the Hb multiplied by 3 should equal the Hct. Deviation from the calculated values suggests microcytosis, macrocytosis, or hypochromia versus the presence of spherocytes (MCHC >36).

In microcytic hypochromic anemia, seek a source of bleeding. The appropriate laboratory tests are serum iron level and TIBC and either serum ferritin level or stain of bone marrow specimen for iron. If the serum iron level is decreased and the TIBC is increased, a diagnosis of iron deficiency can be made, therapy can be initiated, and a search for the cause of the iron deficiency can be started

Anemia [1M]

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Patients with iron deficiency and those with undiagnosed non–transfusion-dependent thalassemia may present similarly. Although the two conditions can be differentiated by hemoglobin typing and iron studies, Piriyakhuntorn et al propose that red cell distribution width values (RDW) can provide a rapid and accurate distinction. They report that an RDW cut-off value of 21.0% (with lower values indicating iron deficiency and higher values indicating non–transfusion-dependent thalassemia) provided a sensitivity of 84.5%, specificity of 70.6%, positive predictive value of 83.1%, and negative predictive value of 72.7%. [13]

With macrocytic anemia, a reasonable approach is to determine whether the bone marrow aspirate is megaloblastic. If so, attempt to incriminate either vitamin B-12 or folic acid deficiency with appropriate laboratory studies. Similar to the establishment of a diagnosis of iron deficiency anemia, a diagnosis of vitamin B-12 or folic acid deficiency does not stop with an abnormal laboratory value for one of these vitamins. Prompt treatment can be instituted, but a continued search for an underlying cause of the vitamin deficiency is indicated.

When a normocytic normochromic anemia is encountered, classify the anemia into three possible etiologies (ie, blood loss, hemolysis, decreased production). In most anemias, one of these causes is the dominant factor. However, in certain anemias, more than a single cause may play an important role.

Anemia [1M]

For example, pernicious anemia is predominantly due to decreased production of erythrocytes, but hemolysis adds significantly to the severity of anemia.

Evaluation for Blood Loss

Obviously, significant hemorrhage produces anemia. Immediately after blood loss, the Hct cannot be used as a reliable method to determine the quantity of lost blood, because the patient loses plasma as well as RBCs. After acute hemorrhage, the Hct falls for 24-48 hours until the plasma volume is replaced. At that time, anemia is normochromic and normocytic with normal cellular indices, because the cells in the peripheral blood have been produced prior to bleeding.

If the patient had adequate iron stores, accelerated production of RBCs occurs, so that 1 week after bleeding, a larger-than-normal number of young RBCs and reticulocytes are circulating in the peripheral blood. Because reticulocytes and young RBCs have a larger volume (MCV of approximately 120), macrocytes may be observed in the peripheral smear, and a slight increase in the MCV occurs.

Anemia [1M]

If hemorrhage was sufficient to deplete iron stores (1-2 L of blood, 500-1000 mg of iron), newly formed erythrocytes are microcytic and hypochromic and gradually replace normal erythrocytes in the circulation that were produced prior to the induction of iron deficiency. Because RBCs normally survive for 120 days in circulation, maximal changes in the MCV and MCHC are not observed until that time. Iron deficiency and the depletion of iron stores can be detected several weeks after bleeding by measurements of the serum iron level and the TIBC (the patient has low serum iron levels and an elevated TIBC) and/or special stains of bone marrow specimens showing an absence of storage iron. A low serum ferritin level provides confirmation of the diagnosis of iron deficiency anemia. The presence of microcytosis and hypochromia is helpful but not diagnostic. The patient notices hemorrhage from most body organs. Epistaxis, hemoptysis, or hematuria of sufficient degree to cause anemia is usually reported to the physician long before iron deficiency ensues. However, bleeding from either the uterus or the GI tract may be disregarded by the patient or be totally undetected until the anemia becomes profound and symptomatic.

