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Anemia is defined as a hemoglobin (Hb) level <12 g/dL in females and <14 g/dL in males or, alternatively, as an Hb level <12.5 g/dL in adults.[1] [2] [3] It is the most common hematologic disorder seen in general medical practice. Risk factors include extremes of age, female sex, lactation, and pregnancy. The most common cause internationally is iron deficiency.[4] Anemia can cause significant morbidity if left untreated, and is often the presenting sign of a more serious underlying condition.[5] The rate at which anemia develops is often as important as the severity, as a rapid decline can overwhelm the compensatory mechanisms of the body.

Pathophysiology:
Erythropoiesis takes place within the bone marrow and is controlled by the stromal network, cytokines, and the hormone erythropoietin. A series of differentiation steps results in the generation of reticulocytes (red blood cells [RBCs] with an intact ribosomal network). Reticulocytes remain in the bone marrow for 3 days before being released into the circulation. After one further day in the circulation, reticulocytes lose their ribosomal network and become mature RBCs, which circulate for 110-120 days before being removed from the circulation by macrophages. At steady state, the rate of RBC production equals the rate of RBC loss. Anemia develops when the rate of RBC production decreases and/or the rate of RBC loss increases.

Morphological classification of anemia:
The most clinically useful classification system is based on the mean corpuscular volume (MCV).[6] [7] [8]

- Microcytic (MCV <80 femtoliters [fL]).
  [Fig-1]
- Normocytic (MCV 80-100 femtoliters [fL]); further subclassified according to the reticulocyte count as:
  - Hyperproliferative (reticulocyte count >2%): the proportion of circulating reticulocytes increases as part of a compensatory response to increased destruction or loss of RBCs. The cause is usually acute blood loss or hemolysis.
  - Hypoproliferative (reticulocyte count <2%): these are primarily disorders of decreased RBC production, and the proportion of circulating reticulocytes remains unchanged.
- Macrocytic (MCV >100 femtoliters [fL]); further subclassified as:
  - Megaloblastic: a deficiency of DNA production or maturation resulting in the appearance of large immature RBCs (megaloblasts) and hypersegmented neutrophils in the circulation.
  - Nonmegaloblastic: encompasses all other causes of macrocytic anemia in which DNA synthesis is normal. Megaloblasts and hypersegmented neutrophils are absent.
  [Fig-2]
Classification of anemia: MCV, mean corpuscular volume; fL, femtoliters

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Etiology

Anemia occurs when the production of red blood cells (RBCs) is decreased, the destruction of RBCs is accelerated, or there is a loss of RBCs due to bleeding. In many cases, a combination of these mechanisms is present. Anemia is the most common hematologic disorder seen in general medical practice. Risk factors include extremes of age, female sex, lactation, and pregnancy.

Nutrient deficiency, acquired bone marrow disease, genetic disorders, drugs, toxins, and chronic systemic diseases may all lead to reduced RBC production.

Hemolytic anemias are a group of anemias resulting from increased destruction of RBCs with a resultant increase in circulating indirect bilirubin.[9] [10] [11] Clinical jaundice appears once bilirubin levels rise above 2-4 mg/dL. Additional disease-specific symptoms may also be present. The resulting anemia can be microcytic or hyperproliferative normocytic, depending on the cause.

Microangiopathic hemolytic anemias are often considered as a group. They produce a hyperproliferative normocytic anemia. The underlying disease process produces endothelial damage and activates the coagulation cascade, leading to fibrin deposition on the damaged endothelial surfaces. In small vessels, the endothelial fibrin causes mechanical fragmentation and shearing of RBCs, leading to hemolysis. The irregular-shaped RBC fragments produced by this process are called schistocytes and can be seen on a peripheral blood smear.

Hemodilution can occur following expansion of plasma volume. This drop in hemoglobin concentration is known as “dilutional anaemia.” This is often iatrogenic (e.g., following intravenous fluid administration) and may result in unnecessary transfusions.

Blood loss

Acute hemorrhage

• Any acute hemorrhage can cause a normocytic anemia. A reticulocytosis is seen within 6 hours of the onset of bleeding. By contrast, chronic slow bleeding leads to ongoing iron loss and produces a microcytic anemia due to iron deficiency.
• The most common causes are trauma (including gunshot wounds, major fractures, or crush injuries), acute gastrointestinal (GI) bleeding, rupture of a vascular aneurysm (especially abdominal aortic aneurysm), and recent surgery.
• Patients are at increased risk of hemorrhage if they are taking anticoagulant therapy, have an underlying defect in hemostasis, or have a consumptive or dilutional coagulopathy following repeated blood transfusions.

Gradual, prolonged bleeding

• Bleeding due to any cause produces iron depletion, because two-thirds of the total body iron is contained in circulating hemoglobin (Hb).
• Excessive menstrual losses are a common cause in females.
• The GI tract is a common site of bleeding. Common causes include hemorrhoids, salicylate ingestion, peptic ulcer disease, hiatal hernia, diverticulosis, neoplastic disease, and ulcerative colitis.
• Rare causes include hookworm, cows’ milk allergy in infants, Meckel diverticulum, schistosomiasis, trichuriasis, and hereditary hemorrhagic telangiectasia. Rare sources of blood loss from other sites include pulmonary bleeding (seen in idiopathic pulmonary hemosiderosis and Goodpasture
Nutrient deficiency or depletion

Iron deficiency anemia

- The most common cause of anemia worldwide. It includes a range of underlying causes. Approximately 4% of women in the US between the ages of 20 and 49 years have been estimated to be iron deficient. The formation of the heme moiety in hemoglobin, myoglobin, and cytochrome requires iron; inadequate intake or absorption of iron, or excessive iron loss, leads to a microcytic anemia.
- Meat provides the main source of heme iron, and iron deficiency is common in geographic regions where meat is sparse and there is poor dietary iron intake. There is a strong relationship between pica (a medical disorder in which children develop an appetite for non-nutritive substances) and iron deficiency.
- Gradual prolonged bleeding due to any cause produces iron depletion, because two-thirds of the total body iron is contained in circulating Hb.
- Iron malabsorption occurs due to achlorhydria, gastric surgery, destruction of small bowel absorptive area in chronic diseases such as celiac disease, or following extensive resection of the proximal small bowel.
- Runner’s anemia is caused by volume expansion accompanied by increased destruction of RBCs due to repetitive impact of the foot on the ground.
- Hemoglobinuria (iron loss in the urine) is rare. The usual cause is paroxysmal nocturnal hemoglobinuria, but hemoglobinuria can occur following rapid intravascular hemolysis of any cause.
- Pregnancy increases physiologic demand on iron, which is needed for fetal brain and placental development.

Vitamin B12 deficiency

- Vitamin B12 is an essential cofactor in DNA synthesis, which is obtained only from the diet or by supplementation. Dietary sources include animal and dairy products such as meat, poultry, milk, and eggs. Deficiency produces neurologic disorders and a megaloblastic anemia.
- Causes include decreased dietary intake (e.g., chronic malnutrition, alcohol abuse, strict vegan diets), diminished breakdown of dietary vitamin B12 (due to pernicious anemia, previous gastric or intestinal surgery, atrophic gastritis), or malabsorption (gastric malabsorption, Crohn disease, celiac disease, bacterial overgrowth). One systematic review concluded that there is no clear evidence linking anemia to subnormal B12 levels in the geriatric population.

Folate deficiency

- Folate is an essential cofactor in DNA synthesis, which is obtained only from the diet or by supplementation. Dietary sources include green leafy vegetables, citrus fruits, and animal products. Deficiency produces a range of signs, including a swollen, red, painful tongue; angular stomatitis; patchy hyperpigmentation of the skin and mucous membranes; a persistent mild pyrexia (in the absence of infection); and a megaloblastic anemia.
- Common causes include decreased dietary intake (e.g., chronic malnutrition, alcohol abuse, dietary restriction of protein intake), impaired absorption (achlorhydria, celiac disease, tropical sprue, zinc
deficiency, bacterial overgrowth), and increased folate requirement (infancy, pregnancy, lactation, malignancy).

- Patients with vitamin B12 deficiency can have excessive renal folate excretion. Similarly, chronic alcohol abuse can lead to excessive biliary folate excretion.
- Rarely, hypothyroidism and congenital enzyme deficiencies may impair folate metabolism.

Generalized malnutrition

- Often causes iron deficiency. Patients often have associated vitamin B12 and/or folate deficiency, in which case the resulting anemia is normocytic. Associated copper deficiency is rare, but should be considered in patients on prolonged total parenteral nutrition (TPN).

**Acquired bone marrow disease**

**Myelodysplastic syndrome**[19]

- A heterogeneous group of clonal stem cell disorders. Uncontrolled proliferation and clonal expansion of neoplastic multipotential hematopoietic stem cells compromise the production of normal cells, producing a range of cytopenias.
- Usually due to acquired chromosomal abnormalities, but can be caused by chemotherapy or radiation therapy.
- The anemia is a nonmegaloblastic macrocytic anemia, but the peripheral blood smear may show hypersegmented neutrophils similar to those seen in megaloblastic macrocytic anemias. A normal random distribution of red cell width (RDW) in the setting of macrocytic anemia in an older adult should raise this suspicion.

**Leukemias**

- Acute lymphocytic leukemia, acute myelogenous leukemia, and chronic myelogenous leukemia are caused by the uncontrolled proliferation and clonal expansion of abnormal progenitor cells. These diseases affect progenitor cells at different stages of the differentiation process, but all cause anemia by compromising the production of normal RBCs.

**Infiltration of the bone marrow by secondary malignancy**

- Metastasis of solid tumors to the bone marrow can cause anemia by infiltration of the marrow space. Any tumor can metastasize to the bone marrow, but the most commonly seen are neuroblastoma in children, and breast, prostate, and lung cancer in adults. Metastasis to the bone marrow is a poor prognostic sign.

**Aplastic anemia (AA)**[20] [21]

- A disorder of stem cell failure, leading to pancytopenia in the absence of splenomegaly.
- Can be due to an inherited bone marrow failure syndrome or acquired (induced by a variety of disorders, e.g., autoimmune or toxic) where immune mechanisms with local activation of interferon gamma may be a common etiologic pathway.
- Affected patients typically present with recurrent infections due to neutropenia, bleeding episodes due to thrombocytopenia, and, less often, fatigue due to anemia.
- Toxic causes include benzene, dipyrone, chloramphenicol, penicillamine, and gold.
• Patients with paroxysmal nocturnal hemoglobinuria can develop aplastic anemia, although the mechanism is not known.

• Definitive diagnosis is established following bone marrow aspiration and biopsy. In AA, characteristic findings include:[20]
  • Profoundly hypocellular marrow with a decrease in all elements; marrow space is composed of fat and marrow stroma
  • Residual hematopoietic cells that are morphologically normal
  • The absence of malignant infiltrates or fibrosis
  • Hematopoiesis is nonmegaloblastic.

Pure red cell aplasia

• Caused by congenital or acquired impairment of erythroid progenitor cells. Acquired forms can be self-limited or chronic.
• Self-limited acquired disease can be caused by infections or medications. The most common infectious cause is parvovirus B19. Other infectious causes include infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps.
• Medications exert a toxic effect on erythroid progenitor cells that is reversible once the medication is discontinued. Examples include antiepileptic medications (phenytoin, carbamazepine, valproate sodium), azathioprine, chloramphenicol (which can also cause aplastic anemia), sulfonamides, isoniazid, and procainamide.
• Chronic acquired disease is caused by autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polyarteritis nodosa, scleroderma), persistent infection (persistent parvovirus B19 infection in immunosuppressed patients, chronic active hepatitis), and thymomas.
• Congenital forms are produced by in-utero damage of erythroid progenitor cells. The cause is unknown.
• Autoimmune diseases can also cause autoimmune hemolytic anemia.

