

in which the [blood](#) has a reduced ability to carry [oxygen](#). This can be due to a lower than normal number of [red blood cells](#), a reduction in the amount of [hemoglobin](#) available for oxygen transport, or abnormalities in hemoglobin that impair its function.^{[3][4]} The name is derived from [Ancient Greek](#) ἀν- (*an-*) 'not' and αἷμα (*haima*) 'blood'.^[5]

When anemia comes on slowly, the symptoms are often vague, such as [tiredness](#), [weakness](#), [shortness of breath](#), [headaches](#), and a [reduced ability to exercise](#).^[1] When anemia is acute, symptoms may include [confusion](#), [feeling like one is going to pass out](#), [loss of consciousness](#), and [increased thirst](#).^[1] Anemia must be significant before a person becomes noticeably [pale](#).^[1] Additional symptoms may occur depending on the underlying cause.^[1] Anemia can be temporary or long term and can range from mild to severe.^[6]

Anemia can be caused by [blood loss](#), decreased red blood cell production, and increased [red blood cell breakdown](#).^[1] Causes of blood loss include [bleeding due to inflammation of the stomach or intestines](#), bleeding from [surgery](#), serious [injury](#), or [blood donation](#).^[1] Causes of decreased production include [iron deficiency](#), [folate deficiency](#), [vitamin B₁₂ deficiency](#), [thalassemia](#) and a number of [bone marrow tumors](#).^[1] Causes of increased breakdown include [genetic disorders](#) such as [sickle cell anemia](#), infections such as [malaria](#), and certain [autoimmune diseases](#) like [autoimmune hemolytic anemia](#).^[1]

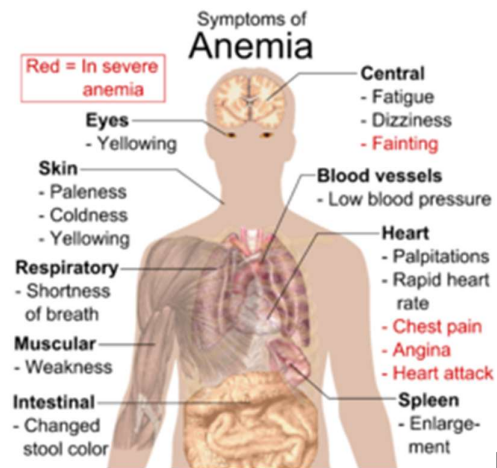
Anemia can also be classified based on the [size of the red blood cells](#) and [amount of hemoglobin in each cell](#).^[1] If the cells are small, it is called [microcytic anemia](#); if they are large, it is called [macrocytic anemia](#); and if they are normal sized, it is called [normocytic anemia](#).^[1] The diagnosis of anemia in men is based on a hemoglobin of less than 130 to 140 g/L (13 to 14 g/dL); in women, it is less than 120 to 130 g/L (12 to 13 g/dL).^{[1][7]} Further testing is then required to determine the cause.^{[1][8]}

Treatment depends on the specific cause. Certain groups of individuals, such as pregnant women, can benefit from the use of [iron pills](#) for prevention.^{[1][9]} [Dietary supplementation](#), without determining the specific cause, is not recommended.^[1] The use of [blood transfusions](#) is typically based on a person's signs and symptoms.^[1] In those without symptoms, they are not recommended unless hemoglobin levels are less than 60 to 80 g/L (6 to 8 g/dL).^{[1][10]} These recommendations may also apply to some people with acute bleeding.^[1] [Erythropoiesis-stimulating agents](#) are only recommended in those with severe anemia.^[10]

Anemia is the most common blood disorder, affecting about a fifth to a third of the global population.^{[1][11][12][13]} [Iron-deficiency anemia](#) is the most common cause of anemia worldwide, and affects nearly one billion people.^[14] In 2013, anemia due to iron deficiency resulted in about 183,000 deaths – down from 213,000 deaths in 1990.^[15] This condition is most prevalent in children^{[16][17]} with also an above average prevalence in elderly^[1] and women of reproductive age (especially during pregnancy).^[14] Anemia is one of the six [WHO](#) global nutrition targets for 2025 and for diet-related global targets endorsed by [World Health Assembly](#) in 2012 and 2013. Efforts to reach global targets contribute to reaching [Sustainable Development Goals](#) (SDGs),^[18] with anemia as one of the targets in [SDG 2](#) for achieving zero world hunger.^[19]

Signs and symptoms

[\[edit\]](#)



Main symptoms that may appear in anemia^[20]



The hand of a person with severe anemia (on the left, with ring) compared to one without (on the right)

A person with anemia may not have any symptoms, depending on the underlying cause, and no symptoms may be noticed, as the anemia is initially mild, and then the symptoms become worse as the anemia worsens. A patient with anemia may report [feeling tired](#), weak, decreased ability to concentrate, and sometimes [shortness of breath](#) on [exertion](#).^[21] These symptoms are unspecific and none of the symptoms alone or in combination show a good predictive value for the presence of anemia in non-clinical patients.^[22]



Symptoms of anemia are written in [Bengali](#), Hindi and English language on a board at [AIIMS Kalyani](#), [West Bengal](#).