Anemia [1M]

Menstrual bleeding among healthy females varies monthly from 10-250 mL. Unless the patient observes a change in menses, she relates that menses are normal unless specific questions are asked. The presence of clots, abdominal cramps, excessive gushing of blood upon removal of tampons, the need for both tampons and pads, and the use of an unusual number of pads or tampons can be used to determine if menstrual bleeding may be sufficient to induce iron deficiency anemia.

GI bleeding is the other occult cause of anemia due to blood loss. If hemorrhage is profuse, it is usually detected before evidence of iron deficiency anemia occurs, because hematochezia or melena causes the patient to seek medical attention. However, if the bleeding occurs slowly, it is usually undetected until anemia ensues, because stools appear normal.

Every patient with iron deficiency anemia should have a stool examination for occult blood. A positive result necessitates a careful search of the GI tract to identify the site of bleeding. Unfortunately, a negative result does not exclude GI blood loss, because bleeding can be intermittent and require several examinations for detection. Also, less than 20-30 mL of blood in the stool per day may go undetected due to the insensitivity of the test.

The two methods used to detect small daily losses of blood from the gut are as follows: (1) placing the patient on a meat-free diet for several days and using more sensitive methods, such as a benzidine test, and (2) labeling the patient's RBCs with chromium 51 and collecting stool specimens for the detection of the radioisotope.

Anemia [1M]

In addition, GI bleeding can be investigated using endoscopy and radiographic studies.

Additional considerations

Iron deficiency anemia in an adult in the United States should be attributed to bleeding unless other causes can be proved. Aside from recent multiparity, other causes are relatively uncommon and include prolonged dietary idiosyncrasies (eg, clay eating, laundry starch consumption, protein deprivation for several years), urinary loss of iron due to intravascular hemolysis (eg, artificial aortic valves, paroxysmal nocturnal hemoglobinuria), gastrectomy or other upper GI surgery, and upper GI disease.

Microcytic hypochromic anemia is observed in conditions other than iron deficiency anemia. Certain types of these disorders are iron-overloading states in which the administration of iron can be deleterious to the patient. Similarly, low serum iron levels can be observed in chronic inflammatory states with normal body stores of iron. However, in the latter, the TIBC is usually decreased rather than increased, and stainable iron can be demonstrated in bone marrow aspirates.

Anemia [1M]

Whenever the diagnosis of iron deficiency anemia is in doubt, follow-up blood work after administration of iron to show correction of the anemia can be helpful in confirming the diagnosis.

Evaluation for Hemolysis

Normally, RBCs survive in the circulation for 120 days. If the erythrocytic life span is shortened significantly (< 40 d), the patient has a hemolytic disorder that may be demonstrated by showing increased production of erythrocytes, increased destruction, or both. The former is revealed most readily by the presence of sustained reticulocytosis and the latter by the occurrence of indirect bilirubinemia. Other laboratory tests are available to detect hemolysis, but they are either more expensive or less reliable.

Anemia [1M]

Anemia solely due to hemolysis does not occur until RBCs are being destroyed at 6-8 times the normal rate, reducing the mean RBC life span to less than 20 days because of the bone marrow's capacity to undergo 6-fold hypertrophy and hyperplasia. Thus, if the clinician relies on the presence of anemia to detect hemolytic states, the clinician misses most of them and, perhaps, an important clue to an underlying disorder. On the other hand, if reticulocytosis and indirect bilirubinemia are used to detect hemolytic states, they are usually found when the mean life span is less than 40-50 days. More sophisticated methods, such as measurements of RBC lifespan, are required to detect less severe shortening of erythrocyte life span (50-100 d) and are only occasionally needed in clinical practice.

All patients with reticulocytosis and indirect bilirubinemia have a hemolytic disorder. All patients with sustained reticulocytosis have a hemolytic disorder. Unfortunately, the contrary is not the case, and significant hemolysis can occur without reticulocytosis if the bone marrow is unable to produce cells at an accelerated rate (eg, pernicious anemia, leukemia, aplasia).