Toxin exposure

Drugs

• Certain drugs may produce immune-mediated or direct RBC hemolysis; interfere directly with DNA synthesis; impair the absorption, metabolism, or action of important DNA synthesis cofactors; or have a toxic effect on progenitor cells in the bone marrow.
• A wide range of drugs are known to cause hemolytic anemia. Common examples include penicillin, methyldopa, levodopa, quinidines, cephalosporins, and some non-steroidal anti-inflammatory drugs (NSAIDs).
• Drugs that directly interfere with DNA synthesis include purine analogs (6-mercaptopurine, 6-thioguanine, acyclovir), pyrimidine analogs (5-fluorouracil, 5-azacytidine, zidovudine), and ribonucleotide reductase inhibitors (hydroxyurea, cytarabine arabinoside).
• Antifolates act by impairing folic acid function, and include methotrexate and trimethoprim. Anticonvulsants (phenytoin, phenobarbital, primidone) interfere with folate absorption. Other drugs that can decrease folate levels include oral contraceptives and cycloserine.
• Drugs that interfere with vitamin B12 metabolism include p-aminosalicylic acid, metformin, colchicine, neomycin, and biguanides.
• Drugs and chemicals that produce a toxic effect on a range of progenitor cells, producing aplastic anemia, include benzene, chloramphenicol, penicillamine, and gold.
• Drugs that produce a toxic effect on erythroid progenitor cells, producing pure red cell aplasia, include antiepileptic medications (phenytoin, carbamazepine, valproate sodium), azathioprine, chloramphenicol (which can also cause aplastic anemia), sulfonamides, isoniazid, and procainamide.
• Drugs that inhibit erythroid stimulation and suppress erythropoietin production include ACE inhibitors and angiotensin-II receptor blockers.[22]

Radiation exposure

• Radiation exposure can produce a pancytopenia.

Lead toxicity

• Occurs after occupational or home exposure to lead. Anemia can occur because lead competes with zinc, an important cofactor in heme synthesis. Some patients also have a concurrent iron deficiency anemia.

Alcohol abuse

• Long-term alcohol intake directly suppresses the bone marrow, independent of any concurrent liver disease or vitamin deficiency. The effect resolves only after months of abstinence, and may persist even after normalization of vitamin B12 and folate levels.

**Chronic systemic disease**

Anemia of chronic disease[6] [23]

• Can be a mild hypoproliferative normocytic anemia or, in severe cases, a microcytic anemia when coexisting with iron deficiency anemia. It is caused by chronic inflammation. Proinflammatory cytokines, especially interleukin-6 (IL-6), trigger a cascade of events, mediated via upregulation of hepcidin, that decrease RBC production (by lowering serum iron and erythropoietin levels) and increase RBC destruction (by stimulating erythrophagocytosis and oxygen free radical formation).[24]
• Common underlying processes include infection, neoplasms, autoimmune reactions, and injury to tissue from trauma or major surgery.

Chronic kidney disease[25]

• Produces a normocytic or microcytic anemia. The etiology is complex and multifactorial. The main cause is decreased erythropoietin production, leading to decreased RBC production and a hypoproliferative normocytic anemia. Inhibitors of erythropoiesis accumulate, further exacerbating the effects of decreased erythropoietin. Serum ferritin may be elevated in chronic kidney disease, but patients should still receive concurrent iron supplementation with erythropoietin-stimulating agent (ESA) therapy as long as serum ferritin is <500 micrograms/L.[26]
• Other causes of anemia may also be present. Secondary hyperparathyroidism exacerbates anemia in patients with renal failure, but the mechanism is unclear. Concurrent hyperparathyroidism should also be addressed, as treatment improves the management of anemia in this setting.[26] Chronic blood loss, inflammation, and nutritional deficiency cause an iron deficiency anemia (which would be microcytic rather than normocytic). Patients often need to reduce their protein intake, which leads to decreased meat in the diet and poor iron intake. Poor iron absorption may also occur.
therapy and chronic inflammation can cause functional iron deficiency, produced by an inability to mobilize iron stores effectively.

Chronic liver disease

- A mild to moderate nonmegaloblastic macrocytic anemia is a common feature of a range of liver diseases, and is produced by a combination of intravascular dilution due to volume overload, increased RBC destruction, and impaired bone marrow compensatory responses.

Hypothyroidism

- Causes a mild hypoproliferative normocytic anemia due to the loss of the stimulatory effect of thyroid hormones on erythropoiesis.

Immune reactions

Autoimmune hemolytic anemia[27] [28]

- RBCs are attacked by autoantibodies and targeted for extravascular destruction. This usually occurs either as part of other autoimmune conditions (e.g., systemic lupus erythematosus, rheumatoid arthritis, or scleroderma) or in relation to a lymphoproliferative disorder (usually non-Hodgkin lymphoma or chronic lymphocytic leukemia).
- Autoimmune diseases can also cause pure red cell aplasia.

Alloimmune hemolytic anemia

- Can be caused by transfusion reactions, usually due to ABO incompatibility.

Infections

A range of infections can produce a hemolytic anemia, including cytomegalovirus, infectious mononucleosis, and toxoplasmosis. Leishmaniasis produces combined RBC hemolysis, bone marrow suppression, and blood loss.

Causes of pure red cell aplasia include parvovirus B19, infectious mononucleosis, viral hepatitis, malaria,[29] respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps.

Genetic disorders

Thalassemias[30] [31]

- Hemolytic anemias. A group of autosomal-recessive genetic conditions that result in decreased or absent production of the alpha-globin (alpha-thalassemia) or beta-globin (beta-thalassemia) chains in the Hb molecule. The decreased or absent globin production results in impairment of erythropoiesis. Increased RBC destruction occurs, producing hemolytic anemia.
- Alpha-thalassemia has at least four distinct forms: silent carrier (one affected alpha-globin gene), which does not cause anemia; alpha-thalassemia trait (two affected alpha-globin genes); Hb H disease (typically three affected alpha-globin genes); and Hb Bart hydrops fetalis syndrome (typically deletion of all four alpha-globin genes), which is incompatible with life. Polymerase chain reaction (PCR) DNA testing and Southern blot analysis may be used to determine the specific defect in alpha-thalassemia trait.[32]
Evaluation of anemia

Overview

• Beta-thalassemia is classified as silent carrier, beta-thalassemia minor, beta-thalassemia intermedia, or beta-thalassemia major, depending on the clinical and hematological features. Disease severity depends on the underlying mutation, and ranges from asymptomatic (in silent carriers and beta-thalassemia minor) to a severe transfusion-dependent anemia with skeletal changes (beta-thalassemia major). Note that in the presence of iron deficiency, a normal HbA2 does not exclude beta-thalassemia trait. Genetic testing is not typically performed as increases in hemoglobin F are readily seen on electrophoresis.

Sickle cell anemia[30]

• A hemolytic anemia caused by an autosomal-recessive single gene defect in the beta chain of Hb (HbA), which results in sickle cell Hb. RBCs containing sickle cell Hb become rigid and are distorted into a crescent shape.
• Patients are prone to episodes of vaso-occlusion due to the rigid, deformed RBCs, and to a prothrombotic state created by the accompanying leukocytosis, which increases cytokine release. Persistent pain in the abdomen, chest, or skeleton and dactylitis are the key presenting symptoms.

Hereditary spherocytosis

• A hemolytic anemia caused by an autosomal-dominant inherited abnormality of RBCs that produces defects in the skeletal proteins of the red cell membrane. As a result, RBCs lose their biconcave structure and become spherical (spherocytes). Spherocytes are fragile, and are selectively removed and destroyed by the spleen. Increased RBC destruction leads to anemia with hyperbilirubinemia and splenomegaly.
• Disease severity ranges from asymptomatic to a transfusion-dependent anemia with jaundice, depending on the severity of the underlying membrane defect.

Glucose-6-phosphate dehydrogenase (G6PD) deficiency[33]

• An inherited (X-linked) hemolytic anemia due to an enzyme deficiency that is common among populations originating from parts of the world where malaria is or was common, such as sub-Saharan Africa, Asia, the Mediterranean region, and the Middle East.
• G6PD catalyzes a reaction that is linked to the generation of reduced glutathione, a key antioxidant defense of the cell. Deficiency of the enzyme renders cells vulnerable to oxidant damage toward the end of their lifespan. RBCs rely solely on reduced glutathione as an antioxidant defense, so deficiency of G6PD increases RBC destruction.
• The severity of the disease varies, depending on the severity of the underlying mutation. Most patients are asymptomatic. Symptomatic disease produces episodes of acute hemolysis, with pallor and jaundice, following exposure to oxidant stress. Triggers include fava beans (favism), sulfa drugs, aspirin, nitrofurantoin, naphthalene, and febrile illness. The resulting hemolysis is usually self-limited. Life-threatening symptoms are more common with the Mediterranean variant.

Congenital bone marrow failure syndromes

• Fanconi anemia is the most common. It is usually autosomal recessive, but can also be X-linked. Mutations in 13 genes have been identified. The genes code for proteins that form a nuclear complex involved in the DNA damage response. However, the precise mechanisms by which the mutations produce bone marrow failure are not known.
• Dyskeratosis congenita is characterized by the triad of abnormal nails, reticulated skin rash, and leukoplakia. X-linked, autosomal-dominant, and autosomal-recessive inheritance patterns have been
observed. The genetic defects all decrease telomerase function. Telomeres maintain chromosomal stability, and the bone marrow is heavily dependent on telomere preservation to support its high rate of cell proliferation. Loss of telomerase produces bone marrow failure.

- Shwachman-Diamond syndrome is a rare autosomal-recessive disease that produces exocrine pancreatic dysfunction, anemia, neutropenia (which can be intermittent), and skeletal abnormalities. About 90% of patients harbor mutations in a gene known as the SBDS gene, but the relationship of the mutations to bone marrow failure is not understood.

**Microvascular disease**

Hemolytic uremic syndrome (HUS)[34]

- Damage to the endothelium of the glomerular bed produces hemolytic anemia (due to fragmentation and shearing of RBCs), thrombocytopenia (due to platelet consumption), and nephropathy.
- Causes include verotoxins, produced by *Escherichia coli*; neuraminidase, produced by streptococcal species; inherited defects in proteins that control complement; and drugs (cyclosporine and some chemotherapy agents).

Disseminated intravascular coagulation (DIC)[34] [35]

- An acquired syndrome produced by activation of coagulation pathways, resulting in the formation of intravascular thrombi and the depletion of platelets and coagulation factors.
- DIC can be triggered by major trauma; burns; organ failure (pancreatitis, acute liver failure); sepsis[36] or severe infection; severe obstetric disorders (amniotic fluid embolism, eclampsia, abruptio placentae, retained dead fetus syndrome); malignancies (acute myelocytic leukemia or metastatic mucin-secreting adenocarcinoma); major vascular disorders (hemangiomas, large aortic aneurysms); and severe toxic or immunologic reactions.
- A hemolytic anemia is produced by fragmentation and shearing of RBCs against clots in the small vessels.

Thrombotic thrombocytopenic purpura (TTP)[34] [37]

- A clinical syndrome of microangiopathic hemolytic anemia and thrombocytopenic purpura.
- Believed to be due to the production of abnormally large von Willebrand factor (vWF) multimers. The abnormal vWF triggers aggregation of circulating platelets at sites of high intravascular shear stress, which in turn results in thrombi in the microvasculature system.
- A hemolytic anemia is produced by fragmentation and shearing of RBCs against clots in the small vessels. Thrombocytopenia is produced by excessive consumption of platelets; purpura and other signs of bleeding appear in a small proportion of patients. Thrombus formation in the microvasculature also produces severe central nervous system (CNS) symptoms and renal disease.

Hemangiomas[34]

- Vascular tumors that occur as a result of abnormal angiogenesis and overproliferation of blood vessels. These range from obvious superficial lesions to internal organ hemangiomas.
- A local consumptive coagulopathy (Kasabach-Merritt syndrome) can occur as a complication, leading to thrombus formation and thrombocytopenia. Shearing and fragmentation of RBCs against the clots in the small vessels of the hemangiomas can lead to a hemolytic anemia.
- Kasabach-Merritt syndrome can also produce DIC in severe cases.

Malignant hypertension
• A hypertensive emergency with systolic BP >210 mmHg and diastolic BP >130 mmHg, associated with rapid deterioration of vital organ function. Common causes include untreated essential hypertension, renal disease, eclampsia, use of sympathomimetic drugs, and use of monoamine oxidase inhibitors. The disease is more common in older people, males, and those of black ethnicity.
• Causes endothelial injury and endothelial fibrin deposition. Mechanical RBC shearing and fragmentation, resulting from high pressures and fibrin in the small vessels, produces hemolytic anemia.

Prosthetic valves and surfaces[38]

• The shear stresses and turbulence created by the foreign surface cause shearing and fragmentation of RBCs. Improved prosthetics have reduced the incidence of this complication, and the anemia, if it occurs, is usually mild.

