

Diagnosing Anemia

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Anemia is a common finding in primary care, with some 3.5 million US residents estimated to have some form of the disease. Thus, it is important for clinicians to understand normal red blood cell and hemoglobin biochemistry, genetics, physiology, and pathology. The universally available electronic complete blood count and the reticulocyte count provide an efficient, cost-effective diagnostic tool; along with conducting a thorough history, physical examination, and common laboratory testing, primary care providers can identify the cause of anemia in most cases. Only a small number of patients with unclear results require referral to a hematologist for further investigation.

Blood is a life-sustaining substance with many critical functions, including oxygen and nutrient delivery, heat distribution, carbon dioxide elimination, and communication. Blood comprises about 54% water-based plasma, 1% white blood cells and platelets, and 45% red blood cells.

Anemia (from the Greek word *anaimia*, “without blood”) is defined as a reduction in the number of red cells, blood hemoglobin content, or the hematocrit. Approximately 3.5 million Americans have anemia in some form.¹ According to population-based estimates, anemia affects about 6.6% of men and 12.4% of women.^{2,3}

RED BLOOD CELLS

The red cells transport oxygen from the lungs to the organs and peripheral tissues, then return to the lungs carrying carbon dioxide to be exhaled. Each cubic millimeter of blood contains 4.7 million to 6.0 million red cells.⁴ The red cell, a pliable biconcave disc measuring 7 to 8 microns, is perfectly designed to traverse the small capillary beds (3 to 4 microns). Red cells contain the oxygen-carrying protein hemoglobin and enzymes for energy production—all encased by a semipermeable, pliable lipid membrane.

Hemoglobin, the predominant protein in the red cell, binds oxygen and carbon dioxide. The normal red cell is composed of three types of hemoglobin: type A (97%), type A₂ (2%), and type F or fetal (1%).⁵ Hemoglobin A is composed of two β -globin chains and two α -globin chains bonded to four iron-containing heme groups. Hemoglobin production requires iron, synthesis of the protoporphyrin ring, and production of the globin chains. Any mutation of the amino acid

sequence on the chromosomes that code β -globin chain production will cause one of the more than 600 known hemoglobinopathies.

Red Cell Production

In the human adult, red cells, white cells, and platelets are manufactured in the axial skeleton bone marrow factory. There, stem cells divide and differentiate into the various cell types, as regulated by specific growth factors. As the red cell matures and forms the hemoglobin necessary for its life span, the nucleus is extruded, and the cell enters the blood circulation as a reticulocyte.

The normal red cell has a 120-day life span. At senescence, it is phagocytized by macrophages, and its contents are metabolized in the reticuloendothelial system.⁶ Bilirubin, a breakdown product of hemoglobin, is conjugated in the liver and excreted in the biliary system. Isolated increase in indirect (pre-liver) bilirubin is a very specific indicator of hemolysis.

In response to low tissue oxygen levels, the endothelial cells in the kidneys' peritubular capillaries secrete the hormone erythropoietin (EPO),⁷ stimulating bone marrow red cell production. The anemia of renal disease results, in part, because this feedback loop is blunted.

PATIENT PRESENTATION

Anemia is clinically suspected in patients with the presenting symptoms and signs of weakness, fatigue, palpitations, increased heart rate, and dyspnea. Acute anemia may be associated with positional nonvertigo dizziness, syncope, bleeding from any site, and new-onset angina. It should be suspected with physical findings of tachycardia, orthostatic fall in blood pressure, pallor, or jaundice.

Anemia may be detected on the routine diagnostic screening using the electronic complete blood count (CBC) or finger-stick hemoglobin determination. The diagnostic approach should include a thorough history, physical exam, and laboratory evaluation. Normal adult values for the CBC and reticulocyte count are shown in [Table 1](#).