Anemia [1M]

A single demonstration of an elevated reticulocyte count is insufficient to establish a diagnosis of hemolysis, because transient reticulocytosis may occur without hemolysis (eg, in the treatment of iron deficiency anemia).

Almost all patients with indirect bilirubinemia have a hemolytic disorder. In adults, the exception is patients with Gilbert disease. These patients can be distinguished from those with hemolytic disorders and those who have no other obvious stigmata of hemolysis (eg, anemia, reticulocytosis, Coombs test) by having the patient fast for 3 days. In Gilbert disease, indirect bilirubin doubles with starvation, whereas in hemolytic disorders, it does not. Once the presence of hemolysis has been established, the etiology of the increased rate of RBC destruction can be sought.

All causes of hemolytic disorders are either hereditary or acquired. Similarly, they are due to either an intrinsic abnormality of the RBC (intracorpuscular defect) or external factors that shorten the erythrocyte life span (extracorpuscular). Using this nomenclature, only 4 groups of hemolytic disorders are possible—hereditary intracorpuscular, hereditary extracorpuscular, acquired intracorpuscular, and acquired extracorpuscular.

Anemia [1M]

Hereditary hemolytic disorders

All hereditary hemolytic disorders are due to intracorpuscular defects, and most acquired disorders are due to extracorpuscular abnormalities (see Table 4). Hereditary etiologies of hemolytic disease are suggested strongly in any patient with a family history of anemia, jaundice, cholelithiasis, or splenectomy. Whenever possible, family members, particularly parents, siblings, and children, should undergo a hematologic examination, including a hemogram with reticulocyte count, an indirect bilirubin determination, and a careful examination of the peripheral smear.

If a specific hereditary hemolytic disorder (eg, hereditary spherocytosis, hemoglobinopathy) is suggested in a patient, examine blood from family members for that entity by appropriate laboratory methods. Establishment of a hemolytic defect in other closely related family members permits a presumptive diagnosis of hereditary intracorpuscular hemolytic disorder in the patient. Showing a similar RBC abnormality (eg, spherocytes, abnormal Hb, G-6-PD deficiency) among family members establishes the basic etiology. Once the probability of a hereditary hemolytic disorder is established, a planned approach to determine the definitive abnormality is usually simple.

Anemia [1M]

A careful examination of the peripheral smear may reveal spherocytes in hereditary spherocytosis, ovalocytes in hereditary elliptocytosis, sickle cells in patients with major hemoglobinopathies associated with sickle Hb, target cells in patients with Hb C or E disease, and marked poikilocytosis with target cells, microcytes, and hypochromic RBCs in thalassemia.

Even in certain rare disorders, abnormal erythrocyte morphology may provide an important clue. Examples are acanthocytosis in abetalipoproteinemia, stomatocytosis in the hereditary disorder of this name, and numerous target cells in lecithin cholesterol acyltransferase deficiency. Other laboratory studies of value in the hereditary hemolytic disorders include the following: [14]

Hereditary spherocytosis - MCHC greater than 36%, incubated osmotic fragility in oxalate, and detection of the underlying molecular defect

Hemoglobinopathies - Sickle cell preparation, Hb electrophoresis at 1 or more pH, heat denaturation test for unstable Hbs, oxygen disassociation for Hbs with abnormal oxygen affinity

Anemia [1M]

Thalassemia - A2 and fetal Hb, Hb electrophoresis, characterization of the molecular defect, quantification of alpha and beta chains

Congenital dyserythropoietic anemias - Demonstration of abnormalities of erythroid precursors in bone marrow aspirates, positive acid hemolysis (Ham) test, with normal result of sucrose hemolysis test in one form of this disease (hereditary erythroblastic multinuclearity with a positive acidified serum test [HEMPAS])

Hereditary RBC enzymatic deficiencies - Specific RBC enzyme assay

In clinical practice, approximately 90% of hereditary RBC enzymatic deficiencies with significant clinical manifestations are either G-6-PD deficiencies or abnormalities of pyruvic kinase. The age at which a hemolytic disorder is detected is not always helpful in determining whether the disorder is hereditary. Although the abnormality is inherited, congenital manifestations may be unusual. An infant with sickle cell anemia or beta thalassemia appears healthy at birth. Clinical manifestations usually do not occur in infants younger than 6 months, because fetal Hb has not been replaced by adult Hb until that age.