Symptoms of anemia can come on quickly or slowly.^[23] Early on there may be few or no symptoms.^[23] If the anemia continues slowly (chronic), the body may adapt and compensate for this change. In this case, no symptoms may appear until the anemia becomes more severe.^{[20][24]} Symptoms can include feeling tired, weak, [dizziness](#), headaches, [intolerance to physical exertion](#), shortness of breath, difficulty concentrating, [irregular](#) or [rapid](#) heartbeat, cold hands and feet, [cold intolerance](#), [pale](#) or [yellow](#) skin, [poor appetite](#), easy bruising and bleeding, and [muscle weakness](#).^[23]

Anemia that develops quickly, often, has more severe symptoms, including, [feeling faint](#), [chest pain](#), sweating, increased thirst, and confusion.^{[23][25][26][27]} There may be also additional symptoms depending on the underlying cause.^[1]

In more severe anemia, the body may compensate for the lack of oxygen-carrying capability of the blood by increasing [cardiac output](#). The person may have symptoms related to this, such as [palpitations](#), [angina](#) (if pre-existing [heart disease](#) is present), intermittent [claudication](#) of the legs, and symptoms of [heart failure](#).^[28]

On examination, the signs exhibited may include [pallor](#) (pale skin, [mucosa](#), [conjunctiva](#) and [nail beds](#)), but this is not a reliable sign.

Iron-deficiency anemia may give symptoms that can include [spoon-shaped](#) nails, restless legs syndrome, and pica (the medical condition indicates the desire for things that are not food, such as ice, dirt, etc.).^[29] A blue coloration of the [sclera](#) may be noticed in some cases of iron-deficiency anemia.^[30] Vitamin B₁₂ deficiency anemia may result in decreased ability to think, memory loss, confusion, personality or mood changes, depression, difficulty walking, blurred vision, and irreversible nerve damage.^{[31][32]} Other specific causes of anemia may have signs and/or complications such as, [jaundice](#) with the rapid break down of [red blood cells](#) as with [hemolytic anemia](#), bone abnormalities with [thalassemia major](#), or leg [ulcers](#) as seen in [sickle cell disease](#).

In severe anemia, there may be signs of a [hyperdynamic circulation](#): [tachycardia](#) (a fast heart rate), [bounding pulse](#), [flow murmurs](#), and [cardiac ventricular hypertrophy](#) (enlargement). There may

be signs of [heart failure](#). [Pica](#), the consumption of non-food items such as ice, paper, wax, grass, hair or dirt, may be a symptom of iron deficiency;^[29] although it occurs often in those who have normal levels of [hemoglobin](#). Chronic anemia may result in behavioral disturbances in children as a direct result of impaired neurological development in infants, and reduced academic performance in children of school age. [Restless legs syndrome](#) is more common in people with [iron-deficiency anemia](#) than in the general population.^[33]

Causes

[\[edit\]](#)

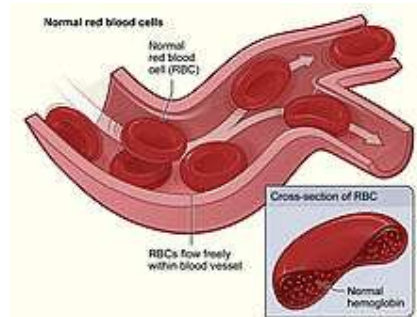


Figure shows normal red blood cells flowing freely in a blood vessel. The inset image shows a cross-section of a normal red blood cell with normal hemoglobin.^[34]

The causes of anemia may be classified as impaired red blood cell (RBC) production, increased RBC destruction (hemolytic anemia), blood loss and fluid overload ([hypervolemia](#)). Several of these may interplay to cause anemia. The most common cause of anemia is blood loss, but this usually does not cause any lasting symptoms unless a relatively impaired RBC production develops, in turn, most commonly by [iron deficiency](#).^[4]

Impaired production

[\[edit\]](#)