TABLE 1
The Complete Blood Cell Count

Parameter	Normal adult range	Indications
Hemoglobin	Male: 14.0 – 17.4 mg/dL Female: 12.0 – 16.0 mg/dL	Low: Anemia High: Polycythemia
Hematocrit	Male: 42% – 52% Female: 35% – 48%	Low: Anemia High: Polycythemia

RBC count	Male: 4.5 – 5.5 x 10 ⁶ /μL Female: 4.0 – 5.0 x 10 ⁶ /μL	Low: Anemia High: Polycythemia
WBC count	5.0 – 10.0 x 10 ³ /μL	Low: Leukopenia High: Leukocytosis
Platelet count	140 – 400 x 10 ³ /μL	Low: Thrombocytopenia High: Thrombocytosis
Reticulocyte count	0.5% – 1.5% 25 – 85 x 10 ³ /μL	Low in anemia: Low marrow output High: RBC loss
RBC, red blood cell; WBC, white blood cell.		
Data extracted from: Fischbach FT. <i>A Manual of Laboratory and Diagnostic Tests</i> . Philadelphia, Pa: Lippincott Williams & Wilkins; 2003: 47.		

The initial work-up should include a red cell morphology examination, as microscopic observation can yield many diagnoses. Evaluation of red cell morphology on blood smear is critical in evaluating any hemolytic anemia. Possible morphology findings and their significance are shown in [Table 2](#).

TABLE 2
Red Cell Morphology

Possible findings	Significance
Burr cells	Uremia, low potassium, artifact, stomach cancer, peptic ulcer disease
Spur cells	Liver disease, abetalipoproteinemia
Stomatocyte	Hereditary condition, alcoholic liver disease
Spherocyte	Hereditary condition, immune hemolytic anemia, water dilution, posttransfusion
Schistocyte, helmet	Thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, vasculitis, myelophthisic glomerulonephritis, prosthetic heart valve
Elliptocyte, ovalocyte	Hereditary, iron deficiency, megaloblastic anemias
Teardrop cells	Iron deficiency, myelophthisic, megaloblastic anemias
Sickle cells	Sickle cell disease
Target cells	Postsplenectomy thalassemia, hemoglobinopathy
Parasites	Malaria, babesiosis

Basophilic stippling	Thalassemia, lead toxicity
Bite cells	G6PD deficiency
G6PD, glucose-6-phosphate dehydrogenase.	
Data extracted from: Fischbach FT. <i>A Manual of Laboratory and Diagnostic Tests</i> . Philadelphia, Pa: Lippincott Williams & Wilkins; 2003:84-86.	

Reticulocyte Count

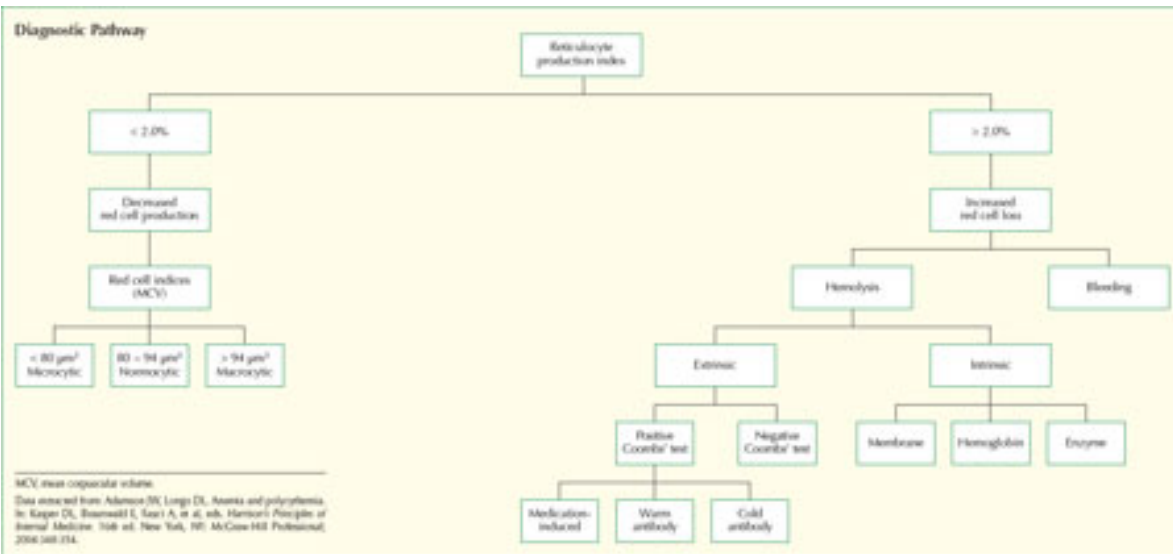
This is the best indicator of how anemia is affecting the bone marrow factory. It must be corrected for the reduction in red cell count to accurately reflect erythrocyte production. This correction is made by calculating an absolute reticulocyte count— either by multiplying the raw reticulocyte percentage by the erythrocyte count; or by multiplying the raw reticulocyte percentage by either the observed hematocrit (percentage) divided by the normal hematocrit, or the observed hemoglobin (mg/dL) divided by the normal hemoglobin.⁸