Anemia [1M]

Usually, thalassemia minor is not detected until a routine hemogram is performed, and, then, it is often mistaken for iron deficiency anemia because of the microcytosis and hypochromia. Thus, the physician dealing with adult patients must be as aware of these disorders as the pediatrician.

The most common place of the hereditary disorders is G-6-PD deficiency, because it occurs in 10% of the African American population living in the United States. In this population, G-6-PD deficiency usually remains undetected until oxidant drugs are administered. Then, it produces a mild to moderate hemolytic anemia that is transient in nature. In white populations of Mediterranean derivation, G-6-PD deficiency can produce a chronic hemolytic anemia without exposure to drugs. Exposure to oxidant drugs can produce lethal hemolysis.

Anemia [1M]

Acquired hemolytic disorders

Acquired hemolytic disorders occur in a large number of disease states and can vary considerably in severity. In addition, hemolysis may be observed as a result of physical injury to the RBC or following exposure to drugs, chemicals, or venoms. In many patients, the etiology of the hemolytic disorder is apparent because of other manifestations of the disease (eg, infections, collagen vascular disease).

A confirmed positive Coombs test result can be extremely helpful in this group of disorders. It provides assurance that the hemolytic disorder is an acquired extracorpuscular defect and limits it to the group of disorders associated with autoimmune hemolytic anemia; these disorders include the following:

- Drug-dependent antibodies (eg, to penicillin, quinidine, alpha methyldopa)
- Coexistence of an underlying disease (eg, hematologic malignancies, lupus erythematosus, certain viral infections)
- Idiopathic groups in which an underlying disease cannot be demonstrated

Anemia [1M]

Usually, the acquired hemolytic disorders with intracorpuscular defects are not difficult to diagnose. Vitamin B-12 and folic acid deficiencies are associated with macrocytic anemia, the presence of hypersegmented polymorphonuclear leukocytes in the peripheral smear, megaloblastic bone marrow, physical findings of the underlying cause of the deficiency state, and abnormal serum levels for the deficient vitamin.

Iron deficiency in the United States is rarely of sufficient severity to cause significant hemolysis and is merely mentioned herein for the sake of completeness.

Paroxysmal nocturnal hemoglobinuria is diagnosed only if the physician considers it in the differential diagnosis, and it may manifest by either a pancytopenia or a hemoglobinuria. However, flow cytometry to detect the absence or reduced expression of CD59 and CD55 on the patient's RBCs can help to exclude this cause of hemolysis.

Additional considerations

The major diagnostic problems encountered with hemolytic disorders are when the known causes for hemolysis have been excluded by history, physical examination, and laboratory studies; the Coombs test result is negative; and not enough family members can be tested to differentiate between hereditary intracorpuscular hemolytic disorders and acquired extracorpuscular defects.

A donor cell chromium survival study can be helpful in differentiating between a hereditary hemolytic disorder and an acquired hemolytic disorder.

Anemia [1M]

Labeled RBCs from a healthy blood donor in a compatible blood group allow for a normal survival rate in patients with hereditary hemolytic disease and a shortened life span in those with an acquired extracorpuscular defect.

Evaluation for Decreased RBC Production

Diminished production of RBCs is suggested in all patients without evidence of either blood loss or hemolysis. Thus, a patient with anemia without evidence of bleeding or iron deficiency, with normal indirect bilirubin and normal or decreased reticulocyte count, probably has a defect in the production of erythrocytes. Many of these patients have pancytopenia or other abnormalities of the leukocytes or the platelets that can be detected with an examination of a peripheral smear.

