Anemia

What is anemia?

Anemia is a condition that occurs when the number of red blood cells (RBCs) and/or the amount of hemoglobin found in the red blood cells drops below normal. Red blood cells and the hemoglobin contained within them are necessary for the transport and delivery of oxygen from the lungs to the rest of the body. Without a sufficient supply of oxygen, many tissues and organs throughout the body can be adversely affected. Anemia can be mild, moderate or severe depending on the extent to which the RBC count and/or hemoglobin levels are decreased. It is a fairly common condition, affecting both men and women of all ages, races, and ethnic groups. However, certain people are at an increased risk of developing anemia. These include people with diets poor in iron and vitamins, chronic diseases such as kidney disease, diabetes, cancer, inflammatory bowel disease, a family history of inherited anemia, chronic infections such as tuberculosis or HIV, and those who have had significant blood loss from injury or surgery.

In general, anemia has two main causes:

- Impaired or decreased production of RBCs as, for example, in iron deficiency, B vitamin deficiencies, and aplastic anemia
- Decreased survival, increased destruction of red blood cells as in hemolytic anemia

There are several different types of anemia and various causes. Some of the most common types are summarized in the table below. Click on the links to read more about each one.

Type of Anemia	Description	Examples of Causes
Iron Deficiency	Lack of iron leads to decreased amounts hemoglobin; low levels of hemoglobin in turn leads to decreased production of normal RBCs	Blood loss; diet low in iron; poor absorption of iron
Pernicious Anemia and B Vitamin Deficiency	Lack of B vitamins does not allow RBCs to grow and then divide as they normally would during development; leads to decreased production of normal RBCs	Lack of intrinsic factor; diet low in B vitamins; decreased absorption of B vitamins

Aplastic	Decreased production of all cells produced by the bone marrow of which RBCs are one type	Cancer therapy, exposure to toxins, autoimmune disorders, viral infections
Hemolytic	RBCs survive less than the normal 120 days in the circulation; leads to overall decreased numbers of RBCs	Inherited causes include sickle cell and thalassemia; other causes include transfusion reaction, autoimmune disease, certain drugs (penicillin)
Anemia of Chronic Diseases	Various conditions over the long term can cause decreased production of RBCs	Kidney disease, diabetes, tuberculosis or HIV

Anemia may be acute or chronic. Chronic anemia may develop slowly over a period of time with long-term illnesses such as diabetes, chronic kidney disease, or cancer. In these situations, the anemia may not be apparent because symptoms are masked by the underlying disease. The presence of anemia in chronic conditions may often go undetected for a period of time and sometimes may only be discovered during tests or examinations for other conditions.

Anemia may also occur in acute episodes such as with certain hemolytic anemias in which a significant number of RBCs are destroyed. Signs and symptoms may become apparent very quickly and the cause determined from a combination of physical examination, medical history, and testing.

Signs and Symptoms

Though different types of anemias have different causes, the signs and symptoms can be very similar. Mild or moderate forms of anemia may cause few, if any, symptoms. The most common symptoms are:

- a general feeling of tiredness or weakness (fatigue)
- lack of energy

Other signs and symptoms that may develop as the anemia becomes more severe include headache, dizziness, feeling of cold or numbness in hands and/or feet, pale complexion, shortness of breath, fast or irregular heartbeat, and chest pain.

Laboratory Tests

Complete Blood Count (CBC)

Anemia may first be detected when a Complete Blood Count (CBC) is done during a health exam or as part of testing for other conditions. A CBC is often ordered as part of a yearly physical exam. It is a routine test that counts the number and relative proportion of each of the different types of cells in your blood stream. It gives your doctor information about the size, shape, and relative maturity of the blood cells present in your blood at that moment.

Blood Smear and Differential

If results of the CBC indicate anemia, it may be followed up with an examination of a Blood Smear or a Differential. Results from these tests may give clues as to the cause. Several other tests may be run to help determine the cause of the anemia and to guide treatment. See the individual discussions of the different types of anemia for more on these.

Iron Deficiency Anemia

Iron deficiency anemia is the most common cause of anemia. Symptoms are related to the overall decrease in number of red blood cells and/or level of hemoglobin. The most common signs and symptoms include:

- feeling of tiredness, fatigue
- lack of energy

Symptoms that are more unique to iron deficiency and that may appear as iron stores in the body are increasingly depleted may include brittle or spoon-shaped nails, swollen or sore tongue, cracks or ulcers at the corners of the mouth, or a craving to eat unusual non-food substances such as ice or dirt (also known as “pica”).