- Disturbance of proliferation and differentiation of stem cells
 - [Pure red cell aplasia](#)^[35]
 - [Aplastic anemia](#)^[35] affects all kinds of [blood cells](#). [Fanconi anemia](#) is a hereditary disorder or defect featuring aplastic anemia and various other abnormalities.
 - Anemia of [kidney failure](#)^[35] due to insufficient production of the [hormone erythropoietin](#)
 - Anemia of [endocrine disease](#)^[36]
- Disturbance of proliferation and maturation of [erythroblasts](#)
 - [Pernicious anemia](#)^[35] is a form of [megaloblastic anemia](#) due to [vitamin B₁₂ deficiency](#) dependent on impaired absorption of [vitamin B₁₂](#). Lack of dietary B₁₂ causes non-pernicious megaloblastic anemia.
 - Anemia of [folate deficiency](#),^[35] as with vitamin B₁₂, causes [megaloblastic anemia](#)

- [Anemia of prematurity](#), by diminished erythropoietin response to declining [hematocrit](#) levels, combined with blood loss from laboratory testing, generally occurs in premature infants at two to six weeks of age.
- Iron-deficiency anemia, resulting in deficient heme synthesis^[35]
- [Thalassemias](#), causing deficient globin synthesis^[35]
- [Congenital dyserythropoietic anemias](#), causing ineffective erythropoiesis
- Anemia of kidney failure^[35] (also causing stem cell dysfunction)
- Other mechanisms of impaired RBC production
 - [Myelophthitic anemia](#)^[35] or [myelophthitis](#) is a severe type of anemia resulting from the replacement of bone marrow by other materials, such as malignant tumors, fibrosis, or granulomas.
 - [Myelodysplastic syndrome](#)^[35]
 - anemia of [chronic inflammation](#)^[35]
 - Leukoerythroblastic anemia is caused by space-occupying lesions in the [bone marrow](#) that prevent normal production of blood cells.^[37]

Increased destruction

[\[edit\]](#)

Further information: [Hemolytic anemia](#)

Anemias of increased [red blood cell destruction](#) are generally classified as [hemolytic anemias](#). These types generally feature [jaundice](#), and elevated levels of [lactate dehydrogenase](#).^{[38][39]}

- Intrinsic (intracorpuseular) abnormalities^[35] cause premature destruction. All of these, except [paroxysmal nocturnal hemoglobinuria](#), are hereditary [genetic disorders](#).^[40]
 - [Hereditary spherocytosis](#)^[35] is a hereditary defect that results in defects in the RBC cell membrane, causing the erythrocytes to be sequestered and destroyed by the [spleen](#).
 - [Hereditary elliptocytosis](#)^[35] is another defect in membrane skeleton proteins.
 - [Abetalipoproteinemia](#),^[35] causing defects in membrane lipids
 - Enzyme deficiencies
 - [Pyruvate kinase](#) and [hexokinase](#) deficiencies,^[35] causing defect [glycolysis](#)
 - [Glucose-6-phosphate dehydrogenase deficiency](#) and [glutathione synthetase](#) deficiency,^[35] causing increased [oxidative stress](#)
 - [Hemoglobinopathies](#)
 - [Sickle cell anemia](#)^[35]
 - Hemoglobinopathies causing unstable hemoglobins^[35]

- [Paroxysmal nocturnal hemoglobinuria](#)^[35]
- Extrinsic (extracorporeal) abnormalities
 - [Antibody](#)-mediated
 - [Warm autoimmune hemolytic anemia](#) is caused by autoimmune attack against red blood cells, primarily by IgG. It is the most common of the [autoimmune hemolytic](#) diseases.^[41] It can be [idiopathic](#), that is, without any known cause, drug-associated or secondary to another disease such as [systemic lupus erythematosus](#), or a malignancy, such as [chronic lymphocytic leukemia](#).^[42]
 - [Cold agglutinin hemolytic anemia](#) is primarily mediated by IgM. It can be idiopathic^[43] or result from an underlying condition.
 - [Rh disease](#),^[35] one of the causes of [hemolytic disease of the newborn](#)
 - [Transfusion reaction](#) to [blood transfusions](#)^[35]
 - Mechanical trauma to red blood cells
 - [Microangiopathic hemolytic anemias](#), including [thrombotic thrombocytopenic purpura](#) and [disseminated intravascular coagulation](#)^[35]
 - Infections, including [malaria](#)^[35]
 - [Heart surgery](#)^[medical citation needed]
 - [Haemodialysis](#)^[medical citation needed]
 - Parasitic
 - [Trypanosoma congolense](#) alters the surfaces of RBCs of its host and this may explain *T. c.* induced anemia^[44]

Blood loss

[\[edit\]](#)