When this group of disorders is suspected, the most important laboratory test is a bone marrow biopsy and aspiration.

Anemia [1M]

The bone marrow biopsy permits categorization of these disorders into the following three separate groups, as shown in the image below:

- Aplastic or hypoplastic

- Hyperplastic

- Bone marrow replaced with nonhematopoietic elements (infiltration of bone marrow)

Whenever possible, a cause for the aplastic anemia should be uncovered, because cessation of exposure may lead to recovery. Identification of the offending agent is likewise important in determining the prognosis.

Infiltration of the bone marrow with fibrous tissue, neoplastic cells, or other cells that replace normal hematopoietic tissue can diminish the production of RBCs, granulocytes, and platelets. The diagnosis of myelofibrosis or neoplastic involvement of bone marrow is often suggested by evidence of myeloid metaplasia in the peripheral smear (ie, erythroid and granulocyte precursors).

Anemia [1M]

Replacement of bone marrow with nonhemopoietic cells leads to activation of fetal sites of blood production in organs such as the liver and the spleen, with release of abnormally shaped erythrocytes and normoblasts, immature granulocytes and normoblasts, immature granulocytes, and large platelets into the peripheral blood. Myeloid metaplasia does not occur in aplastic disease. Thus, its presence in a patient who is anemic suggests bone marrow infiltration, even before the biopsy specimen is obtained.

Imaging and Procedures

- Imaging studies are useful in the workup for anemia when a neoplastic etiology is suggested. They permit discovery of the neoplasm or centrally located adenopathy. Occasionally, they are useful in detecting or confirming the existence of splenomegaly.

- Investigate GI bleeding by endoscopy and radiographic studies to identify the bleeding site. However, even these methods may leave a source of GI bleeding undetected, because these procedures do not detect the bleeding site or the lesion if small.

Anemia [1M]

Examples of these causes include the following:

- Coagulation abnormalities induced by aspirin or platelet dysfunction
- Hookworm infestation
- Hemangiomas of the small bowel
- Lymphosarcoma and other tumors
- Adenomas of the gallbladder
- Self-administration of anticoagulants

Bone marrow aspirates and biopsy findings are particularly useful in establishing the etiology of anemia in patients with decreased production of RBCs. They help to differentiate aplasia; megaloblastic hyperplasia; and infiltration of marrow with neoplasia, myelodysplasia, and myelofibrosis. In addition, they lead to a definitive histologic diagnosis of leukemias, lymphomas, myelomas, and metastatic carcinomas. These procedures are less useful in detecting hemolytic anemia (except to detect lymphoma or leukemia), and they are also less useful in diagnosing congenital dyserythropoietic anemia, in which they reveal the multinuclearity of erythroid precursors. Iron stains of the bone marrow aspirate can be used to document the existence of iron deficiency anemia or the sideroblastic anemias.

Anemia [1M]

Approach Considerations

The purpose of establishing the etiology of an anemia is to permit selection of a specific and effective therapy. For example, corticosteroids are useful in the treatment of autoimmune hemolytic anemia.

Therapy and medical care vary considerably in the group of hereditary disorders. Splenectomy has been advantageous in hereditary spherocytosis and hereditary elliptocytosis, in some of the unstable hemoglobinopathies, and in certain patients with pyruvic kinase deficiency. It has little value in most other hereditary hemolytic disorders.

Drugs and chemicals capable of producing aplasia or a maturation arrest of erythroid precursors should be discontinued or avoided. Similarly, diseases known to be associated with anemia should be appropriately treated. Guidelines for the treatment of chemotherapy-associated anemia are available.

Surgery is useful to control bleeding in patients who are anemic. Most commonly, bleeding is from the GI tract, uterus, or bladder. Patients should be hemodynamically stable before and during surgery. A blood transfusion may be needed.