Iron is an essential trace element and is necessary for the production of healthy red blood cells (RBCs). It is one component of heme, a part of hemoglobin, the protein in RBCs that binds to oxygen and enables RBCs to transport oxygen throughout the body. If not enough iron is taken in compared to what is needed by the body, then iron that is stored in the body begins to be used up. If iron stores are depleted, fewer red blood cells are made and they have decreased amounts of hemoglobin in them resulting in anemia.

Some of the causes of iron deficiency include:

- Bleeding—if bleeding is excessive or occurs over a period of the time (chronic), the body may not take in enough iron or have enough stored to produce enough hemoglobin and/or red blood cells to replace what is lost. In women, iron deficiency may be due to heavy menstrual periods, but in older women and in men, the bleeding is usually from disease of the intestines such as ulcers and cancer.
- Dietary deficiency—iron deficiency may be due simply to not eating enough iron in the diet. In children and pregnant women especially, the body needs more iron. Pregnant and nursing women frequently develop this deficiency since the baby requires large amounts of iron for growth. Lack of iron can lead to low birth weight babies and premature delivery. Pre-pregnant and pregnant women are routinely given iron supplements to prevent these complications. Newborns who are nursing from deficient mothers tend to have iron deficiency anemia as well.
- Absorption problem—certain conditions affect the absorption of iron from food in the gastrointestinal (GI) tract and over time can result in anemia. These include, for example, Celiac disease and Crohn’s disease.

Laboratory Tests

Initial blood tests typically include a complete blood count (CBC). Results may show:

- Hemoglobin (Hb)—may be normal early in the disease but will decrease as anemia worsens
- Red blood cell indices—early on, the RBCs may be a normal size and color (normocytic, normochromic) but as the anemia progresses, the RBCs become smaller (microcytic) and paler (hypochromic) than normal.
    - Average size of RBCs (MCV)—may be decreased
    - Average amount of Hb in RBCs (MCH)—may be decreased
    - Increased variation in the size of RBCs (red cell distribution width (RDW))

A blood smear may reveal RBCs that are smaller and paler than normal as well as RBCs that vary in size (anisocytosis) and shape (poikilocytosis).

If your doctor suspects that your anemia is due to iron deficiency, she may run several follow-up tests to confirm the iron deficiency. These may include:

- Serum iron—the level of iron in your blood; the result is usually decreased.
- Ferritin—reflects the amount of stored iron in your body and is usually low. It is considered to be the most specific for identifying iron deficiency anemia, unless infection or inflammation are present.
- Total iron-binding capacity (TIBC) and transferrin—measurement of the protein that carries iron through the blood will be increased.

If the iron deficiency is thought to be due to abnormal blood loss, such as chronic bleeding from the gastrointestinal (GI) tract, then other tests and procedures may be performed. Laboratory tests that may be able to detect GI bleeding are:

- Fecal occult blood test (FOBT)
- Fecal immunochemical test (FIT)

A test for Helicobacter pylori may detect a bacterium that can cause ulcers in the GI tract that may be a cause of chronic bleeding. If any of these tests are positive or if it is strongly suspected that a GI bleed exists, then procedures such as endoscopy or colonoscopy may be done to find the location of the bleeding so that it can be treated.

Treatment of iron deficiency typically involves iron supplements. However, if iron-deficiency is suspected to result from abnormal blood loss, further testing is often required to determine the reason for the bleeding. When the underlying cause is found and treated, then the anemia usually resolves.

Pernicious Anemia and Other B Vitamin Deficiencies

Pernicious anemia is a condition in which the body does not make enough of a substance called “intrinsic factor”. Intrinsic factor is a protein produced by parietal cells in the stomach that binds to vitamin B12 and allows it to be absorbed from the small intestine. Vitamin B12 is important in the production of red blood cells (RBCs). Without enough intrinsic factor, the body cannot absorb vitamin B12 from the diet and cannot produce enough normal RBCs, leading to anemia. In addition to lack of intrinsic factor, other causes of vitamin B12 deficiency and anemia include dietary deficiency and conditions that affect absorption of the vitamin from the small intestine such as surgery, certain drugs, digestive disorders (Celiac disease, Crohn’s disease), and infections. Of these, pernicious anemia is the most common cause of symptoms.