Other causes

Pregnancy[39]

• Anemia in pregnancy may be due to a dilutional effect, as the plasma volume expands out of proportion to the RBC mass. To account for this effect, anemia in pregnancy is defined as an Hb <10g/dL. Iron deficiency is the cause in 95% of cases, due to an increase in demand for iron, and one third of women will have either iron deficiency or folate deficiency by the third trimester.[40]
• Despite being an important problem in pregnancy with effective treatment available, there is a lack of high-quality evidence on the benefits of a national screening program for anemia in pregnancy in terms of reduced maternal and infant morbidity.[41]

Thermal burns

• Patients with burns affecting more than 10% of the body's surface area can develop a hemolytic anemia due to intravascular hemolysis of RBCs (at the site of the burn and systemically), loss of red cell mass due to thrombus formation, and damage to RBCs from systemically released proteases and oxygen free radicals.[42]

Hospital-acquired anemia

• New-onset anemia in hospitalized patients with previously normal hemoglobin. Hospital-acquired anemia (HAA) is typically related to increased phlebotomy and iatrogenic blood loss from invasive procedures or hemodilution. Acute inflammatory response to illness decreases compensatory erythropoiesis. HAA is associated with increased morbidity and length of hospital stay.[43]
**Urgent considerations**

(See **Differential diagnosis** for more details)

Anemia is life threatening if there is more than 40% loss of total body volume. These patients should receive packed red blood cell (RBC) transfusions for stabilization as soon as possible, especially if there are underlying cardiac or pulmonary comorbidities. A reticulocyte count, ferritin, and peripheral smear should be obtained before transfusion, if possible, as this makes subsequent workup more accurate. Dilutional, or consumptive, coagulopathy from tissue injury may result from the decrease of platelets and coagulation factors (factor V, factor VIII, and fibrinogen) in massive transfusions and must be corrected by the addition of these factors.

Generally, healthy individuals tolerate extreme anemia well, with cardiovascular status being the major limiting factor. The landmark TRICC study showed that, in hemodynamically stable patients without active bleeding, Hb levels between 7 and 9 g/dL were well tolerated with equivalent or lower mortality/morbidity outcomes compared with a liberal transfusion trigger of <10 g/dL.[44] It is generally recommended that determination of transfusion requirements are based upon severity of illness parameters rather than arbitrary Hb levels. Clinical guidelines from the AABB (formerly known as the American Association of Blood Banks) suggest a restrictive transfusion threshold of 7 g/dL in hospitalized hemodynamically stable patients, and 8 g/dL in those undergoing orthopedic or cardiac surgeries, or with pre-existing cardiovascular disease, unless there is an underlying acute coronary syndrome, severe thrombocytopenia, or chronic transfusion dependence.[45] Transfusion thresholds in ischemic coronary artery disease and resuscitation of septic shock remain controversial.

**Acute hemorrhage**

Causes of acute hemorrhage include trauma (such as gunshot wounds, major fractures, and crush injuries), acute gastrointestinal (GI) bleeding, rupture of a vascular aneurysm (especially abdominal aortic aneurysm), and recent surgery. Rapid evaluation, identification, and control of bleeding are essential before any further workup. Dilution does not occur acutely, so hemoglobin (Hb) and hematocrit levels do not provide an accurate reflection of the degree of blood loss and anemia. Perfusion to critical organs must be maintained through early goal-directed therapy, including crystalloid volume resuscitation (using 2-4 times the estimated volume of blood loss), blood pressure support, and tissue perfusion.

A meta-analysis concluded that the use of hydroxyethyl starch (HES) solutions to decrease volume overload in large volume resuscitations was associated with increased risk of acute kidney injury and death.[46] HES solutions for infusion have been significantly restricted across the European Union and are contraindicated in critically ill patients and those with sepsis or renal impairment. These measures were introduced to protect patients from the increased risk of kidney injury and death associated with HES.[47] The restrictions followed a January 2018 review by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee, which recommended that HES should be suspended from the market because, despite initial warnings, it was still being used in these at-risk patient populations.[48]

Crossmatched blood (or O negative, if crossmatch is unavailable) should be given as soon as possible.

In addition, bleeding following major trauma requires coagulation support and monitoring, and the appropriate use of local hemostatic measures, tourniquets, calcium, desmopressin, and consideration for tranexamic acid.[49] [50]
Tranexamic acid has been shown to reduce mortality in trauma patients with hemorrhage when given within 3 hours of injury, and should be administered as soon as possible in people with acute severe hemorrhage due to trauma.[50] [51] A meta-analysis of data from over 40,000 patients with traumatic bleeding or postpartum hemorrhage found that delays in administration of tranexamic acid were associated with reduced survival (survival benefit decreasing by about 10% for every 15 minutes of treatment delay until 3 hours, after which there was no benefit).[52]

Definitive management of acute hemorrhage depends on the underlying cause, but usually requires surgery.

**Microangiopathic hemolytic anemias**

Hemolytic uremic syndrome, disseminated intravascular coagulation (DIC), and thrombotic thrombocytopenic purpura (TTP) produce life-threatening rapid hemolysis.[34] The underlying cause must be quickly assessed and treatment tailored accordingly to minimize end-organ damage and the likelihood of death. Treatment of DIC is aimed at the underlying cause. Corticosteroids and immunosuppression should be commenced if hemolytic uremic syndrome or TTP are suspected. Intravenous immunoglobulins (IVIG) or urgent plasmapheresis may be necessary for rapid clearance of autoantibodies. Antibody screening should be done prior to blood transfusion. Antibody-free blood products should be used to prevent additional alloimmune hemolysis.

**Malignant hypertension**

This condition is characterized by very high blood pressure in association with bilateral retinal changes, including exudates and hemorrhages, with or without papilledema. The most common symptoms include headaches (often occipital), visual disturbances, chest pain, dyspnea, and neurologic deficits. Results include cerebral infarction or hemorrhage, transient blindness or paralyses, seizures, stupor, or coma. The initial goal of therapy in hypertensive emergencies is to reduce mean arterial BP by no more than 25% (within minutes to 1 hour), then, if stable, to 160/100 to 110 mmHg within the next 2 to 6 hours. Labetalol is the agent of choice.

**Sickle cell vaso-occlusive crisis**

This is a common complication of sickle cell anemia, which presents with severe pain precipitated by cold, dehydration, infection, or ischemia (often due to strenuous exercise). The crisis may give rise to skeletal pain due to bone infarction or avascular necrosis, especially of the hip or shoulder. Other presentations include acute abdominal pain and acute chest syndrome, which is clinically indistinguishable from pneumonia. Treatment involves adequate analgesia, hydration with oral or intravenous fluids, oxygen, and treatment of the underlying cause.

**Combined vitamin B12 and folate deficiency**

If a patient has folate deficiency, it is essential to check for and correct any coexisting vitamin B12 deficiency before giving folate. Folate is believed to exacerbate inhibition of vitamin B12-containing enzymes, thereby worsening vitamin B12-associated neuropathy and subacute combined degeneration of the spinal cord.[53] If vitamin B12 levels are normal, methylmalonic acid levels should be checked to definitively exclude vitamin B12 deficiency, as this is a more sensitive test. An elevated serum methylmalonic acid indicates vitamin B12 deficiency, unless there is a history of renal insufficiency, where levels may be artificially elevated due to inadequate renal clearance.
Leukemias or aplastic anemia

Usually present with a normocytic anemia and coexisting neutropenia and thrombocytopenia. Circulating blasts may be reported on peripheral smear. If these conditions are suspected, an immediate hematology consultation is required for bone marrow biopsy and flow cytometry studies. If the anemia requires transfusion, only leukoreduced, irradiated blood products should be used, as these patients may be transplant candidates.[20] [54]

Decreased physiologic reserve

It is important to identify patients with decreased physiologic reserve, such as those with coexisting cardiovascular or pulmonary disease, as these patients are less able to tolerate anemia and have more severe symptoms.
Step-by-step diagnostic approach

Patients may present in several ways. The urgency with which anemia is evaluated depends on the severity at presentation. Patients with an acute severe hemorrhage present with hypovolemia and symptoms and signs of the underlying cause.[9]

Initial assessment

Evaluation should include identification of any source of active or acute bleeding.

• The initial goal in a patient with acute bleeding is rapid hemodynamic stabilization. Up to 30% of total blood volume (TBV) may be lost before clinical manifestations are appreciated at rest. Key signs include hypotension, pallor, cold clammy skin, a thready pulse, tachycardia, dyspnea or air hunger, altered mental status, confusion, and coma. Flat neck veins when supine indicate at least 30% to 40% total body volume loss. All orifices should be examined for bleeding. The mechanism and site of any trauma should also be determined.

• History of prior episodes of gastrointestinal (GI) bleeding, gastritis, inflammatory bowel disease, non-steroidal anti-inflammatory drug (NSAID) or corticosteroid use, alcohol use, or cirrhosis should prompt suspicion of GI bleeding. NSAIDs and corticosteroids are associated with peptic ulcer disease. Alcohol use and cirrhosis are associated with coagulation disorders and esophageal varices. A lower GI bleed presents with fresh red rectal bleeding (hematochezia). Melena and/or hematemesis with or without abdominal pain indicate an upper GI bleed. Sudden tearing pain should prompt suspicion of a ruptured vascular aneurysm; the pain may be spontaneous, or precipitated by trauma or by cocaine or amphetamine use. Loss of consciousness may occur if a major vessel is involved. A history of hypertension or collagen disorders may also be present. A wide pulse pressure suggests a ruptured aneurysm. A pulsatile abdominal mass may indicate an abdominal aortic aneurysm. Flank or abdominal ecchymosis suggests intra-abdominal bleeding.

• If there is a history of recent surgery, ongoing blood loss at the surgical site must be considered. A detailed history of the pre-, intra-, and postoperative course should be obtained, including any complications noted during the operation. A history of bleeding disorders or excessive bruising may indicate an underlying coagulation disorder. Any antibiotics administered should be noted, as some can produce a decrease in platelet levels.

• Jaundice, especially accompanied by fatigue and pallor, with episodic dark urine suggests a hemolytic process, especially with recent infection, new medications, or history of malignancy.

• Tests are guided by the history and exam and the suspected etiology of active bleeding. These may include the following procedures.

• CBC, which shows a normocytic anemia with a high reticulocyte count (>2%) and a normal or decreased hematocrit (Hct). Dilution does not occur initially, so hemoglobin (Hb) and Hct do not accurately reflect the true severity of the anemia.

• Prothrombin time/activated partial prothrombin time, which is usually normal, but tested to identify patients with decreased coagulation due to anticoagulants, underlying defects in hemostasis, or consumptive coagulopathy. In patients with upper GI bleeding, elevated BUN may be seen, even in absence of renal issues, due to digestion of blood, which is a source of urea.

• Abdominal ultrasound scan: allows rapid identification of intra-abdominal bleeding and indicated if abdominal trauma or a ruptured abdominal aortic aneurysm are suspected.
• Joint x-rays, indicated in patients with trauma to identify fractures. Long-bone fractures can be a significant source of bleeding.

• Upper GI endoscopy, required to identify sources of upper GI bleeding. Nasogastric lavage with saline is no longer routinely recommended in initial management unless it is done to facilitate subsequent direct visualization for endoscopic procedures.[55] [56] [57]

• Colonoscopy, required to identify sources of lower GI bleeding. A retrospective review of the medical records of a sample of patients with colorectal cancer found that anemia was one of the commonest symptoms/signs in those considered to have had a missed diagnostic opportunity (a clinical encounter where, even in the presence of presumptive symptoms of colorectal cancer, the colorectal cancer diagnostic process was not started).[58]

• Capsule endoscopy may have diagnostic, but not therapeutic, utility in situations where there is concern for GI bleeding in inaccessible areas such as the small bowel.[59]

• Exploratory laparotomy, which may be required in patients with abdominal bleeding to identify the source, especially if there is a history of abdominal trauma or previous abdominal surgery.

• Computed tomography (CT) scanning of the body region affected by trauma or aneurysm rupture, which will identify internal injuries or the extent and nature of the aneurysm, and identify sources of bleeding.

Many anemic patients with no acute or active bleeding are asymptomatic, and the anemia is only noted on a CBC taken as part of the assessment of an unrelated condition. Symptoms of anemia may include pallor, fatigue, weakness, decreased exercise tolerance, and shortness of breath with exercise. A CBC should be ordered if these symptoms are present. Jaundice is an additional sign seen in patients with hemolytic anemias.

The first step in diagnosis is to identify the type of anemia that is present, using the results of the CBC. Due to their relative reproducibility, mean corpuscular volume (MCV) and red cell width (RDW) are the most useful components in the initial classification of most anemias.

The anemia may be:

• Microcytic (MCV <80 femtoliters [fL]): serum iron studies should be performed.[60]

• Normocytic (MCV 80-100 femtoliters [fL]): the reticulocyte count should be examined to determine if the anemia is hypoproliferative (<2%) or hyperproliferative (>2%).