The normal mean absolute reticulocyte count is $50,000/\mu\text{L} \pm 25,000$. The normal corrected reticulocyte production index is 1.0% to 2.0%. A calculation below 2.0% indicates that the anemia is the result of decreased marrow production; a figure above 2.0% indicates anemia caused by red cell loss (ie, bleeding or hemolysis). This is the first step in identifying the anemia's cause.⁸

THE ANEMIAS OF DECREASED MARROW PRODUCTION

The bone marrow slows or stops production because of insufficient EPO stimulation or a lack of raw materials (iron, amino acids, protein, carbohydrates, lipids, folate, vitamins B₁₂ and C)—or because the marrow has been infiltrated or attacked by a virus, toxin, or cancer. All associated disorders are characterized by a low reticulocyte count.

The mean corpuscular volume (MCV) is the most useful parameter to evaluate a low–reticulocyte count anemia. An MCV below $80 \mu\text{m}^3$ indicates a *microcytic* differential diagnosis, with possible hemoglobin production problems; an MCV higher than $94 \mu\text{m}^3$ suggests a *macrocytic* work-up, possibly caused by DNA production problems. An MCV between these figures indicates a *normocytic* pathway;² ie, systemic disease reduces red cell production, or the number of stem cells needed to produce red cells is compromised. See “Diagnostic Pathway.”



(Click image above to view a larger version)

Microcytic Anemias

These are among the most common anemias encountered in primary care. Laboratory tests should include measures of serum iron, total iron-binding capacity, percent saturation, and serum ferritin level⁹ (see [Table 3](#)⁹). The best peripheral test for stored iron is the ferritin level; a result below 20 ng/mL confirms iron deficiency.

TABLE 3
Laboratory Findings in Microcytic Anemias

	Red cell morphology	Serum iron level	Total iron-binding capacity	Percent saturation	Serum ferritin level
Iron deficiency anemia	Microcytic, hypochromic	Decreased	Increased	< 16%	Decreased
Anemia of chronic inflammation	Normocytic, microcytic	Decreased	Decreased	10% – 20%	Increased
Sideroblastic anemia	Microcytic, hypochromic	Increased	Normal	50% – 100%	Increased
Thalassemia	Microcytic, target cells	Normal or increased	Normal	30% – 100%	Normal or increased

Data extracted from: Massey. *Med Clin North Am.* 1992⁹; Adamson JW. Iron deficiency and other hypoproliferative anemias. In: Kasper DL, Braunwald E, Fauci A, et al, eds. *Harrison's Principles of Internal Medicine.* 16th ed. New York, NY: McGraw-Hill Professional; 2004:660-666.

The differential diagnosis for microcytic anemias can be remembered by the mnemonic “**TICS**.”

T: The *thalassemia syndromes* result from inherited genetic abnormalities that cause decreased synthesis of α -globin or β -globin chains, and thus, decreased production of hemoglobin A. In *β -thalassemia major*, or *Cooley's anemia*, patients present with severe anemia, jaundice, and hepatosplenomegaly in the first year of life.