Vitamin B12 deficiency can result in general symptoms of anemia as well as nerve problems. These may include:

- weakness or fatigue
- lack of energy
- numbness and tingling that start first in the hands and feet

Additional symptoms may include muscle weakness, slow reflexes, loss of balance and unsteady walking. Severe cases can lead to confusion, memory loss, depression, and/or dementia.

Folic acid is another B vitamin, and deficiency in this vitamin may also lead to anemia. Folic acid, also known as folate, is found in many foods, especially in green, leafy vegetables. Folic acid is added to most grain products in the United States so that deficiency in folic acid is rarely seen in the U.S. today. Folic acid is needed during pregnancy for normal development of the brain and spinal cord. It is important for women considering pregnancy to take folate supplements before they get pregnant and during pregnancy to make sure they are not folate deficient. Folate deficiency early in pregnancy can cause problems in the development of the brain and spinal cord of the baby.

Anemias resulting from vitamin B12 or folate deficiency are sometimes referred to as “macrocytic” or “megaloblastic” anemia because red blood cells are larger than normal. A lack of these vitamins does not allow RBCs to grow and then divide as they normally would during development, which leads to their large size. This leads to a reduced number of abnormally large RBCs and anemia.

Laboratory Tests

Symptoms of anemia will usually be investigated initially with a complete blood count (CBC) and differential. In pernicious anemia or vitamin B12 deficiency, these usually reveal:

- A low hemoglobin level
- For red cell indices, the mean corpuscular volume (MCV), which is the average size of RBCs, is often high.
- A blood smear will reveal red blood cells that are abnormally large.

Folic acid deficiency can cause the same pattern of changes in hemoglobin and red cell size as vitamin B12 deficiency. If the cause of your anemia is thought to be due to pernicious anemia or dietary deficiency of B12 or folate, additional tests are usually done to make the diagnosis. Some of these include:

- Vitamin B12 level—blood level may be low when deficient in B12
- Folic acid level—blood level may be low if deficient in this B vitamin
- Methylmalonic acid (MMA)—may be high with vitamin B deficiency
- Homocysteine—may be high with either folate or vitamin B deficiency
- Reticulocyte count—is usually low
- Antibodies to intrinsic factor or parietal cell antibodies—may be present in pernicious anemia

Sometimes a bone marrow aspiration may be performed. This may reveal larger than normal sizes in the cells that eventually mature and become RBCs (precursors).

Treatment in these conditions involves supplementation with the vitamin that is deficient. If the cause of deficiency is the inability to absorb the vitamin from the digestive tract, then the vitamin may be given as injections. Treatment of underlying causes such as a digestive disorder or infection may help to resolve the anemia.

Aplastic Anemias

Aplastic anemia is a rare disease, caused by a decrease in the number of all types of blood cells produced by the bone marrow. Normally, the bone marrow produces a sufficient number of new red blood cells (RBCs), white blood cells (WBCs), and platelets for normal body function. Each type of cell enters the blood stream, circulates, and then dies within a certain time frame. For example, the normal lifespan of RBCs is about 120 days. If the bone marrow is not able to produce enough blood cells to replace those that die, a number of symptoms, including those due to anemia, may result.

Symptoms of aplastic anemia can appear abruptly or can develop more slowly. Some general symptoms that are common to different types of anemia may appear first and are due to the decrease in number of RBCs. These include:

- feeling of tiredness, fatigue
- lack of energy

Some additional signs and symptoms that occur with aplastic anemia include those due to decreased platelets:

- prolonged bleeding

- frequent nosebleeds
- bleeding gums
- easy bruising

and due to a low WBC count:

- increased number and severity of infections

Causes of aplastic anemia usually have to do with damage to the stem cells in the bone marrow that are responsible for blood cell production. Some factors that may be involved with bone marrow damage and that can lead to aplastic anemia include:

- exposure to toxic substances such as arsenic, benzene or pesticides
- cancer therapy (radiation or chemotherapy)
- autoimmune disorders such as lupus or rheumatoid arthritis
- viral infections such as hepatitis, EBV, HIV, CMV, or parvovirus B19

Rarely, aplastic anemia is due to an inherited (genetic) disorder such as Fanconi anemia.

Laboratory Tests

The initial test for anemia, the complete blood count (CBC), may reveal many abnormal results.

- Hemoglobin and/or hematocrit may be low.
- RBC and WBC counts are low.
- Platelet count is low.
- Red blood cell indices are usually normal.
- The differential white blood count shows a decrease in most types of cells but not lymphocytes.