- [Anemia of prematurity](#), from frequent blood sampling for laboratory testing, combined with insufficient RBC production
- [Trauma](#)^[35] or [surgery](#), causing acute blood loss
- Gastrointestinal tract lesions,^[35] causing either acute bleeds (e.g. variceal lesions, [peptic ulcers](#), [hemorrhoids](#)^[45]) or chronic blood loss (e.g. [angiodysplasia](#))
- Gynecologic disturbances,^[35] also generally causing chronic blood loss
- From [menstruation](#), mostly among young women or older women who have [fibroids](#)
- Many type of cancers, including colorectal [cancer](#) and cancer of the [urinary bladder](#), may cause acute or chronic blood loss, especially at advanced stages
- Infection by intestinal [nematodes](#) feeding on blood, such as [hookworms](#)^[46] and the whipworm [Trichuris trichiura](#)^[47]

- [iatrogenic anemia](#), blood loss from repeated blood draws and medical procedures. ^{[48][49]}

The roots of the words *anemia* and *ischemia* both refer to the basic idea of "lack of blood", but anemia and [ischemia](#) are not the same thing in modern medical terminology. The word *anemia* used alone implies [widespread effects](#) from blood that either is too scarce (e.g., blood loss) or is dysfunctional in its oxygen-supplying ability (due to whatever type of hemoglobin or erythrocyte problem). In contrast, the word *ischemia* refers solely to the lack of blood (poor [perfusion](#)). Thus ischemia in a body part can cause localized anemic effects within those tissues. ^[50]

Fluid overload

[\[edit\]](#)

Fluid overload (hypervolemia) causes decreased hemoglobin concentration and apparent anemia: ^[51]

- General causes of hypervolemia include excessive sodium or fluid intake, sodium or water retention and fluid shift into the intravascular space. ^[52]
- From the 6th week of pregnancy, hormonal changes cause an increase in the mother's blood volume due to an increase in plasma. ^[53]

Intestinal inflammation

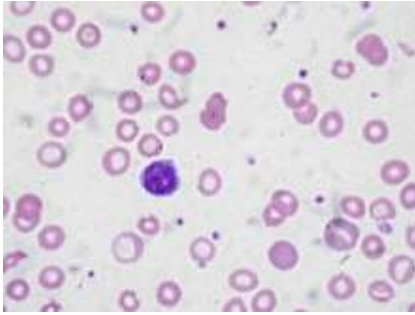
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Certain gastrointestinal disorders can cause anemia. The mechanisms involved are multifactorial and not limited to malabsorption but mainly related to chronic intestinal inflammation, which causes dysregulation of [hepcidin](#) that leads to decreased access of iron to the circulation. ^{[54][55][56]}

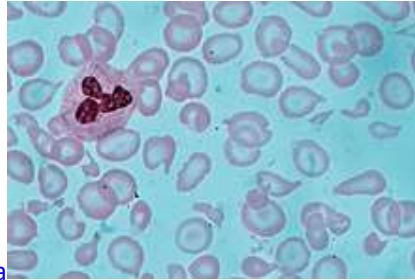
- [Helicobacter pylori](#) infection. ^[57]
- Gluten-related disorders: untreated [celiac disease](#) ^{[56][57]} and [non-celiac gluten sensitivity](#). ^[58] Anemia can be the only manifestation of celiac disease, in absence of gastrointestinal or any other symptoms. ^[59]
- [Inflammatory bowel disease](#). ^{[60][61]}

Diagnosis

[\[edit\]](#)



Peripheral blood smear microscopy of a patient with [iron-](#)



[deficiency anemia](#)

A Giemsa-stained blood film from a person with iron-deficiency anemia. This person also had hemoglobin Kenya.

Definitions

[\[edit\]](#)

There are a number of definitions of anemia; [reviews](#) provide comparison and contrast of them.^[62] A strict but broad definition is an absolute decrease in red blood cell mass,^[63] however, a broader definition is a lowered ability of the blood to carry [oxygen](#).^[64] An [operational definition](#) is a decrease in whole-blood [hemoglobin](#) concentration of more than 2 [standard deviations](#) below the [mean](#) of an age- and sex-matched [reference range](#).^[65]

It is difficult to directly measure RBC mass,^[66] so the [hematocrit](#) (amount of RBCs) or the hemoglobin (Hb) in the [blood](#) are often used instead to indirectly estimate the value.^[67] Hematocrit; however, is concentration dependent and is therefore not completely accurate. For example, during pregnancy a woman's RBC mass is normal but because of an increase in blood volume the hemoglobin and hematocrit are diluted and thus decreased. Another example would be bleeding where the RBC mass would decrease but the concentrations of hemoglobin and hematocrit initially remains normal until fluids shift from other areas of the body to the intravascular space.^[citation needed]

The anemia is also classified by severity into mild (110 g/L to normal), moderate (80 g/L to 110 g/L), and severe anemia (less than 80 g/L) in adults.^[68] Different values are used in pregnancy and children.^[68]

Testing

[\[edit\]](#)