In *β -thalassemia minor*, splenomegaly may be present, and the peripheral smear often shows target cells and basophilic stippling. Iron study results are normal. Hemoglobin electrophoresis shows increases in hemoglobin types A₂ and F.¹⁰ Symptoms are usually absent, and no specific therapy is required. Therapeutic iron supplements are not recommended unless a low serum ferritin level confirms concurrent iron deficiency.¹¹

α -Thalassemia has its highest incidence in peoples of Southeast Asian, Mediterranean, and African descent. Diagnosis is based on CBC evidence of more microcytosis than anemia and an elevated red cell count. Hemoglobin electrophoresis is normal.

I: *Iron deficiency anemia* occurs when body iron stores are depleted by prolonged bleeding without adequate replacement.^{9,11} The daily iron requirement for a man or a nonmenstruating woman is 1.0 mg; for a woman who menstruates, 2.0 mg; and for a pregnant woman, 3.0 to 4.0 mg. The normal daily diet contains 10 mg of iron, of which 5% to 10% is absorbed. Bleeding can lead to a loss of 50 mg of iron per 100 cc of whole blood.

Laboratory findings may include anemia with a low reticulocyte production index, low MCV, and low mean corpuscular hemoglobin concentration. Physical examination may reveal glossitis, koilonychia (spoon nails), gastritis, and angular stomatitis. The clinician must determine the deficiency's underlying cause by excluding occult gastrointestinal bleeding, excessive menstrual loss, and inadequate dietary intake.

C: Anemia of *chronic inflammation*. Long-standing infections, neoplastic diseases, and chronic inflammatory processes (eg, rheumatoid arthritis, systemic lupus erythematosus) block iron transportation from the storage sites to the bone marrow factory.^{12,13} An elevated Westergren sedimentation rate or C-reactive protein level can be a nonspecific indicator of inflammation. A normal or elevated ferritin level with a high percent saturation should prompt a close review of the electronic CBC (which may reveal an elevated red cell count, suggesting thalassemia), hemoglobin electrophoresis, the blood smear, and a lead level.

S: *Sideroblastic anemias* are a diverse group characterized by the presence of "ringed" sideroblasts in the bone marrow; basophilic stippling may be present on a peripheral smear. Acquired sideroblastic anemias are associated with use of antituberculous medications (eg, isoniazid, pyrazinamide¹⁴), alcohol abuse, lead poisoning, chronic inflammation, and preleukemic states, especially after chemotherapy. Lead levels should be obtained in children and in patients exposed to lead-based paints, car batteries, or "moonshine,"¹⁵ and in those with crampy abdominal pain, peripheral neuropathy, or encephalopathy.

Macrocytic Anemias

Common causes of macrocytic (or *megaloblastic*) anemias include chemotherapy and vitamin B₁₂ and folate deficiency; a less common cause is marrow malignancy. Rarely, inherited defects in DNA synthesis or vitamin metabolism may be the cause. The peripheral blood changes include macro-ovalocytes, neutropenia with hypersegmented neutrophils, and thrombocytopenia with large platelets.¹⁶ Levels of serum vitamin B₁₂, serum folate, and red cell folate should be measured. The differential diagnosis is represented by the mnemonic “**BIG FAT RED CELLS.**”

B: Vitamin B₁₂ (*cobalamin*) deficiency.^{16,17} Patients may present with weakness, fatigue, dyspnea, paresthesias, and mental clouding. Physical signs include edema, pallor, jaundice, smooth tongue, decreased vibratory and position sensation, peripheral neuropathy, and long tract findings.¹⁸

In the US, inadequate B₁₂ intake usually occurs only in strict vegans. However, about 70% of cases of vitamin B₁₂ deficiency are caused by pernicious anemia—in which inadequate intrinsic factor or other conditions result in B₁₂ malabsorption. This diagnosis is confirmed by the presence of anti-intrinsic factor antibodies or by positive results on the Schilling test.¹⁹

I: *Inherited disorders* (eg, orotic aciduria, Lesch-Nyhan syndrome, Di Guglielmo’s syndrome). These are rare.¹⁸

G: *Gastrointestinal disease or surgery.* Small bowel disease, nontropical sprue, regional enteritis, ileal resection, celiac disease, fish tapeworm, or bacterial overgrowth all may block absorption of vitamin B₁₂.