Some additional tests that may be performed to help determine the type and cause of anemia include:

- Reticulocyte count—result is usually low.
- Erythropoietin—usually increased in aplastic anemia.
- A bone marrow aspiration will show a decrease in the number of all types of mature cells.
- Tests for infections such as hepatitis, EBV, CMV help to determine the cause.
- Test for arsenic (a heavy metal) and other toxins

- Iron tests or tests for vitamin B12 may be done to rule out other causes.
- Antibody tests such as ANA to determine if the cause is autoimmune disease.

A physical examination or complete medical history may reveal possible causes for aplastic anemia such as exposure to toxins or certain drugs (for example, chloramphenicol) or prior treatment for cancer. Some cases of aplastic anemia are temporary while others have lasting damage to the bone marrow. Treatment depends on the cause. Reducing or eliminating exposure to certain toxins or drugs may help resolve the condition. Medications may be given to stimulate bone marrow production, to treat infections, or to suppress the immune system in cases of autoimmune disorders. Blood transfusions and a bone marrow transplant may be needed in severe cases.

Hemolytic Anemias

Rarely, anemia is due to problems that cause the red blood cells (RBCs) to die or be destroyed prematurely. Normally, red cells live in the blood for about 4 months. In hemolytic anemia, this time is shortened, sometimes to only a few days. The bone marrow is not able to produce new RBCs quickly enough to replace those that have been destroyed, leading to a decreased number of RBCs in the blood, which in turn leads to a diminished capacity to supply oxygen to tissues throughout the body. This results in the typical symptoms of anemia including:

- weakness and/or fatigue
- lack of energy

Depending on the cause, different forms of hemolytic anemia can be chronic, developing and lasting over a long period or lifetime, or may be acutesigns and symptoms. The various forms can have a wide range of signs and symptoms. See the discussions of the various types below for more on this.

The different causes of hemolytic anemia fall into two main categories:

- Inherited forms in which a gene or genes are passed from one generation to the next that result in abnormal RBCs or hemoglobin
- Acquired forms in which some factor other than inherited results in the early destruction of RBCs

Inherited Hemolytic Anemia

Two of the most common causes of inherited hemolytic anemia are sickle cell anemia and thalassemia:

Sickle cell anemia can cause minor difficulties as the “trait” (when you carry one mutated gene from one of your parents), but severe clinical problems as the “disease” (when you carry two mutated genes, one from each of your parents). The red blood cells are misshapen, unstable (leading to hemolysis) and can block blood vessels, causing pain and anemia. Screening is usually done on newborns – particularly those of African descent. Sometimes

screening is done prenatally on a sample of amniotic fluid. Follow-up tests for hemoglobin variants may be performed to confirm a diagnosis. Treatment is usually based on the type, frequency and severity of symptoms.

Thalassemia is a hereditary abnormality of hemoglobin production and results in small red blood cells that resemble those seen in iron deficiency. In its most severe form, the red cells have a shortened life span. In milder forms, anemia is usually mild or absent, and the disease may be detected by finding small blood cells on a routine CBC. This genetic disease is found frequently in people of Mediterranean, African, and Asian heritage. The defect in production may involve one of two components of hemoglobin called the alpha and beta protein chains. The disease is defined as alpha thalassemia or beta thalassemia accordingly. The "beta minor" form (sometimes called beta thal trait, as with sickle cell) occurs when a person inherits half normal genes and half beta thalassemia genes. It causes a mild anemia and no symptoms. The "beta major" form (due to inheriting two beta thalassemia genes and also called Cooley's anemia) is more severe and may result in growth problems, jaundice, and severe anemia.

Other less common types of inherited forms of hemolytic anemia include:

- Hereditary spherocytosis—results in abnormally shaped RBCs that may be seen on a blood smear
- Hereditary elliptocytosis—another cause of abnormally shaped RBCs seen on a blood smear
- Glucose-6-phospate dehydrogenase (G6PD) deficiency—G6PD is an enzyme that is necessary for RBC survival. Its deficiency may be diagnosed with a test for its activity.
- Pyruvate kinase deficiency—Pyruvate kinase is another enzyme important for RBC survival and its deficiency may also be diagnosed with a test for its activity.

Laboratory Tests

Since some of these inherited forms may have mild symptoms, they may first be detected on a routine CBC and blood smear, which can reveal various abnormal results that give clues as to the cause. Follow-up tests are then usually performed to make a diagnosis. Some of these include:

- Tests for hemoglobin variants such as hemoglobin electrophoresis
- DNA analysis—not routinely done but can be used to help diagnose hemoglobin variants, thalassemia, and to determine carrier status.
- G6PD test—to detect deficiency in this enzyme
- Osmotic fragility test—detects RBCs that are more fragile than normal, which may be found in hereditary spherocytosis.