Anemia is typically diagnosed on a [complete blood count](#). Apart from reporting the number of [red blood cells](#) and the hemoglobin level, the [automatic counters](#) also measure the size of the red blood cells by [flow cytometry](#), which is an important tool in distinguishing between the causes of anemia. Examination of a stained [blood smear](#) using a [microscope](#) can also be helpful, and it is sometimes a necessity in regions of the world where automated analysis is less accessible.^[citation needed]

WHO's Hemoglobin thresholds used to define anemia^[69] (1 g/dL = 0.6206 mmol/L)

Age or gender group	Hb threshold (g/dL)	Hb threshold (mmol/L)
Children (0.5–5.0 yrs)	11.0	6.8
Children (5–12 yrs)	11.5	7.1
Teens (12–15 yrs)	12.0	7.4
Women, non-pregnant (>15yrs)	12.0	7.4
Women, pregnant	11.0	6.8
Men (>15yrs)	13.0	8.1

A blood test will provide counts of white blood cells, red blood cells and platelets. If anemia appears, further tests may determine what type it is, and whether it has a serious cause. although of that, it is possible to refer to the genetic history and physical diagnosis.^[70] These tests may also include [serum ferritin](#), [iron studies](#), [vitamin B₁₂](#), genetic testing, and a [bone marrow sample](#), if needed.^{[71][72]}

Reticulocyte counts, and the "kinetic" approach to anemia, have become more common than in the past in the large medical centers of the United States and some other wealthy nations, in part because some automatic counters now have the capacity to include reticulocyte counts.

A [reticulocyte](#) count is a quantitative measure of the [bone marrow](#)'s production of new red blood cells. The [reticulocyte production index](#) is a calculation of the ratio between the level of anemia and the extent to which the reticulocyte count has risen in response. If the degree of anemia is significant, even a "normal" reticulocyte count actually may reflect an inadequate response.

If an automated count is not available, a reticulocyte count can be done manually following special staining of the blood film. In manual examination, activity of the bone marrow can also be gauged qualitatively by subtle changes in the numbers and the morphology of young RBCs by examination under a microscope. Newly formed RBCs are usually slightly larger than older RBCs and show polychromasia. Even where the source of blood loss is obvious, evaluation of [erythropoiesis](#) can help assess whether the bone marrow will be able to compensate for the loss and at what rate.

When the cause is not obvious, clinicians use other tests, such as: [ESR](#), serum iron, [transferrin](#), [RBC folate level](#), [hemoglobin electrophoresis](#), [renal function](#) tests (e.g. [serum creatinine](#)) although the tests will depend on the clinical hypothesis that is being investigated.

When the diagnosis remains difficult, a [bone marrow examination](#) allows direct examination of the precursors to red cells, although is rarely used as is painful, invasive and is hence reserved for cases where severe pathology needs to be determined or excluded.^[medical citation needed]

Red blood cell size

[\[edit\]](#)

In the morphological approach, anemia is classified by the size of red blood cells; this is either done automatically or on microscopic examination of a peripheral blood smear. The size is reflected in the [mean corpuscular volume](#) (MCV). If the cells are smaller than normal (under 80 fl), the anemia is said to be [microcytic](#); if they are normal size (80–100 fl), normocytic; and if they are larger than