F: *Folic acid deficiency.*¹⁶ Patient history may reveal anemia symptoms, alcoholism, or a diet lacking in fresh, uncooked fruits and vegetables (folates are rapidly destroyed by heat). Physical examination may show stigmata of alcoholic liver disease.

The minimum daily requirement of folic acid is 50 µg; the average diet contains 700 µg, of which 10% is absorbed. Pregnant women, patients with hemolytic anemia, and those undergoing dialysis have increased folic acid requirements.

A: *Alcoholism* (chronic).^{17,19}

T: *Thiamine-responsive anemia.* This rare, unexplained condition is correctable with thiamine.

R: *Reticulocytes* in large numbers may inflate the MCV, because they are larger than mature red cells.¹⁹

E: *Endocrine disturbances* (hypothyroidism).¹⁹

D: *Dietary deficiencies*, particularly folate, vitamin B₁₂, protein, or lipids.¹⁶

C: *Chemotherapeutic drugs*, including methotrexate and 5-fluorouracil.²⁰

E: *Erythroleukemia*. Circulating abnormal immature erythrocytes are larger than normal mature cells, inflating the MCV.

L: *Liver disease*.¹⁷ Chronic hepatitis, alcoholism, and cirrhosis may increase MCV by altering the red cell membrane lipid composition.

L: *Lesch-Nyhan syndrome*.²¹ This rare hereditary deficiency of hypoxanthine-guanine phosphoribosyltransferase activity is manifested by hyperuricemia, self-mutilation, mental retardation, spasticity, and choreoathetosis.

S: *Splenectomy*. Loss of splenic filtration function results in larger erythrocytes with increased membrane, nucleated red blood cells (nRBCs), and nuclear fragments (Howell-Jolly bodies).²²

Normocytic Anemias

Diagnosis may be confirmed by reviewing the patient's blood urea nitrogen and creatinine levels, erythrocyte sedimentation rate, results of urinalysis and pregnancy testing (if appropriate), and thyroid profile. A bone marrow biopsy is often necessary to obtain the diagnosis if these simple tests do not reveal pancytopenia, or if the blood smear shows nRBCs, early white cells, and/or teardrop-shaped red cells. The mnemonic for this differential diagnosis is "**NORMAL SIZE.**"

N: *Normal pregnancy*. Anemia of pregnancy results in part from a 30% expansion in the plasma volume.²

O: *Overhydration and expanded plasma volume*.

R: *Chronic renal disease*. Anemia resulting from relative decrease in EPO production responds to recombinant EPO therapy.^{2,7,23}

M: *Myelophthisic anemia* results from replacement of the bone marrow by a tumor, granulomatous infectious disease, fibrosis, or leukemia.²⁴

A: *Acute blood loss*.

L: *Leukemia and liver disease*. Chronic hepatitis, alcoholism, and cirrhosis may increase plasma volume and alter red cell survival.

SI: *Systemic inflammation (anemia of chronic inflammation)*.^{12,13}

Z: *Zero production*. Aplastic anemia usually presents with pancytopenia.²⁵

E: *Endocrine disorders* (eg, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypogonadism).²

HEMOLYTIC ANEMIAS

The hallmark of hemolysis is an elevated reticulocyte count with a stable or falling hemoglobin concentration, an isolated elevation of indirect bilirubin, elevated serum lactate dehydrogenase, decreased haptoglobin levels, hemoglobinemia, and/or hemoglobinuria. Chronic hemolysis causes erythroid hyperplasia, as detected on bone marrow examination.