• Macrocytic (MCV >100 femtoliters [fL]): the peripheral smear should be examined for megaloblasts and hypersegmented neutrophils. If these cells are present, the anemia is megaloblastic. If they are absent, the anemia is nonmegaloblastic.
**Microcytic anemia: abnormal serum iron studies**

A low serum iron, an elevated total iron-binding capacity (TIBC), and a low ferritin indicate iron deficiency anemia.

- Iron deficiency produces an associated reactive thrombocytosis that provides an additional clue. Iron deficiency is not a diagnosis and requires further investigation to elucidate the cause.\[13\] \[14\] \[15\]
- Diets low in meat produce iron deficiency. Generalized malnutrition often produces combined vitamin B12 and/or folate deficiency, in which case the resulting anemia is normocytic. Children may have pica.
- There may be a history of bleeding. Females may have a history of excessive menstrual losses. Coffee-ground vomiting, hematemesis, or melena indicate upper GI bleeding. NSAIDs and corticosteroids are associated with peptic ulcer disease. Alcohol use and cirrhosis are associated with coagulation disorders and esophageal varices. Fresh red rectal bleeding indicates a lower GI bleed. Rectal pain may indicate hemorrhoids, which will be seen on rectal examination. Hemoptysis may indicate Goodpasture syndrome or idiopathic pulmonary hemosiderosis. Rarely, a history of excessive blood donation or self-harm may be elicited. Patients who are avid runners may have runner’s anemia from repetitive mechanical trauma (also known as march hematuria). A history of gastric surgery, celiac disease, or extensive small bowel resection suggests malabsorption as the cause. Pregnancy is a common cause.\[20\] A history of dark-colored urine may indicate paroxysmal nocturnal hemoglobinuria.
- Signs of iron deficiency include koilonychia, angular cheilosis, glossitis, and thinning hair.
- Investigations are guided by the history and examination, and include the following.
- Fecal occult blood testing, which should be done in all patients and is positive if GI bleeding is present.
- Upper GI endoscopy, which should be performed if there is a history of upper GI bleeding or a positive fecal occult blood test. It may identify sources of an upper GI bleed (peptic ulcer disease, gastritis, esophageal varices), hiatus hernia, Meckel diverticulum, or increased gastric pH in achlorhydria.
- Following negative endoscopy in the setting of persistent iron deficiency anemia, *Helicobacter pylori* may be considered when malignancies, B12 deficiency, and idiopathic thrombocytopenic purpura have been excluded.[61]
- Immunoglobulin A-tissue transglutaminase (IgA-tTG) test should be performed in all patients and is positive in celiac disease.
- Colonoscopy, which should be performed if there is a history of lower GI bleeding or a positive fecal occult blood test. It may reveal malignancy, diverticulosis, ulcerative colitis, or rare causes such as hereditary hemorrhagic telangiectasia; malignancy should be considered in all patients aged over 40 years with symptoms of rectal bleeding or a positive fecal occult blood test.
- Flow cytometry should be considered if there is a history of passing red urine, or red blood cell (RBC) results consistent with a hemolytic anemia. It detects decreased expression of RBC surface proteins (CD55 and CD59) and is diagnostic of paroxysmal nocturnal hemoglobinuria.
- Transvaginal ultrasound, which may reveal causes of menorrhagia including hyperplasia, dysplasia, fibroids, or polyps; malignancy should be considered in patients with menorrhagia who are over 40 years old.
- Stool microscopy, which may identify hookworm, whipworm, or *Schistosoma* eggs. This should be performed if clinical features suggest the diagnosis or there is a history of travel to endemic areas.

A low serum iron, a low total iron-binding capacity, and a low/normal ferritin suggest coexistence of anemia of chronic disease with iron deficiency.

- A history of an underlying inflammatory process (infection, neoplasms, autoimmune reactions, and injury to tissue from trauma or major surgery) is usually present. A serum erythropoietin level should be considered; the result is usually normal or mildly elevated. Hypothyroidism and vitamin C deficiency may produce a falsely low ferritin level.[62]

**Microcytic anemia: normal serum iron studies**

The most important cause to exclude is thalassemia. A family history is usually present. The disease is more common in individuals of Mediterranean, Middle Eastern, or Southeast Asian descent. The severity ranges from asymptomatic to severe transfusion-dependent symptoms.[30] [31]

The examination findings may be normal, or reveal splenomegaly, jaundice, abdominal distension, and icterus. Morphologic changes including skeletal abnormalities, a large head, chipmunk facies, and misaligned teeth are seen in beta-thalassemia intermedia and major.

Distinct features on the CBC that suggest the diagnosis include a marked decrease in MCV (usually close to 70 femtoliters [fL]) with a low mean corpuscular Hb, target cells on the peripheral smear, and an elevated reticulocyte count (>2%). A Mentzer index (MCV/RBC) <13 is suggestive of thalassemia, and an index >14 suggests iron deficiency.[63] In a meta-analysis of various mathematical indices used to distinguish between iron deficiency anemia and thalassemias, the microcytic to hypochromic RBC ratio (M/H) showed the best
performance, although the authors concluded that none were high enough to make definitive diagnoses.[64]

Initial workup for thalassemia relies on Hb electrophoresis. The presence of Hb H, Hb Bart, and concomitant hemoglobinopathies (Hb E, Hb S, Hb C, Hb D) is suggestive of alpha-thalassemia, although more accurate diagnosis relies on DNA genotyping. A high HbF with minimal or absent HbA and an elevated HbA2 is suggestive of beta-thalassemia.

**Normocytic anemia: hypoproliferative**

Potential diagnoses

- These include disorders that decrease RBC production.
- Hematological malignancies and aplastic anemia[20] are the most important diagnoses to exclude, and are usually associated with multiple cytopenias.
- An isolated anemia is usually due to pure red cell aplasia, which may be self-limited or persistent. Chronic kidney disease[25] or hypothyroidism can also cause an isolated anemia.
- Secondary hyperparathyroidism exacerbates the anemia of chronic kidney disease.

History

- Symptoms of bleeding, easy bruising, night sweats, or weight loss suggest hematologic malignancy or aplastic anemia. Parvovirus infection, infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, and mumps can result in a self-limited pure red cell aplasia, and these should be excluded.
- Antiepileptic medications (phenytoin, carbamazepine, valproate sodium), azathioprine, sulfonamides, isoniazid, and procainamide cause pure red cell aplasia. Benzene, penicillamine, and gold can cause aplastic anemia. Chloramphenicol can cause either aplastic anemia or pure red cell aplasia. Chemotherapy causes pancytopenia.[65] Discontinuation of causative medications leads to resolution of the anemia.
- Radiation therapy, especially to pelvic or sternal areas, can cause pancytopenia.
- A history of immunosuppression or chronic hepatitis suggests persistent pure red cell aplasia. There may be a history or features of chronic kidney disease or hypothyroidism.

Exam

- Ecchymoses or petechiae due to thrombocytopenia suggest hematologic malignancy, myelodysplastic syndrome, or aplastic anemia. Lymphadenopathy or fever suggest malignancy or infections (e.g., infectious mononucleosis). Splenomegaly may be seen in hematologic malignancies.
- Clinical features of systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, polyarteritis nodosa, or scleroderma resulting in persistent pure red cell aplasia may be present. Abnormal lung exam (if lung cancer is the primary cancer) or a breast mass (if breast cancer is the primary) may be present.
- A positive Trousseau sign or Chvostek sign in patients with chronic kidney disease indicates hypocalcemia, probably due to associated secondary hyperparathyroidism.

Initial investigations

- Should be guided by the history and examination findings.
- CBC may show an associated cytopenia and characteristic changes specific to a hematological malignancy. A pancytopenia suggests aplastic anemia, or may be due to chemotherapy or radiation therapy. An isolated anemia suggests pure red cell aplasia or anemia due to chronic kidney disease.
Evaluation of anemia

**Diagnosis**

- Bone marrow biopsy is required for the definitive diagnosis of acute leukemia (acute lymphocytic leukemia, acute myelogenous leukemia), chronic myelogenous leukemia (CML), aplastic anemia, or bone marrow metastases.
- Antiparvovirus antibodies are positive in parvovirus infection, the most common infectious cause of pure red cell aplasia.

**Other tests to consider**

- Hepatitis serology, to exclude acute or chronic active hepatitis
- Monospot test or Epstein-Barr virus (EBV) IgM, to exclude infectious mononucleosis
- Thick and thin peripheral smear, to exclude malaria if history and clinical findings suggest the diagnosis
- Thyroid function tests; thyroid-stimulating hormone (TSH) is elevated and free thyroxine (T4) reduced in hypothyroidism
- Antinuclear antibodies, which are positive in systemic lupus erythematosus or scleroderma
- Rheumatoid factor, which is positive in rheumatoid arthritis
- Serum creatine kinase (CK), which is elevated in dermatomyositis
- Chest x-ray, which may show infiltrates in atypical pneumonia or a smooth mass in thymoma
- Erythropoietin levels, which may be inappropriately decreased in patients with chronic kidney disease. Serum calcium and parathyroid hormone levels should be considered if associated secondary hyperparathyroidism is suspected.

**Normocytic anemia: hyperproliferative**

**Potential diagnoses**

- Include hemolytic anemias.
- These conditions can be caused by microangiopathic hemolytic anemias, autoimmune hemolytic anemia, drugs, infections, inherited conditions, transfusion reactions, or burns.

**History**

- Drugs that can cause hemolysis include penicillin, methyldopa, levodopa, quinidines, cephalosporins, and some NSAIDs. Cyclosporine, tacrolimus, clopidogrel, oral contraceptive pills, and some chemotherapy drugs may cause hemolytic uremic syndrome. Discontinuation of causative medications leads to resolution of the anemia.
- There may be a history suggestive of microangiopathic disease. Known triggers of disseminated intravascular coagulation (DIC) include ongoing severe infection, sepsis, malignancy, obstetric emergency, trauma, burns, envenomation, drug overdose, or any cause of endothelial damage. The presence of acute-onset neurologic symptoms, including headache, confusion, focal weakness, seizures, or coma, should prompt suspicion of thrombotic thrombocytopenic purpura (TTP). Female patients may have associated menorrhagia. Sudden-onset dizziness, headache, mental status changes, loss of sensation or motor strength, chest pain or pressure, dyspnea, or edema in a patient with known hypertension should prompt suspicion of malignant hypertension; a history of renal failure or eclampsia may also be present. An expanding vascular skin lesion in a young infant or child should prompt suspicion of a hemangioma. A history of prosthetic valve replacement may indicate hemolysis induced by the prosthesis.
- Cutaneous burns affecting more than 10% of the body surface area can cause a hemolytic anemia, or trigger DIC.
Evaluation of anemia

Diagnosis

• Infective causes include cytomegalovirus (CMV), infectious mononucleosis, toxoplasmosis, and leishmaniasis. Bloody diarrhea should prompt suspicion of *Escherichia coli* infection and hemolytic uremic syndrome.

• Patients with inherited hemolytic anemias such as sickle cell anemia, hereditary spherocytosis, or glucose-6-phosphate dehydrogenase (G6PD) deficiency may have a positive family history. Persistent pain in the skeleton, chest, or abdomen; priapism; lower-extremity skin ulcers; or an acute pneumonia-like syndrome suggest sickle cell anemia.

• There may be a previous history of autoimmune disease (e.g., systemic lupus erythematosus, rheumatoid arthritis, or scleroderma) or lymphoproliferative disorders (usually non-Hodgkin lymphoma or chronic lymphocytic leukemia), which can lead to autoimmune hemolytic anemia. Note that autoimmune diseases may also cause pure red cell aplasia, in which case the reticulocyte count would be low, with normal lactate dehydrogenase, haptoglobin, and bilirubin levels.

• Recent blood transfusion may indicate hemolysis due to a transfusion reaction.

• Occupational or home exposure to lead should prompt suspicion of lead toxicity.

Examination

• Features of microangiopathic disease: there may be purpura or ecchymoses due to bleeding. Systolic BP >210 mmHg and diastolic BP >130 mmHg indicate malignant hypertension; associated signs may include new murmurs, S3 on auscultation of the heart, jugular venous distension, rales or lower-extremity edema, oliguria or polyuria, focal neurologic signs, and hypertensive retinopathy. Cutaneous reddish-brown or violaceous vascular lesions may indicate hemangioma.[34]

• Splenomegaly is seen in hereditary spherocytosis. Clinical features of underlying autoimmune diseases may be present. Lymphadenopathy may indicate infectious mononucleosis, leukemia, lymphoma, or autoimmune disease.