Anemia [1M]

Management of beta-thalassemia major and major hemoglobinopathies

Patients with beta-thalassemia major and the major hemoglobinopathies associated with sickle hemoglobin (Hb) usually require medical attention at frequent intervals for the treatment of anemia, infection, pain, and leg ulcers because of the serious nature of these illnesses. Conversely, many of the other hereditary abnormalities have minimal or no clinical manifestations; the patient requires only reassurance.

Luspatercept, an erythroid maturation agent, is approved for anemia in adults with beta thalassemia who require regular red blood cell transfusions. The drug is a recombinant fusion protein that diminishes Smad2/3 signaling by binding several endogenous TGF-beta superfamily ligands. In a model of beta thalassemia, luspatercept decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis.

Anemia [1M]

Transfusion

Transfusion of packed red blood cells (RBCs) should be reserved for patients who are actively bleeding and for patients with a severe and symptomatic anemia. [16] Transfusion is palliative and should not be used as a substitute for specific therapy. In chronic diseases associated with anemia of chronic disorders, erythropoietin may be helpful in averting or reducing transfusions of packed RBCs.

Hemolytic transfusion reactions and transmission of infectious disease are risks of blood product transfusions. Patients with autoimmune antibodies against RBCs are at greater risk of a hemolytic transfusion reaction because of difficulty in cross-matching the blood. Occasionally, the blood of patients with autoimmune hemolytic anemia cannot be cross-matched in vitro. In these cases, the patients require in vivo cross-matching, in which incompatible blood is transfused slowly and periodic determinations are made to ensure that the patient is not developing hemoglobinemia. This method should be used only in patients with either significant hypoxia from the anemia or evidence of coronary insufficiency.

Anemia [1M]

Iron Supplementation

The appropriate treatment of anemia due to blood loss is correction of the underlying condition and oral administration of ferrous sulfate until the anemia is corrected and for several months afterward to ensure that body stores are replete with iron. Relatively few indications exist for the use of parenteral iron therapy, and blood transfusions should be reserved for the treatment of shock or hypoxia.

Although the traditional dosage of ferrous sulfate is 325 mg (65 mg of elemental iron) orally three times a day, lower doses (eg, 15-20 mg of elemental iron daily) may be as effective and cause fewer side effects. To promote absorption, patients should avoid tea and coffee and may take vitamin C (500 units) with the iron pill once daily. If ferrous sulfate has unacceptable side effects, ferrous gluconate, 325 mg daily (35 mg of elemental iron) is a possible alternative for patients who cannot tolerate ferrous sulfate. [17]

Anemia [1M]

Nutritional Therapy and Dietary Considerations

Nutritional therapy is used to treat deficiencies of iron, vitamin B-12, and folic acid. Pyridoxine may be useful in the treatment of certain patients with sideroblastic anemia, even though this is not a deficiency disorder. A strict vegetarian diet requires iron and vitamin B-12 supplementation.

Iron deficiency anemia is prevalent in geographic locations where little meat is in the diet. Many of these locations have sufficient dietary inorganic iron to equal the iron content in persons residing in countries in which meat is eaten. However, heme iron is more efficiently absorbed than inorganic food iron. Folic acid deficiency occurs among people who consume few leafy vegetables. Coexistence of iron and folic acid deficiency is common in developing nations.

Management of Aplastic Disorders

- Treatment of aplastic disorders includes removal of the offending agent whenever it can be identified, supportive therapy for the anemia and thrombocytopenia, and prompt treatment of infection. Avoid transfusion in patients with a potential bone marrow donor, because transfusion worsens the probability of cure from transplantation.