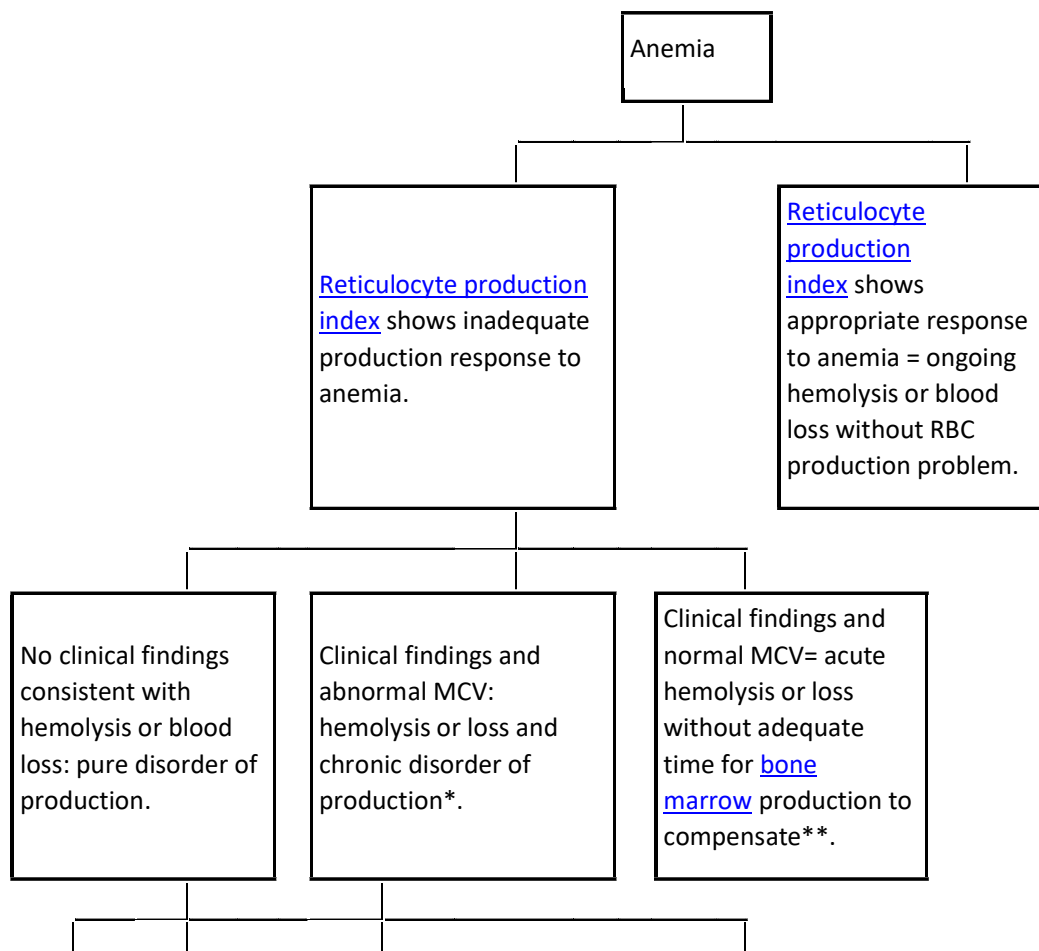
normal (over 100 fl), the anemia is classified as [macrocytic](#). This scheme quickly exposes some of the most common causes of anemia; for instance, a microcytic anemia is often the result of [iron deficiency](#).

In clinical workup, the MCV will be one of the first pieces of information available, so even among clinicians who consider the "kinetic" approach more useful philosophically, morphology will remain an important element of classification and diagnosis. Limitations of MCV include cases where the underlying cause is due to a combination of factors – such as iron deficiency (a cause of microcytosis) and vitamin [B12 deficiency](#) (a cause of macrocytosis) where the net result can be normocytic cells. [\[medical citation needed\]](#)

Production vs. destruction or loss

[\[edit\]](#)

The "kinetic" approach to anemia yields arguably the most clinically relevant classification of anemia. This classification depends on evaluation of several hematological parameters, particularly the blood reticulocyte (precursor of mature RBCs) count. This then yields the classification of defects by decreased RBC production versus increased RBC destruction or loss. Clinical signs of loss or destruction include abnormal [peripheral blood smear](#) with signs of hemolysis; elevated [LDH](#) suggesting cell destruction; or clinical signs of bleeding, such as guaiac-positive stool, radiographic findings, or frank bleeding. [\[medical citation needed\]](#) The following is a simplified schematic of this approach: [\[medical citation needed\]](#)



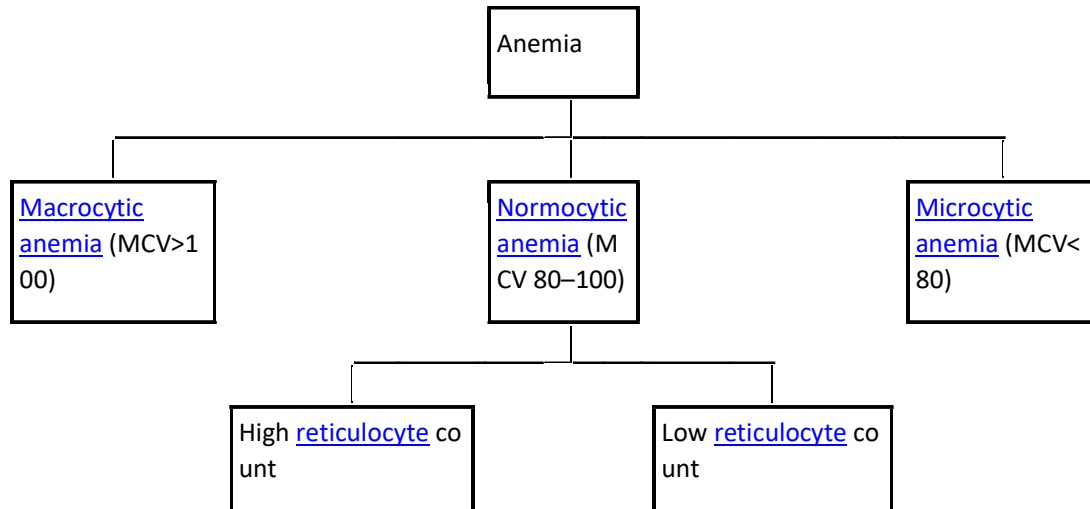
[Macrocytic anemia](#) (MCV>100)