Initial investigations

• The CBC and peripheral blood smear should be examined for clues to the underlying cause. A thrombocytopenia with schistocytes strongly suggests a microangiopathic hemolytic anemia. Spherocytes suggest autoimmune hemolytic anemia or hereditary spherocytosis. Hereditary spherocytosis is also associated with increased mean corpuscular Hb. Sickling of RBCs is diagnostic of sickle cell anemia.[30] Heinz bodies, eccentricocytes, or bite cells are seen in G6PD deficiency.

• If hemolytic anemia is suspected, serum lactate dehydrogenase, haptoglobin, and bilirubin should be measured. Elevated lactate dehydrogenase and bilirubin levels with a decreased haptoglobin are strongly suggestive of a hemolytic anemia. Clinical jaundice is seen once bilirubin levels rise above 2 to 4 mg/dL.

Tests to consider in suspected microangiopathic hemolytic anemias

• Serum creatinine, which may be elevated in patients with hemolytic uremic syndrome or malignant hypertension. Kidney biopsy provides a definitive diagnosis of hemolytic uremic syndrome.

• Prothrombin time and activated partial prothrombin time, which are prolonged in DIC but normal in other microangiopathic hemolytic anemias. DIC panel shows elevated D-dimers and fibrin degradation products with low fibrinogen in patients with DIC. X-rays and magnetic resonance imaging (MRI) scanning of suspected regions reveal internal hemangiomas.

Tests to consider in other hemolytic anemias

• Direct antiglobulin (Coombs) test, which is positive in autoimmune hemolytic anemia.
• Tests to identify hereditary causes. Sickle cell anemia is diagnosed on CBC. Osmotic fragility test is positive in hereditary spherocytosis; cells lyse on exposure to hypo-osmotic solution. G6PD assays identify deficiencies of the enzyme.
• Tests to identify infection. Monospot test or EBV IgM is positive in infectious mononucleosis. CMV IgM is positive in CMV infection. Double-sandwich IgM enzyme-linked immunosorbent assay (ELISA) or IgG avidity test is positive for IgM in acute toxoplasmosis. Splenic or bone marrow aspirate shows amastigotes of the parasite in leishmaniasis.
• Blood lead levels, which are elevated in lead toxicity.

**Macrocyclic anemia: megaloblastic**

Potential diagnoses

• The main causes to consider are vitamin B12 or folate deficiency, or drugs that interfere with DNA synthesis. Autoimmune thyroid disease may coexist with pernicious anemia and atrophic gastritis, which decrease B12 absorption. Therefore, screening for B12 deficiency when the etiology of hypothyroidism is thought to be autoimmune is recommended.[66]
• Discontinuation of causative medications leads to resolution of the anemia.

History

• Poor intake due to malnutrition, alcohol abuse, or strict vegan or low-protein diets can produce deficiency of vitamin B12 and/or folate.
• A history of celiac disease, tropical sprue, Crohn disease, previous gastric or intestinal surgery, or bacterial overgrowth may indicate malabsorption.
• A swollen, red, painful tongue; angular stomatitis; patchy hyperpigmentation of the skin and mucous membranes; and a persistent mild pyrexia are symptoms of folate deficiency.
• Drug history: known causative medications include purine analogs, pyrimidine analogs, reductase inhibitors, methotrexate, trimethoprim, anticonvulsants, oral contraceptives, cycloserine, p-aminosalicylic acid, metformin, colchicine, neomycin, and biguanides. Hydroxyurea, in particular, is known to cause oval macrocytosis with MCV>110 femtoliters (fL).

Initial investigations

• Serum vitamin B12 levels are decreased and serum methylmalonic acid levels are elevated in vitamin B12 deficiency. The latter is more sensitive and should be used to definitively exclude vitamin B12 deficiency. An MCV of >115 fL is typically seen in nutritional deficiency.
• Serum folate levels are low in folate deficiency. If folate levels are low, serum vitamin B12 and methylmalonic acid levels should be measured to exclude concurrent vitamin B12 deficiency before folate levels are corrected. Normal serum homocysteine levels make folate deficiency unlikely. RBC folate is a more accurate indicator of folate deficiency than serum folate level.
• Anti-intrinsic factor and parietal cell antibodies are positive in pernicious anemia.

**Macrocyclic anemia: nonmegaloblastic**

Potential diagnoses

• Causes to consider include alcohol abuse, myelodysplastic syndrome, chronic liver disease, and congenital bone marrow failure syndromes.
History

- High alcohol intake indicates alcohol-induced anemia, which usually persists for months after total abstinence. A history of chronic liver disease indicates liver disease-induced anemia.
- History of prior exposure to petroleum distillates (especially benzene), chemotherapy, or radiation therapy should prompt suspicion of myelodysplastic syndrome.
- A history of fever, chills, fatigue, weakness, recurrent infection, anorexia, night sweats, shortness of breath, and easy bruising should prompt suspicion of myelodysplastic syndrome.
- Recurrent infections in an infant should prompt suspicion of congenital bone marrow failure syndromes.

Exam

- May reveal stigmata of chronic alcoholism or chronic liver disease.
- Dyskeratosis congenita is characterized by the triad of abnormal nails, reticulated skin rash, and leukoplakia.
- Skeletal abnormalities and growth retardation are seen in Shwachman-Diamond syndrome.

Investigations

- CBC shows associated neutropenia and thrombocytopenia with macro-ovalocytes in myelodysplastic syndrome.
- Bone marrow aspiration and biopsy shows myeloblasts with immature precursors in myelodysplastic syndrome. Diagnostic features of congenital bone marrow failure syndromes are also identified.
- Cytogenetics reveal chromosomal translocations in myelodysplastic syndrome.
- Additional tests for congenital bone marrow syndromes: diepoxybutane or mitomycin-c fragility test is positive in Fanconi anemia. Genetic testing reveals underlying mutations.
## Differential diagnosis overview

### Common

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<td>Rupture of a vascular aneurysm</td>
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<td>Iron deficiency</td>
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<td>Myelodysplastic syndrome</td>
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<td>Acute lymphocytic leukemia</td>
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<td>Acute myelogenous leukemia</td>
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<td>Chronic myelogenous leukemia</td>
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<td>Hairy cell leukemia</td>
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<tr>
<td>Acquired aplastic anemia</td>
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<tr>
<td>Infiltration by secondary malignancy</td>
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<td>Pure red cell aplasia</td>
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<td>Drug toxicity</td>
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<td>Anemia of chronic disease</td>
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<td>Chronic kidney disease</td>
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<td>Chronic liver disease</td>
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<td>Pregnancy</td>
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<tr>
<td>Generalized malnutrition</td>
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<td>Cytotoxic chemotherapy</td>
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<td>Autoimmune hemolytic anemia (AIHA)</td>
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<td>Malaria</td>
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<td>Viral hepatitis</td>
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<td>Leishmaniasis</td>
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<td>Parvovirus B19 infection</td>
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<td>Infectious mononucleosis</td>
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<td>Cytomegalovirus (CMV)</td>
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<td>Sickle cell anemia</td>
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<td>Thalassemias</td>
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<td>Hereditary spherocytosis</td>
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<td>Glucose-6-phosphate dehydrogenase deficiency (G6PD)</td>
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<td>Bone marrow failure syndromes</td>
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<tr>
<td>Hemolytic uremic syndrome</td>
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<tr>
<td>Disseminated intravascular coagulation (DIC)</td>
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</table>
### Uncommon

- Thrombotic thrombocytopenic purpura
- Hemangioma
- Malignant hypertension
- Prosthetic valves and surfaces
- Cutaneous burns
## Differential diagnosis

### Common

<table>
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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of trauma (including gunshot wounds, major fractures, crush injuries); history of prior bleeding episodes; or use of anticoagulants or non-steroidal anti-inflammatory drug (NSAIDs)</td>
<td>evidence of injury (wounds, bruises, deformities), hypotension, pallor, tachycardia, dyspnea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total body volume loss</td>
<td>»CBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response, thrombocytopenia from dilutional effect of multiple transfusions</td>
<td>»diagnostic laparotomy: identification of bleeding source »CT scan of affected body region: identification of internal injuries</td>
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<td>»reticulocyte count: &gt;2%</td>
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<td>»prothrombin time/activated partial thromboplastin time: usually normal; prolonged with anticoagulants, underlying defects in hemostasis, or consumptive coagulopathy</td>
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<td>Consumptive coagulopathy may be due to repeated blood transfusions or to disseminated intravascular coagulation.</td>
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<td>»joint or spine x-rays: identification of fractures</td>
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### Acute gastrointestinal (GI) bleeding

<table>
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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
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<tbody>
<tr>
<td>history of prior episodes of GI bleeding, gastritis, peptic ulcer disease, hiatal hernia, neoplastic disease, nonsteroidal anti-inflammatory</td>
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<tr>
<td>hypotension, pallor, tachycardia, dyspnea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least</td>
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## Common

### Acute gastrointestinal (GI) bleeding

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<tr>
<td>drug (NSAID) or corticosteroid use, alcohol use, cirrhosis, anticoagulants, ulcerative colitis, diverticulosis; symptoms of rectal bleeding, melena, hematemesis, abdominal pain</td>
<td>30% to 40% total blood volume loss; ascites, hepatomegaly/ splenomegaly, cirrhotic hard liver, caput medusae, gynecomastia, melena, or bright red blood on rectal examination</td>
<td>reticulocyte count: &gt;2%</td>
<td>ultraschall of affected region: shows extent and nature of aneurysm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>prothrombin time (PTT)/ activated partial thromboplastin time: usually normal; prolonged in cirrhosis, anticoagulant therapy, or underlying defects in hemostasis; elevated BUN may be seen</td>
<td></td>
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<td></td>
<td></td>
<td>upper GI endoscopy: bleeding varices or ulcers if source is from upper GI tract</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>colonoscopy: visualization of bleeding lesion or mass</td>
<td></td>
</tr>
</tbody>
</table>

### Rupture of a vascular aneurysm

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>may be sudden tearing pain, may be accompanied by loss of consciousness if major vessel involved; history of hypertension, collagen disorders, trauma, cocaine or amphetamine use</td>
<td>hypotension, pallor, tachycardia, dyspnea/ air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total blood volume loss; wide pulse pressure or absent distal pulses; may rapidly progress to circulatory collapse and death</td>
<td>CBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response</td>
<td>chest x-ray: may show widened mediastinum in thoracic aortic aneurysm [Fig-6]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>reticulocyte count: &gt;2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ultrasonography of affected region: shows extent and nature of aneurysm Infravascular ultrasound is more accurate if patient is stable.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT scan of affected region: shows extent and nature of aneurysm</td>
<td></td>
</tr>
</tbody>
</table>
### Common

**Rupture of a vascular aneurysm**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rupture of a vascular aneurysm</td>
<td>hypotension, pallor, tachycardia, continuous bleeding from surgical wound, petechiae, purpura; severe bleeding produces dyspnea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total blood volume loss</td>
<td>CBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response</td>
<td>Spiral CT or MRI are better if patient is stable. [Fig-5]</td>
</tr>
</tbody>
</table>

**Surgery**

<table>
<thead>
<tr>
<th>History</th>
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<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recent surgery with at least moderate blood loss; history of bleeding disorders or excessive bruising; use of antibiotics</td>
<td>hypotension, pallor, tachycardia, continuous bleeding from surgical wound, petechiae, purpura; severe bleeding produces dyspnea/air hunger, altered mental status or confusion; flat neck veins when supine indicate at least 30% to 40% total blood volume loss</td>
<td>CBC: normal or decreased Hct; decreased Hb; reactive leukocytosis and thrombocytosis due to a stress response</td>
<td>Reticulocyte count: &gt;2%</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Ultrasound of affected region: shows source and extent of bleeding</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>CT scan of affected region: shows source and extent of bleeding</td>
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<tr>
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<td></td>
<td>Diagnostic laparotomy: shows source and extent of bleeding</td>
</tr>
</tbody>
</table>

**Menorrhagia**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive menstrual bleeding lasting &gt;7 days; fatigue, dyspnea on exertion, pica; use of hormone therapy, history of fibroids</td>
<td>pallor, adnexal masses or fibroids</td>
<td>CBC: chronic microcytic anemia with normal WBC; reactive thrombocytosis if iron deficient</td>
<td>Pregnancy test: negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum ferritin: &lt;15 micrograms/L if iron deficient</td>
<td>Prothrombin time/activated partial thromboplastin time: usually normal; prolonged with anticoagulants, underlying defects in hemostasis, or consumptive coagulopathy</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>Thyroid-stimulating hormone (TSH)/free thyroxine (T4): elevated TSH with low free T4 in hypothyroidism</td>
</tr>
</tbody>
</table>
### Common