Tests used to identify the cause of hemolysis are the direct antiglobulin or Coombs' test, hemoglobin electrophoresis, the Heinz body stain, the osmotic fragility test, and the blood smear.¹⁰ Consider the mnemonic "**HEMATOLOGIST.**"

H: *Hemoglobinopathies*, with sickle cell disease among the most common; also, paroxysmal nocturnal *hemoglobinuria*.² Manifestations include episodic intravascular hemolysis, thrombotic episodes, and increased infections.¹⁰ Diagnosis is based on flow cytometry for loss of antibodies CD55 and CD59.²⁶

E: *Enzyme deficiency* (eg, inherited pyruvate kinase deficiency, pyrimidine-5'-nucleotidase deficiency).^{27,28}

M: *Medications*, including sulfonamides, high-dose IV penicillin, quinine, quinidine, and chlorpromazine.^{29,30}

A: *Antibodies*. In immune (Coombs'-positive) acquired hemolytic anemias, hemolysis is caused by an antigen that triggers antibody- or complement-mediated red cell destruction. Immune hemolytic anemia may be alloimmune (related to transfusion), autoimmune, or drug induced.^{10,31}

Immunoglobulin G (IgG): Warm reacting antibody anemia³² occurs secondary to lymphoproliferative syndrome (in 30% of cases), collagen vascular diseases (20%), and other tumors (20%), or it can be idiopathic (20%). Laboratory findings are those of anemia with an increased reticulocyte count and detection of microspherocytes on the blood smear. Direct Coombs' testing is positive for IgG or IgG and C3.³³

IgM: Cold reacting antibody anemia³² occurs secondary to viral and mycoplasmal infections, with lymphoproliferative disease, and as idiopathic disorders in the elderly.

T: *Trauma to the red cells*, as from an abnormal endothelium.¹⁰

O: *Ovalocytosis* is an autosomal dominant disorder seen in Southeast Asians.³⁴

L: *Liver disease*, when severe, may lead to abnormal lipid loading in erythrocyte membranes, inducing formation of spur cells with shortened red cell survival.³⁵

O: *Osmotic fragility* occurs with *hereditary spherocytosis* and *hereditary elliptocytosis*.³⁶ The former is caused by autosomal dominant or recessive membrane protein abnormalities that result in sphere formation, membrane budding, and increased permeability to sodium. *Hereditary elliptocytosis* is caused by a defective red cell membrane, resulting from abnormal structural proteins. A finding of numerous elliptocytes on the blood smear is diagnostic.

G: *Glucose-6-phosphate dehydrogenase (G6PD) deficiency*. Inherited G6PD deficiency is linked to the X chromosome, fully affecting homozygous females and males who inherit the deficient gene. Drugs or other substances cause increased oxidant stress within the red cell, triggering precipitation of hemoglobin into Heinz bodies and thereby causing hemolysis (most effectively identified by Heinz bodies on methyl violet stain). G6PD deficiency can be confirmed by molecular techniques or enzyme assay after two to three months. Patients should be advised to avoid antimalarials, high-dose aspirin, sulfa drugs, and fava beans.^{27,37}

I: *Infection*. Intra-erythrocytic parasites (eg, malaria, babesiosis) lyse emerging red cells.¹⁰ They may be identified on examination of a thick smear slide for parasites. *Clostridium* infections and β -hemolytic streptococcal septicemia may cause massive hemolysis.

S: *Splenic destruction* in hypersplenism can occur with splenomegaly, portal hypertension secondary to infections, infiltration with leukemia or lymphoma, and collagen vascular diseases.²²

T: *Transfusion*. Hemolysis may occur in a patient with antibodies directed against an antigen on the transfused red cells.³¹ The patient may experience an immediate acute transfusion reaction, or more commonly, a reaction that is delayed for five to 14 days. Additionally, *thalassemia* must be considered in a patient with hemolytic anemia and a low MCV.

CONCLUSION

Clinicians can use clues from the history, physical examination, CBC, red cell morphology, and reticulocyte count to narrow the cause of a patient's anemia into one of four pathways: microcytic, macrocytic, normocytic, or hemolytic. Further testing can help confirm the diagnosis. In those rare cases that elude diagnosis, patients must be referred to a hematologist for a bone marrow biopsy and other specialized diagnostic studies.

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