[Normocytic anemia](#) (80<MCV<100)

[Microcytic anemia](#) (MCV<80)

** For instance, sickle cell anemia with superimposed iron deficiency; chronic gastric bleeding with B₁₂ and folate deficiency; and other instances of anemia with more than one cause.*

*** Confirm by repeating reticulocyte count: ongoing combination of low reticulocyte production index, normal MCV and hemolysis or loss may be seen in bone marrow failure or anemia of chronic disease, with superimposed or related hemolysis or blood loss. Here is a schematic representation of how to consider anemia with MCV as the starting point:*



Other characteristics visible on the peripheral smear may provide valuable clues about a more specific diagnosis; for example, abnormal [white blood cells](#) may point to a cause in the [bone marrow](#).

Microcytic

[\[edit\]](#)

Main article: [Microcytic anemia](#)

Microcytic anemia is primarily a result of hemoglobin synthesis failure/insufficiency, which could be caused by several etiologies:

- [Heme](#) synthesis defect
 - [Iron-deficiency anemia](#) (microcytosis is not always present)
 - [Anemia of chronic disease](#) (more commonly presenting as normocytic anemia)
- [Globin](#) synthesis defect
 - Alpha-, and beta-[thalassemia](#)
 - HbE syndrome
 - HbC syndrome
 - Various other unstable hemoglobin diseases
- [Sideroblastic](#) defect

- Hereditary sideroblastic anemia
- Acquired sideroblastic anemia, including [lead toxicity](#)^[73]
- Reversible sideroblastic anemia

Iron-deficiency anemia is the most common type of anemia overall and it has many causes. RBCs often appear hypochromic (paler than usual) and microcytic (smaller than usual) when viewed with a microscope.

- Iron-deficiency anemia is due to insufficient dietary intake or absorption of [iron](#) to meet the body's needs. Infants, toddlers, and pregnant women have higher than average needs. Increased iron intake is also needed to offset blood losses due to digestive tract issues, frequent blood donations, or [heavy menstrual periods](#).^[74] Iron is an essential part of hemoglobin, and low iron levels result in decreased incorporation of hemoglobin into red blood cells. In the United States, 12% of all women of childbearing age have iron deficiency, compared with only 2% of adult men. The incidence is as high as 20% among African American and Mexican American women.^[75] In India it is even more than 50%.^[76] Studies have linked iron deficiency without anemia to poor school performance and lower [IQ](#) in teenage girls, although this may be due to socioeconomic factors.^{[77][78]} Iron deficiency is the most prevalent deficiency state on a worldwide basis. It is sometimes the cause of abnormal fissuring of the angular (corner) sections of the lips ([angular stomatitis](#)).
- In the United States, the most common cause of iron deficiency is bleeding or blood loss, usually from the [gastrointestinal tract](#). [Fecal occult blood testing](#), [upper endoscopy](#) and [lower endoscopy](#) should be performed to identify bleeding lesions. In older men and women, the chances are higher that bleeding from the gastrointestinal tract could be due to [colon polyps](#) or [colorectal cancer](#).
- Worldwide, the most common cause of iron-deficiency anemia is parasitic infestation ([hookworms](#), [amebiasis](#), [schistosomiasis](#) and [whipworms](#)).^[79]

The [Mentzer index](#) (mean cell volume divided by the RBC count) predicts whether microcytic anemia may be due to iron deficiency or thalassemia, although it requires confirmation.^[80]^[citation needed]

Macrocytic

[\[edit\]](#)

Main article: [Macrocytic anemia](#)

- [Megaloblastic anemia](#), the most common cause of macrocytic anemia, is due to a deficiency of either [vitamin B₁₂](#), [folic acid](#), or both.^[81] Deficiency in folate or vitamin B₁₂ can be due either to inadequate intake or [insufficient absorption](#). Folate deficiency normally does not produce neurological symptoms, while B₁₂ deficiency does.
 - [Pernicious anemia](#) is caused by a lack of [intrinsic factor](#), which is required to absorb vitamin B₁₂ from food. A lack of intrinsic factor may arise from an [autoimmune](#) condition targeting the [parietal cells](#) (atrophic gastritis) that produce intrinsic factor or against intrinsic factor itself. These lead to poor absorption of vitamin B₁₂.
 - Macrocytic anemia can also be caused by the removal of the functional portion of the stomach, such as during [gastric bypass](#) surgery, leading to reduced vitamin

B₁₂/folate absorption. Therefore, one must always be aware of anemia following this procedure.