#### Menorrhagia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common ◊ Menorrhagia</td>
<td></td>
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</tr>
<tr>
<td>history of poor dietary iron intake, celiac disease, Crohn disease, ulcerative colitis, small bowel resection, peptic ulcer disease, regular running, chronic blood loss (melena, hematuria, menorrhagia, hemoptysis, frequent blood donation, self-harm), pica, salicylate ingestion, gastric bypass, hookworm infestation, pregnancy, or menorrhagia</td>
<td>pallor, dyspnea, poor exercise tolerance, koilonychia, angular cheilosis, glossitis, thinning hair, systolic flow murmur; hemorrhoids, fresh blood or melena on rectal examination; evidence of pregnancy; adnexal masses or fibroids</td>
<td>CBC with peripheral smear: microcytic anemia with thrombocytosis</td>
<td>transvaginal ultrasound: may see hyperplasia, dysplasia, fibroids, or polyps. Endometrial carcinoma should be excluded in patients &gt;40 years.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>serum iron studies: low serum iron, elevated total iron-binding capacity, low ferritin, elevated soluble transferrin receptor</td>
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<td></td>
<td></td>
<td>immunoglobulin A-tissue transglutaminase (IgA-tTG) test: positive in celiac disease</td>
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<td>upper GI endoscopy: identification of source of upper GI bleeding; elevated gastric pH in achlorhydria</td>
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<td>colonoscopy: identification of source of lower GI bleeding or chronic inflammation</td>
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<td></td>
<td>CT colonography: Identification of source of lower GI bleeding. Useful alternative for patients who cannot tolerate colonoscopy.</td>
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<td></td>
<td>flow cytometry: identification of paroxysmal nocturnal hemoglobinuria</td>
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<tr>
<td></td>
<td></td>
<td>transvaginal ultrasound: may see hyperplasia, dysplasia, fibroids, or polyps. Endometrial carcinoma should be excluded in patients aged &gt;40 years.</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>stool microscopy: visualization of hookworm, whipworm, or Schistosoma eggs</td>
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</tbody>
</table>
# Evaluation of anemia

### Common

#### Iron deficiency

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History: iron deficiency</td>
<td>- Exam: macrocytic anemia</td>
<td>- 1st Test: &quot;Helicobacter pylori test&quot;: positive result if <em>H. pylori</em> present. Following negative endoscopy in the setting of persistent iron deficiency anemia, <em>H. pylori</em> testing may be considered when malignancies, B12 deficiency, and idiopathic thrombocytopenic purpura have been excluded. [61]</td>
<td></td>
</tr>
</tbody>
</table>

#### Vitamin B12 deficiency

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>- History: Vitamin B12 deficiency</td>
<td>- Exam: macrocytic anemia</td>
<td>- 1st Test: &quot;CBC with peripheral smear&quot;: megaloblastic macrocytic anemia; basophilic stippling may be seen. &quot;serum vitamin B12 levels&quot;: low. &quot;serum methylmalonic acid levels&quot;: elevated. Confirms deficiency if B12 levels are borderline. &quot;anti-intrinsic factor antibodies&quot;: positive in pernicious anemia. &quot;antiparietal cell antibodies&quot;: positive in pernicious anemia.</td>
<td></td>
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</tbody>
</table>
### DIAGNOSIS

#### Common

**◊ Folate deficiency**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of celiac or Crohn disease, gastric bypass, hemodialysis, pregnancy, alcohol abuse, or use of antiseizure medications; fatigue, palpitations, headaches | mild persistent pyrexia, tachycardia, pallor, hepatosplenomegaly, glossitis, angular stomatitis, patchy hyperpigmentation of skin and mucous membranes | » CBC with peripheral smear; megaloblastic macrocytic anemia; basophilic stippling may be seen | » serum folate; low
» serum vitamin B12 levels; normal; low in combined vitamin B12 and folate deficiency
Neurologic symptoms will worsen if folate is corrected in the presence of low vitamin B12. |

**» serum homocysteine levels; elevated**

#### Myelodysplastic syndrome

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of prior exposure to petroleum distillates (especially benzene), chemotherapy, or radiation therapy; fever, chills, fatigue, weakness, recurrent infection, anorexia, night sweats, shortness of breath, easy bruising | pallor, petechiae, purpura | » CBC: macrocytic anemia with leukopenia, macro-ovalocytes; associated cytopenias include neutropenia and thrombocytopenia | » bone marrow aspiration and biopsy; myeloblasts with immature precursors
» cytogenetics of bone marrow biopsy: multiple chromosomal translocations possible, especially 5q-, 7q-, or trisomy 8 (+8) |

#### Acute lymphocytic leukemia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| malaise, fatigue, easy bruising or bleeding, recurrent infections, fever, arthralgias, infection, anorexia, night sweats, shortness of breath, bony tenderness, epistaxis, | pallor, petechiae, purpura, tachycardia, hepatosplenomegaly, lymphadenopathy, painless scrotal enlargement, bleeding gums | » CBC with peripheral smear; pancytopenia, with ≥20% blasts; normocytic anemia; may see hypereosinophilia | » bone marrow aspirate and biopsy; ≥20% blasts
Immunohistochemistry, cytochemistry, and cytogenetics help to further classify disease. |
## Acute lymphocytic leukemia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
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</tr>
</thead>
<tbody>
<tr>
<td>bleeding gums, gingival hyperplasia</td>
<td></td>
<td>Up to 10% of patients do not have peripherally circulating blasts.</td>
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<tr>
<td></td>
<td></td>
<td>» reticulocyte count: &lt;2%</td>
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</table>

## Acute myelogenous leukemia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of prior chemotherapy or radiation therapy; malaise, night sweats, fatigue, easy bruising or bleeding, recurrent infections, fever, bony tenderness, epistaxis, bleeding gums, gingival hyperplasia</td>
<td>pallor, petechia, purpura, dyspnea, tachycardia</td>
<td>» CBC with peripheral smear: pancytopenia, with ≥20% blasts; normocytic anemia; may see hypereosinophilia</td>
<td>» bone marrow aspirate and biopsy: ≥20% blasts Immunohistochemistry, cytochemistry, and cytogenetics help to further classify disease.</td>
</tr>
<tr>
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<td>Cytoplasmic granules indicate myeloid lineage of blasts. May also see Auer rods. [Fig-7]</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>» reticulocyte count: &lt;2%</td>
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</tbody>
</table>

## Chronic myelogenous leukemia

<table>
<thead>
<tr>
<th>History</th>
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<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>usually in middle-aged patients; fatigue, weight loss, night sweats, early satiety, petechiae, purpura, recurrent fevers, bone pain, gouty arthritis</td>
<td>tender splenomegaly, painful sternum, lymphadenopathy, splenomegaly</td>
<td>» CBC with peripheral smear: normocytic anemia; myeloid maturing cells, elevated basophils, and eosinophils</td>
<td>» cytogenetics: t(19;22) Philadelphia chromosome - bcr-abl translocation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» reticulocyte count: &lt;2%</td>
<td>» serum uric acid: elevated Due to elevated leukocyte count and turnover.</td>
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<tr>
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<td>» bone marrow aspirate and biopsy: hypercellular with granulocytic hyperplasia</td>
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</table>
### Hairy cell leukemia

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<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>weakness, fatigue, weight loss, night sweats, early satiety, petechiae, purpura, recurrent fevers, abdominal discomfort or fullness due to large spleen</td>
<td>massive splenomegaly</td>
<td>» CBC with peripheral smear: pancytopenia with normocytic anemia Characteristic mononuclear &quot;hairy&quot; cells, which stain positive for tartrate-resistant acid phosphatase (TRAP) » reticulocyte count: &lt;2%</td>
<td>» bone marrow aspirate and biopsy: core biopsy shows hairy cells [Fig-8]</td>
</tr>
</tbody>
</table>

### Acquired aplastic anemia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of hepatitis, HIV, benzene exposure, use of known causative medications, radiation exposure, paroxysmal nocturnal hemoglobinuria; malaise, fatigue, easy bruising or bleeding, recurrent infections, fever</td>
<td>pallor, petechiae, purpura, dyspnea, tachycardia</td>
<td>» CBC with peripheral smear: pancytopenia with mild macrocytosis; normocytic anemia » reticulocyte count: &lt;2%</td>
<td>» bone marrow aspirate and biopsy: hypocellular with decrease in all elements, replaced mostly by fat cells; no infiltration by fibrosis or malignant cells » serum vitamin B12: normal » folate: normal</td>
</tr>
</tbody>
</table>

### Infiltration by secondary malignancy

<table>
<thead>
<tr>
<th>History</th>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>weight loss, malaise, fevers, fatigue, dyspnea, easy bleeding or bruising; history of solid organ malignancy (particularly breast, prostate, lung, neuroblastoma)</td>
<td>pallor, petechiae, purpura, tachycardia, abnormal exam or presence of mass (if solid organ malignancy), bruising, cachexia</td>
<td>» CBC with peripheral smear: pancytopenia, teardrop cells, poikilocytes; normocytic anemia » reticulocyte count: &lt;2%</td>
<td>» bone marrow aspirate and biopsy: infiltration of marrow » CT imaging: identification of site of primary malignancy</td>
</tr>
</tbody>
</table>
#### Infiltration by secondary malignancy

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
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</thead>
</table>
| space by malignant cells  
Provide history to pathologist so appropriate stains can be ordered if metastatic malignancy is suspected. | | | |

#### Pure red cell aplasia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| self-limited disease: history of use of known causative medications, clinical features of causative infections (parvovirus B19, infectious mononucleosis, viral hepatitis, malaria, respiratory infections, gastroenteritis, primary atypical pneumonia, mumps); chronic disease: history of autoimmune disease (systemic lupus erythematosus [SLE], rheumatoid arthritis, dermatomyositis, scleroderma, polyarteritis nodosa), persistent infection, or thymoma | clinical signs of underlying infection or autoimmune disease | »CBC: normocytic anemia  
»reticulocyte count: <2%  
»trial of discontinuation of causative medication: anemia resolves  
»antiparvovirus B19 antibodies: positive in parvovirus infection  
The most common infectious cause. | »thick and thin peripheral smear: intracellular parasites seen with Wright or Giemsa staining in malaria infection  
»serum IgM + IgG anti-HAV: positive in hepatitis A infection  
»serum IgM + IgG HBCAb: positive in hepatitis B infection  
»serum HBsAg: positive in hepatitis B infection  
»serum IgM + IgG anti-HCV: positive in hepatitis C infection  
»antinuclear antibodies: positive in SLE or scleroderma  
»ds-DNA, Smith antigen: positive in SLE  
»rheumatoid factor: positive in rheumatoid arthritis  
»serum creatine kinase (CK): elevated in dermatomyositis  
»chest x-ray: infiltrates in atypical pneumonia; |
## Common

### Pure red cell aplasia

<table>
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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>known or suspected ingestion of causative drug prior to onset of anemia, poor exercise tolerance</td>
<td>pallor, jaundice (with hemolytic anemia only), dyspnea</td>
<td>CBC with peripheral smear: typically normocytic anemia; inhibitors of DNA synthesis, folate, or vitamin B12 produce megaloblastic macrocytic anemia; reticulocyte count: &lt;2% if drugs suppress bone marrow; &gt;2% if drugs produce hemolysis; trial of discontinuation of causative medication: anemia resolves</td>
<td>smooth mass in thymoma, typically projecting into one of the hemithoraces and obscuring the aortic arch, or silhouette sign</td>
</tr>
</tbody>
</table>

### Drug toxicity

<table>
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</tr>
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<tbody>
<tr>
<td>known or suspected ingestion of causative drug prior to onset of anemia, poor exercise tolerance</td>
<td>pallor, jaundice (with hemolytic anemia only), dyspnea</td>
<td>CBC with peripheral smear: typically normocytic anemia; inhibitors of DNA synthesis, folate, or vitamin B12 produce megaloblastic macrocytic anemia; reticulocyte count: &lt;2% if drugs suppress bone marrow; &gt;2% if drugs produce hemolysis; trial of discontinuation of causative medication: anemia resolves</td>
<td>serum bilirubin: elevated in hemolytic anemia</td>
</tr>
</tbody>
</table>