These genetic disorders cannot be cured but often the symptoms resulting from the anemia may be alleviated with treatment as necessary.

Acquired Hemolytic Anemia

Some of the conditions or factors involved in acquired forms of hemolytic anemia include:

- Autoimmune disorders—a condition in which the body produces antibodies against its own red blood cells. It is not understood why this may happen.
- Transfusion reaction—result of blood donor-recipient incompatibility. This occurs very rarely but when it does, it can have some serious complications.
- Mother-baby blood group incompatibility—may result in hemolytic disease of the newborn.
- Drugs—certain drugs such as penicillin can trigger the body to produce antibodies directed against RBCs or cause the direct destruction of RBCs.
- Physical destruction of RBCs by, for example, an artificial heart valve or cardiac bypass machine used during open-heart surgery
- Paroxysmal Nocturnal Hemoglobinurina (PNH)—a rare condition in which the different types of blood cells including RBCs, WBCs and platelets are abnormal. Because the RBCs are defective, they are destroyed by the body earlier than the normal lifespan. As the name suggests, people with this disorder can have acute, recurring episodes in which many RBCs are destroyed. This disease occurs due to a change or mutation in a gene called PIGA in the stem cells that make blood. Though it is a genetic disorder, it is not passed from one generation to the next (it is not an inherited condition). Patients will often pass dark urine due to the hemoglobin released by destroyed RBCs being cleared from the body by the kidneys. This is most noticeable first thing in the morning when urine is most concentrated. Episodes are thought to be brought on when the body is under stress during illnesses or after physical exertion.

These types of hemolytic anemias are often first identified by signs and symptoms, during physical examination, and by medical history. A medical history can reveal, for example, a recent transfusion, treatment with penicillin, or cardiac surgery. A CBC and/or blood smear may show various abnormal results. Depending on those findings, additional follow-up tests may be performed. Some of these may include:

- Tests for autoantibodies for suspected autoimmune disorders
- Direct antiglobulin test (DAT) in the case of transfusion reaction, mother-baby blood type incompatibility, or autoimmune hemolytic anemia
- Haptoglobin
- Reticulocyte count

Treatments for hemolytic anemia are as varied as the causes. However, the goals are the same: to treat the underlying cause of the anemia, to decrease or stop the destruction of RBCs, and to increase the RBC count and/or hemoglobin level to alleviate symptoms. This may involve, for example:

- Drugs used to decrease production of autoantibodies that destroy RBCs
- Blood transfusions to increase the number of healthy RBCs
- Bone marrow transplant—to increase production of normal RBCs
- Avoiding triggers that cause the anemia such as the cold in some forms of autoimmune hemolytic anemia or fava beans for those with G6PD deficiency.

Anemia Caused by Chronic Diseases

Chronic (long-term) illnesses can cause anemia. Often, anemia caused by chronic diseases goes undetected until a routine test such as a complete blood count reveals abnormal results. Several follow-up tests may be used to determine the underlying cause. There are many chronic conditions and diseases that can result in anemia. Some examples of these include:

- Kidney disease—Red blood cells are produced by the bone marrow in response to a hormone called erythropoietin, made primarily by the kidneys. Chronic kidney disease can cause anemia resulting from too little production of this hormone; the anemia can be treated by giving erythropoietin injections.
- Inflammatory conditions—Whenever there are chronic diseases that stimulate the body's inflammatory system, the ability of the bone marrow to respond to erythropoietin is decreased. For example, rheumatoid arthritis (a severe form of joint disease caused by the body attacking its own joints, termed an autoimmune disease) can cause anemia by this mechanism.
- Other diseases that can produce anemia in the same way as inflammatory conditions include chronic infections (such as with HIV or tuberculosis, TB), cancer, and cirrhosis.

A number of tests may be used as follow up to abnormal results of initial tests such as a complete blood count (CBC) and blood smear to determine the underlying cause of chronic anemia. Some of these may include:

- Reticulocyte count
- Complete metabolic panel (CMP)
- Tests for inflammation such as CRP
- Erythropoietin
- Tests for infections such as HIV and TB.

Treatment of anemia due to chronic conditions usually involves determining and/or resolving the underlying disease. blood transfusions may be used to treat the condition in the short term.