Anemia [1M]

As part of supportive therapy, British Committee for Standards in Haematology guidelines recommend immunosuppression with antithymocyte globulin and cyclosporine as first-line therapy in the following adult patients [19] :

Patients with severe or very severe aplastic anemia who lack a matched sibling donor (MSD)

Patients with severe or very severe aplastic anemia aged >35-50 years

The British guidelines recommend up-front hematopoietic stem cell transplant (HSCT) for young and adult patients who have an MSD. Similarly, Italian guidelines for treatment of aplasti anemia in children recommend HSCT from an MSD as the treatment of choice, with immunosuppressive therapy or unrelated-donor HSCT as options if an MSD is not available. [20]

Splenectomy may provide sufficient improvement for patients with hypoplastic, but not totally aplastic, marrow so that transfusion is not necessary and platelet and granulocyte counts increase to less dangerous levels. (See Splenectomy.)

Anemia [1M]

Splenectomy

Splenectomy is useful in the treatment of autoimmune hemolytic anemias and in certain hereditary hemolytic disorders (ie, hereditary spherocytosis and elliptocytosis, certain unstable Hb disorders, pyruvic kinase deficiency). Improvement in survival rates has been reported in patients with aplastic anemia, but splenectomy is not the preferred therapy. Leg ulcers have shown improvement in some patients with thalassemia. Prior to splenectomy, patients should be immunized with polyvalent pneumococcal vaccine. Preferably, this should be administered more than 1 week prior to surgery.

Bone Marrow and Stem Cell Transplantation

Bone marrow and stem cell transplantation have been used in patients with leukemia, lymphoma, Hodgkin lymphoma, multiple myeloma, myelofibrosis, and aplastic disease. Survival rates in these patients improved, and hematologic abnormalities were corrected. Allogeneic bone marrow transplantation has successfully corrected phenotypic expression of sickle cell disease and thalassemia and provided enhanced survival in patients who survived transplantation.

Anemia [1M]

However, incomplete immune recovery after hematopoietic stem cell transplantation (HSCT) may predispose to autoimmune cytopenias, including anemia. From 2-6% of pediatric patients develop new-onset autoimmune hemolytic anemia (AIHA) after HSCT. Schuetz et al report that treatment with the anti-CD38 antibody daratumumab, which is approved for use in multiple myeloma, was curative in two of three patients with life-threatening posttransplant AIHA, with the third patient showing a transient response before relapse of AIHA 8 months afterward. [21]

Activity Restriction

Patients with severe anemia should curtail their activity until the anemia is partially corrected. Transfusion can often be avoided by ordering bed rest while therapy is initiated for a patient with correctable anemia (eg, pernicious anemia).

March hemoglobinuria is a rare hemolytic disorder usually observed in young males. Individuals develop hemoglobinuria after marching or running on hard surfaces. Curtailing the precipitating exercise (ie, running on grass rather than concrete) and using shoes with reinforced soles are helpful in preventing this form of hemoglobinuria.

Anemia [1M]

Transfer Considerations

Patients with a benign etiology for anemia usually do not require transfer to another institution. Occasionally, transfer is necessary to establish the etiology of the anemia or to provide a treatment that is not locally available.

If patients are being transferred for diagnostic reasons, transferring them before transfusion is helpful. If the transfusion is necessary before transfer to achieve hematopoietic stability, consult with the receiving physician to determine laboratory tests that should be performed before transfusion. Patients who are hemodynamically unstable should not be transported.

Medication Summary

Therapeutic approaches to anemia include the use of blood and blood products, immunotherapies, hormonal/nutritional therapies, and adjunctive therapies. The goal of therapy in acute anemia is to restore the hemodynamics of the vascular systems and to replace lost red blood cells. To achieve this, the practitioner may use mineral and vitamin supplements, blood transfusions, vasopressors, histamine (H2) antagonists, and glucocorticosteroids.

Anemia [1M]

Documentation of the etiology of anemia is essential in the selection of therapy. Not all microcytic anemias are caused by iron deficiency; some are iron-overloading disorders. Similarly, not all megaloblastic anemias are associated with either vitamin B-12 deficiency or folic acid deficiency. Hereditary hemolytic disorders do not improve with corticosteroid therapy.

Anemia [1M]

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