### Anemia of chronic disease

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>known or suspected ingestion of causative drug prior to onset of anemia, poor exercise tolerance</td>
<td>pallor, fatigue, dyspnea; specific signs of underlying disease</td>
<td>CBC: normocytic anemia; May be microcytic if anemia of chronic disease is coexistent with iron deficiency anemia.</td>
<td>serum erythropoietin level: normal or elevated; often decreased in chronic kidney disease; elevation, if present, is usually inadequate to compensate for the degree of anemia.</td>
</tr>
<tr>
<td>history of known chronic inflammatory, autoimmune, or infectious states, sustained physiologic stress, renal failure, vasculitis or collagen vascular diseases, poor exercise tolerance; anemia correlates with severity of inflammatory process</td>
<td></td>
<td>serum iron studies: low/normal serum iron, low total iron-binding capacity and normal/ elevated ferritin; ferritin</td>
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</tbody>
</table>

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## Common

### Anemia of chronic disease

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>chronic kidney disease, poor exercise tolerance; features of secondary hypoparathyroidism: muscle cramps, bone pain</td>
<td>pallor, fatigue, dyspnea; signs of renal failure: jaundice, skin bruising, lung rales, pericardial rub, edema, poor concentration or memory, myoclonus; positive Chvostek sign or Trousseau sign in associated hyperparathyroidism</td>
<td>normal or elevated in acute-phase reaction When anemia of chronic disease is coexistent with iron deficiency anemia, these parameters may be different.</td>
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### Chronic kidney disease

<table>
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<tr>
<th>History</th>
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<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of chronic liver disease, poor exercise tolerance; may be asymptomatic or with fatigue, weakness, weight loss, recurrent infections, decreased libido; altered mental | pallor, fatigue, dyspnea, jaundice, lower-extremity swelling; hand and nail features: leukonychia, palmar erythema, finger clubbing, spider angiomata; facial | » CBC: normocytic or microcytic anemia with thrombocytosis  
» reticulocyte count: <2%  
» serum creatinine: elevated  
» urinalysis: hematuria and/or proteinuria  
» serum iron studies: low serum iron and normal/elevated ferritin, high total iron-binding capacity in iron deficiency  
» serum erythropoietin level: normal or decreased | » serum calcium level: decreased in associated secondary hyperparathyroidism  
» serum intact parathyroid hormone level: increased in associated secondary hyperparathyroidism  
» renal ultrasound: small kidney size; presence of obstruction or hydronephrosis; kidney stones  
» kidney biopsy: identification of underlying kidney pathology |

### Chronic liver disease

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</thead>
</table>
| history of chronic liver disease, poor exercise tolerance; may be asymptomatic or with fatigue, weakness, weight loss, recurrent infections, decreased libido; altered mental | pallor, fatigue, dyspnea, jaundice, lower-extremity swelling; hand and nail features: leukonychia, palmar erythema, finger clubbing, spider angiomata; facial | » CBC: nonmegaloblastic macrocytic anemia; thrombocytopenia may be present  
» prothrombin time: decreased in hepatic synthetic dysfunction | » abdominal ultrasound, CT, or MRI scanning: liver surface nodularity, small liver, possible hypertrophy of left/ caudate lobe, evidence |
## Common

### ◊ Chronic liver disease

<table>
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<tr>
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<th>Exam</th>
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</tr>
</thead>
<tbody>
<tr>
<td>status in hepatic encephalopathy</td>
<td>features: telangiectasia, bruising, rhinophyma, parotid gland swelling, paper-dollar appearance of skin, seborrheic dermatitis, xanthelasma; abdominal features: caput medusae, bruising, hepatomegaly, splenomegaly, abdominal distension; in males, loss of secondary sexual hair and testicular atrophy, gynecomastia</td>
<td>»liver function tests (LFTs): abnormal; pattern depends on underlying cause</td>
<td>of ascites or collateral circulation »liver biopsy: diagnosis of underlying cause or subsequent cirrhosis</td>
</tr>
</tbody>
</table>

### ◊ Pregnancy

<table>
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<th>Exam</th>
<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>pregnancy, especially in third trimester</td>
<td>abdominal distension consistent with pregnancy</td>
<td>»CBC: microcytic anemia with thrombocytosis in iron deficiency; megaloblastic macrocytic anemia in folate deficiency</td>
<td>»serum iron studies: low serum iron, elevated total iron-binding capacity, low ferritin, elevated soluble transferrin receptor in iron deficiency »serum folate: low in folate deficiency</td>
</tr>
</tbody>
</table>

## Uncommon

### ⇐ Generalized malnutrition

<table>
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<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>protein calorie deprivation; malabsorption syndrome; neglect; history of an eating disorder</td>
<td>loss of subcutaneous fat, apathy and lethargy, depigmentation, enlarged abdomen, winged scapula, flaky skin, bipedal edema</td>
<td>»CBC with peripheral smear: microcytic anemia in iron deficiency; megaloblastic macrocytic anemia in vitamin B12 and folate deficiency; normocytic anemia with combined vitamin and mineral deficiencies</td>
<td>»serum vitamin B12: low »serum folate: low »serum copper level: low Copper deficiency needs to be considered in patients on</td>
</tr>
</tbody>
</table>
### Uncommon

#### Generalized malnutrition

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of myelosuppressive chemotherapy; fatigue; headaches; poor exercise tolerance</td>
<td>pallor, lethargy, dyspnea</td>
<td>serum iron studies: low serum iron, elevated total iron-binding capacity, and low ferritin in iron deficiency</td>
<td>prolonged total parenteral nutrition.</td>
</tr>
</tbody>
</table>

#### Cytotoxic chemotherapy

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of myelosuppressive chemotherapy; fatigue; headaches; poor exercise tolerance</td>
<td>pallor, lethargy, dyspnea</td>
<td>CBC: pancytopenia with a normocytic anemia Counts usually reach nadir 7 to 10 days after administration of chemotherapy.</td>
<td>reticulocyte count: &lt;2%</td>
</tr>
</tbody>
</table>

#### Radiation therapy

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of recent radiation exposure, especially to pelvic or sternal areas; fatigue, headaches, poor exercise tolerance</td>
<td>pallor, lethargy, dyspnea, skin erythema on radiation sites</td>
<td>CBC: anemia (pancytopenia) reticulocyte count: &lt;2%</td>
<td>bone marrow aspirate and biopsy: marrow fibrosis or malignant infiltration</td>
</tr>
</tbody>
</table>

#### Alcohol abuse

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>history of chronic high alcohol intake</td>
<td>overweight status, increased prominence of superficial cutaneous vasculature, peripheral neuropathy, alterations in normal dentition and halitosis, possible signs of liver disease</td>
<td>CBC: macrocytic anemia</td>
<td>diagnostic interview: diagnosis of alcohol dependence alcohol level (breath and blood): elevated</td>
</tr>
</tbody>
</table>
## Evaluation of anemia

### Uncommon

#### Alcohol abuse

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>alcohol abuse history</td>
<td>hepatomegaly or small liver, jaundice, ascites</td>
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</tbody>
</table>

#### Lead toxicity

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of occupational or recreational exposure to lead products or old paint; neuropsychiatric disturbance, insomnia, abdominal pain, poor appetite, pica | blue gingival line (Burton line), hypertension, gout ( saturnine gout); wrist or foot drop | »CBC with peripheral smear: normocytic anemia with basophilic stippling; microcytic anemia if associated iron deficiency is present  
»reticulocyte count: >2%  
»whole blood lead level: elevated | |

#### Hypothyroidism

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| weakness, lethargy, slow speech, feeling cold, forgetfulness, constipation, weight gain, poor exercise tolerance | pallor; dyspnea; coarse, dry skin; eyelid edema; thick tongue; facial edema; bradycardia | »CBC: nonmegaloblastic macrocytic anemia  
»serum TSH: elevated  
»serum T4: reduced | |

#### Autoimmune hemolytic anemia (AIHA)

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of autoimmune diseases (SLE, rheumatoid arthritis, or scleroderma), lymphoproliferative disorders (non-Hodgkin lymphoma or chronic lymphocytic leukemia), recent viral illness, or mononucleosis; may be asymptomatic; symptoms include weakness, fatigue, | pallor, lethargy, dyspnea, tachycardia, jaundice, splenomegaly (especially if extravascular hemolysis) | »CBC with peripheral smear: normocytic anemia, with spherocytes  
»reticulocyte count: >2%; usually 4%  
The elevated reticulocyte count may incorrectly increase mean corpuscular | |
## Uncommon

◊ **Autoimmune hemolytic anemia (AIHA)**

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>headaches, poor exercise tolerance, prior gallstones, dark urine, clay-colored stools</td>
<td></td>
<td>volume (MCV) on automated counters. [Fig-9]</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>«lactate dehydrogenase (LDH): elevated</td>
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<tr>
<td></td>
<td></td>
<td>«haptoglobin: low</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>«direct antiglobulin (Coombs) test: usually positive; negative in 5% to 10% of cases</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>«serum bilirubin: elevated</td>
<td></td>
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</tbody>
</table>

### Transfusion reaction

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>multiple prior transfusions; fever, back pain, and dyspnea, usually within 6 hours of transfusion</td>
<td>pallor, lethargy, dyspnea, dark urine, jaundice</td>
<td>«ABO typing: discrepancy to blood used for transfusion Most commonly a clerical error. Stop transfusion immediately and stabilize patient.</td>
<td>«direct antiglobulin (Coombs) test: IgG anti-A, anti-B, or anti-AB detected on circulating red cells «serum bilirubin: elevated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>«inspection of plasma in centrifuged, anticoagulated venous blood sample: clear or pink-red within first few hours of hemoglobinemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>«inspection of centrifuged urine: clear red in hemoglobinemia</td>
<td></td>
</tr>
</tbody>
</table>
## Uncommon

### Malaria

<table>
<thead>
<tr>
<th><strong>History</strong></th>
<th><strong>Exam</strong></th>
<th><strong>1st Test</strong></th>
<th><strong>Other tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>history of mosquito bite or habitation in malaria-prone region; fatigue, dyspnea, fevers and prostration, decreased exercise tolerance, headaches, malaise; symptoms usually cycle every 48 to 72 hours, coinciding with red blood cell (RBC) destruction</td>
<td>jaundice or pallor, splenomegaly, dyspnea, high flow cardiac murmur, pulmonary edema, dark urine, fevers</td>
<td><strong>» CBC:</strong> normocytic anemia ± thrombocytopenia and leukopenia</td>
<td><strong>» serum bilirubin:</strong> elevated</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>» reticulocyte count:</strong> &gt;2%; usually 4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>» thick and thin peripheral smear:</strong> intracellular parasites seen with Wright or Giemsa staining Banana-shaped gametocytes or multiple signet-ring forms in RBCs are typical for <em>Plasmodium falciparum</em>, which requires hospital admission.</td>
<td></td>
</tr>
</tbody>
</table>

### Viral hepatitis

<table>
<thead>
<tr>
<th><strong>History</strong></th>
<th><strong>Exam</strong></th>
<th><strong>1st Test</strong></th>
<th><strong>Other tests</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>perinatal exposure, direct body fluid transmission, exposure to foodborne outbreak (in hepatitis A); nausea, vomiting, abdominal pain, fever, malaise, fatigue and headache, dark urine, acholic (clay-colored) stools, jaundice, pruritus (in hepatitis B); hepatitis C is usually asymptomatic</td>
<td>jaundice, hepatomegaly, RUQ pain, acholic stools, maculopapular or urticarial skin rash (in hepatitis B); usually normal in hepatitis C</td>
<td><strong>» CBC:</strong> normocytic anemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>» reticulocyte count:</strong> &lt;2%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>» serum aminotransferases:</strong> elevated</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>» serum IgM + IgG anti-HAV:</strong> positive in hepatitis A infection</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>» serum IgM + IgG HBcAb:</strong> positive in hepatitis B infection</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>» serum HBsAg:</strong> positive in hepatitis B infection</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>» serum IgM + IgG anti-HCV:</strong> positive in hepatitis C infection</td>
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</tbody>
</table>
### Uncommon

#### Toxoplasmosis

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| usually seen in pregnant or immunosuppressed patients and newborns; history of exposure to domestic cats, sheep, or cattle, or to raw meat | jaundice, fever, fatigue, lethargy, rash, hepatosplenomegaly; newborns infected in utero may have chorioretinitis, microcephaly, seizures, mental retardation | » **CBC**: normocytic anemia and thrombocytopenia; may see leukocytosis and eosinophilia  
» **reticulocyte count**: >2%; usually 4% | » **PCR for Toxoplasma gondii**: positive |

#### Leishmaniasis

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| history of exposure to sand fly bite, especially in tropical or subtropical zones: AIDS, immunosuppression, or malnutrition; fatigue and anorexia; prolonged, persistent, low-grade intermittent fevers; failure to thrive, distended abdomen | pallor, jaundice, hepatosplenomegaly, lymphadenopathy, diarrhea, skin ulcerations, nasopharyngeal ulcerations | » **CBC**: normocytic anemia, thrombocytopenia, leukopenia, erythroblastosis | » **reticulocyte count**: >2%  
» **splenic or bone marrow aspirate**: presence of amastigotes of the parasite  
Splenic aspirate is most sensitive. | » **direct antiglobulin (Coombs) test**: positive |
### Uncommon

#### Parvovirus B19 infection

**History**
- acute infection: characteristic skin rash with or without arthralgia

**Exam**
- acute infection: “slapped cheek” appearance followed by a reticular erythematous eruption on extremities, and arthritis of hands, wrists, knees, or ankles

**1st Test**
- CBC: normocytic anemia
- reticulocyte count: <2%

**Other tests**
- antiparvovirus B19 antibodies: positive
  Used to exclude parvovirus when typical clinical features are absent.

#### Infectious mononucleosis

**History**
- fatigue, malaise, sore throat, nausea, ocular pain, photophobia

**Exam**
- fever, lymphadenopathy, pharyngitis, rash, tender splenomegaly, palate petechiae, periorbital edema, jaundice

**1st Test**
- CBC with peripheral smear: normocytic anemia, with spherocytes and atypical lymphocytes
- reticulocyte count: >2% and usually 4% in hemolytic anemia, <2% in pure red cell aplasia

**Other tests**
- lactate dehydrogenase (LDH): elevated
- haptoglobin: low
- monospot test or Epstein-Barr virus (EBV) IgM: positive

#### Cytomegalovirus (CMV)

**History**
- infection is usually asymptomatic; a maculopapular rash following administration of antibiotics may occur; fatigue occurs due to anemia; symptomatic infection is a sign of underlying immunosuppression

**Exam**
- usually normal; jaundice occurs due to hemolytic anemia; symptomatic infection produces fever, lymphadenopathy, pharyngitis, rash, tender splenomegaly, palate petechiae, periorbital edema

**1st Test**
- CBC: normocytic anemia
- reticulocyte count: >2%; usually 4%

**Other tests**
- lactate dehydrogenase (LDH): elevated
- haptoglobin: low
- monospot test or Epstein-Barr virus (EBV) IgM: negative
  Rules out EBV, which is clinically indistinguishable from CMV.
- CMV IgM: positive
### Uncommon

#### Sickle cell anemia

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>known diagnosis of sickle cell disease in patient and/or parents; prior painful vaso-occlusive crises; fatigue, poor exercise tolerance; persistent pain in skeleton, chest, or abdomen; priapism, gallstones, stroke, lower-extremity skin ulcers, pneumonia-like syndrome</td>
<td>high fever, pallor, lethargy, dyspnea, jaundice during acute crisis</td>
<td>CBC with peripheral smear: normocytic anemia with sickle cells. Pancytopenia occurs in aplastic crisis (usually self-limited). [Fig-10]</td>
<td>reticulocyte count: &gt;2%</td>
</tr>
</tbody>
</table>

#### Thalassemias

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>family history of blood disorders, especially requiring repeated transfusions; Mediterranean, Middle Eastern, or Southeast Asian descent; variable severity ranging from asymptomatic to severe transfusion-dependent symptoms</td>
<td>splenomegaly, jaundice, abdominal distension, icterus; skeletal abnormalities, large head, chipmunk facies, and misaligned teeth seen in beta-thalassemia intermedia and major</td>
<td>CBC with peripheral smear: microcytic anemia with mean corpuscular volume (MCV) typically closer to 70 fL, low mean corpuscular hemoglobin (Hb); target cells seen</td>
<td>serum ferritin: elevated in iron overload</td>
</tr>
</tbody>
</table>

#### Hereditary spherocytosis

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>family history of blood disorder, splenectomy, or pigmented gallstones;</td>
<td>may be normal or show pallor, jaundice,</td>
<td>CBC with peripheral smear: normocytic anemia, with increased</td>
<td>direct antiglobulin (Coombs) test: negative</td>
</tr>
</tbody>
</table>
## Uncommon

### Hereditary spherocytosis

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
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</thead>
<tbody>
<tr>
<td>may be asymptomatic if extramedullary hematopoiesis compensates</td>
<td>lower leg skin ulcers, splenomegaly</td>
<td>mean corpuscular hemoglobin and spherocytes&lt;br&gt;» reticulocyte count: &gt;2%&lt;br&gt;» osmotic fragility test: positive (cells lyse on exposure to hypo-osmotic solution)</td>
<td>Excludes immune-mediated hemolytic anemias.</td>
</tr>
</tbody>
</table>

### Glucose-6-phosphate dehydrogenase deficiency (G6PD)

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<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| usually in males of African, Mediterranean, Sardinian, or Sephardic Jewish descent; self-limited episodes of acute hemolysis when exposed to oxidant stress; life-threatening symptoms more common with Mediterranean variant | pallor, jaundice, mild dyspnea | CBC with peripheral smear: normocytic anemia with Heinz bodies, eccentrocytes, or bite cells<br>Heinz bodies are rapidly cleared by the spleen within 24 hours, resulting in "bite cells."

» reticulocyte count: >2%<br>» serum haptoglobin: decreased<br>» lactate dehydrogenase (LDH): elevated<br>«G6PD enzyme assays: quantitative or qualitative abnormalities<br>May be falsely negative during the acute hemolytic event, owing to the destruction of affected cells.<br>» serum bilirubin: elevated indirect bilirubin<br>» direct antiglobulin (Coombs) test: negative<br>Distinguishes glucose-6-phosphate dehydrogenase deficiency from immune hemolytic anemias. |

### Bone marrow failure syndromes

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>recurrent infection shortly after birth, fever, easy bleeding or bruising, organ</td>
<td>ill-appearing, with weight loss, pallor, lethargy, dyspnea, petechiae, purpura, and/or thrush</td>
<td>CBC with peripheral smear: pancytopenia with normocytic or macrocytic anemia&lt;br&gt;«bone marrow aspiration and biopsy: varies depending on underlying cause</td>
<td></td>
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</tbody>
</table>
### Uncommon

#### Bone marrow failure syndromes

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>abnormalities, short stature</td>
<td></td>
<td>Causes include Fanconi anemia, dyskeratosis congenita, and Shwachman-Diamond syndrome.</td>
<td>» diepoxbutane or mitomycin-c fragility test: positive in Fanconi anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>» genetic testing: characteristic genetic mutations detected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» reticulocyte count: &lt;2%</td>
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</table>

#### Hemolytic uremic syndrome

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<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
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</tr>
</thead>
<tbody>
<tr>
<td>acute renal failure usually following an enteric bacterial infection (Escherichia coli 0157:H7) with bloody diarrhea, or Streptococcus pneumoniae</td>
<td>pallor, lethargy, dyspnea, petechiae, purpura, bloody diarrhea; usually self-limited in children</td>
<td>» CBC with peripheral smear: normocytic anemia, thrombocytopenia, schistocytes</td>
<td>» prothrombin time/activated partial thromboplastin time: normal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>» erythrocyte count: &gt;2%</td>
<td>Excludes disseminated intravascular coagulation (DIC).</td>
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<tr>
<td></td>
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<td></td>
<td>» serum haptoglobin: decreased</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>» lactate dehydrogenase (LDH): elevated</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>» serum bilirubin: elevated</td>
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<tr>
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<td></td>
<td>» direct antiglobulin (Coombs) test: negative</td>
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<td></td>
<td>Excludes immune-mediated hemolytic anemias.</td>
</tr>
<tr>
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<td></td>
<td>» kidney biopsy: hyaline arteriolar thrombi in absence of inflammatory changes in vessel wall</td>
</tr>
</tbody>
</table>

«serum haptoglobin: decreased»
«lactate dehydrogenase (LDH): elevated»
«serum bilirubin: elevated»
«direct antiglobulin (Coombs) test: negative»
«kidney biopsy: hyaline arteriolar thrombi in absence of inflammatory changes in vessel wall»
## Uncommon

### Disseminated intravascular coagulation (DIC)

<table>
<thead>
<tr>
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<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| ongoing severe infection, sepsis (typically gram-negative), malignancy, obstetric emergency, trauma, burns, envenomations, drug overdose, any cause of endothelial damage | diffuse bleeding, especially from puncture sites or minor trauma; unprovoked clots; clinical signs of underlying cause | » **CBC with peripheral smear:** normocytic anemia, thrombocytopenia, schistocytes  
» **prothrombin time:** prolonged  
» **activated partial thromboplastin time:** varies depending on factor VII levels  
» **DIC panel:** elevated  
D-dimer and fibrin degradation products with low fibrinogen  
Fibrinogen may be normal or elevated as an acute-phase reactant. | |

### Thrombotic thrombocytopenic purpura

<table>
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<tr>
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<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
</table>
| nonspecific prodrome followed by headache, confusion, focal weakness, seizures, coma; menorrhagia may be seen due to bleeding | pallor, lethargy, dyspnea, purpura, ecchymoses | » **CBC with peripheral smear:** normocytic anemia with schistocytes  
» **reticulocyte count:** >2%  
» **direct antiglobulin (Coombs) test:** negative  
Excludes immune-mediated hemolytic anemias. | |

### Hemangioma

<table>
<thead>
<tr>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>typically young child or infant with expanding vascular skin lesion;</td>
<td>depends on location of lesion(s), which are typically reddish-brown</td>
<td>» <strong>CBC with peripheral smear:</strong></td>
<td>» <strong>x-ray of suspected region:</strong> soft-tissue shadows, phleboliths</td>
</tr>
</tbody>
</table>
### Uncommon

#### Hemangioma

**History**  
may also be hepatic or in other visceral site

**Exam**  
or violaceous; other symptoms consistent with anemia

**1st Test**  
normocytic anemia, thrombocytopenia  
Platelet sequestration in enlarging hemangiomas (Kasabach-Merritt syndrome) can cause life-threatening bleeding.

- reticulocyte count:  
  >2%

**Other tests**
- MRI of suspected region: increased signal on both T1- and T2-weighted images with areas of signal void

### Malignant hypertension

**History**  
history of essential hypertension, renal disease, or eclampsia; older age, male gender, black ethnicity; dizziness, headache, mental status changes, loss of sensation or motor strength, chest pain or pressure, dyspnea, edema

**Exam**  
systolic BP >210 mmHg and diastolic BP >130 mmHg, lethargy, new murmurs, S3 on auscultation of heart, jugular venous distension, rales or lower-extremity edema, oliguria or polyuria, focal neurologic signs, hypertensive retinopathy

**1st Test**  
CBC with peripheral smear: normocytic anemia with schistocytes  
reticulocyte count:  
>2%

**Other tests**
- chest x-ray: evidence of pulmonary edema indicating left ventricular failure  
- head CT or MRI: evidence of infarct or hemorrhage

- ECG: evidence of ischemia or infarct such as ST- or T-wave changes  
- serum creatinine: elevated with renal failure

### Prosthetic valves and surfaces

**History**  
history of aortic or mitral metallic valve replacement, with anticoagulation; weakness, fatigue, headaches; poor exercise tolerance, prior gallstones, dark urine

**Exam**  
pallor, lethargy, dyspnea, petechiae, purpura, jaundice

**1st Test**  
CBC with peripheral smear: normocytic anemia with schistocytes  
reticulocyte count:  
>2%

**Other tests**
- direct antiglobulin (Coombs) test: negative
### Uncommon

<table>
<thead>
<tr>
<th>Condition</th>
<th>History</th>
<th>Exam</th>
<th>1st Test</th>
<th>Other tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prosthetic valves and surfaces</td>
<td></td>
<td></td>
<td>Excludes immune-mediated hemolytic anemias.</td>
<td></td>
</tr>
<tr>
<td>Cutaneous burns</td>
<td>burn injury to at least 10% of total body surface area (TBSA); multiple surgical procedures</td>
<td>epidermal or dermal loss consistent with burn injury</td>
<td>»CBC with peripheral smear: normocytic anemia with thrombocytopenia; schistocytes from peripheral destruction seen on blood smear</td>
<td>»reticulocyte count: &gt;2%</td>
</tr>
</tbody>
</table>
Key articles


References


<table>
<thead>
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University of Michigan, specifically the cases of Dr Gilbert R. Upchurch reflecting the Departments of Vascular Surgery and Radiology
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