- [Hypothyroidism](#)
- [Alcoholism](#) commonly causes a [macrocytosis](#), although not specifically anemia. Other types of [liver disease](#) can also cause macrocytosis.
- Drugs such as [methotrexate](#), [zidovudine](#), and other substances may inhibit [DNA replication](#) such as [heavy metals](#)

Macrocytic anemia can be further divided into "megaloblastic anemia" or "nonmegaloblastic macrocytic anemia". The cause of megaloblastic anemia is primarily a failure of DNA synthesis with preserved RNA synthesis, which results in restricted cell division of the progenitor cells. The megaloblastic anemias often present with neutrophil hypersegmentation (six to 10 lobes). The nonmegaloblastic macrocytic anemias have different etiologies (i.e. unimpaired DNA globin synthesis,) which occur, for example, in alcoholism. In addition to the nonspecific symptoms of anemia, specific features of vitamin B₁₂ deficiency include [peripheral neuropathy](#) and [subacute combined degeneration of the cord](#) with resulting balance difficulties from posterior column spinal cord pathology.^[82] Other features may include a smooth, red tongue and [glossitis](#). The treatment for vitamin B₁₂-deficient anemia was first devised by [William Murphy](#), who bled dogs to make them anemic, and then fed them various substances to see what (if anything) would make them healthy again. He discovered that ingesting large amounts of liver seemed to cure the disease. [George Minot](#) and [George Whipple](#) then set about to isolate the curative substance chemically and ultimately were able to isolate the [vitamin B₁₂](#) from the liver. All three shared the 1934 [Nobel Prize in Medicine](#).^[83]

Normocytic

[\[edit\]](#)

Main article: [Normocytic anemia](#)

Normocytic anemia occurs when the overall hemoglobin levels are decreased, but the red blood cell size ([mean corpuscular volume](#)) remains normal. Causes include:

- Acute [blood loss](#)
- [Anemia of chronic disease](#)
- [Aplastic anemia](#) (bone marrow failure)
- [Hemolytic anemia](#)

Dimorphic

[\[edit\]](#)

A dimorphic appearance on a peripheral blood smear occurs when there are two simultaneous populations of red blood cells, typically of different size and hemoglobin content (this last feature affecting the color of the red blood cell on a stained peripheral blood smear). For example, a person recently transfused for iron deficiency would have small, pale, iron deficient red blood cells (RBCs) and the donor RBCs of normal size and color. Similarly, a person transfused for severe folate or

vitamin B12 deficiency would have two cell populations, but, in this case, the patient's RBCs would be larger and paler than the donor's RBCs.

A person with sideroblastic anemia (a defect in heme synthesis, commonly caused by alcoholism, but also drugs/toxins, nutritional deficiencies, a few acquired and rare congenital diseases) can have a dimorphic smear from the sideroblastic anemia alone. Evidence for multiple causes appears with an elevated RBC distribution width (RDW), indicating a wider-than-normal range of red cell sizes, also seen in common nutritional anemia. ^[citation needed]

Heinz body anemia

[\[edit\]](#)

[Heinz bodies](#) form in the cytoplasm of RBCs and appear as small dark dots under the microscope. In animals, Heinz body anemia has many causes. It may be drug-induced, for example in cats and dogs by [acetaminophen](#) (paracetamol), ^[84] or may be caused by eating various plants or other substances:

- In [cats](#) and dogs after eating either raw or cooked plants from the genus [Allium](#), for example, [onions](#) or garlic. ^[85]
- In [dogs](#) after ingestion of [zinc](#), for example, after eating [U.S. pennies](#) minted after 1982. ^[84]
- In [horses](#) which eat dry or wilted [red maple](#) leaves. ^[86]

Hyperanemia

[\[edit\]](#)

Hyperanemia is a severe form of anemia, in which the [hematocrit](#) is below 10%. ^[87]

Refractory anemia

[\[edit\]](#)

Refractory anemia, an anemia which does not respond to [treatment](#), ^[88] is often seen secondary to myelodysplastic syndromes. ^[89] Iron-deficiency anemia may also be refractory as a manifestation of gastrointestinal problems which disrupt [iron absorption](#) or cause [occult bleeding](#). ^[90]

Transfusion dependent

[\[edit\]](#)

Transfusion dependent anemia is a form of anemia where ongoing blood transfusion are required. ^[91] Most people with myelodysplastic syndrome develop this state at some point in time. ^[92] [Beta thalassemia](#) may also result in transfusion dependence. ^{[93][94]} Concerns from repeated blood transfusions include [iron overload](#). ^[92] This iron overload may require [chelation therapy](#). ^[95]

Treatment

[\[edit\]](#)

The global market for anemia treatments is estimated at more than USD 23 billion per year and is fast growing because of the rising prevalence and awareness of anemia. The types of anemia treated with drugs are iron-deficiency anemia, [thalassemia](#), aplastic anemia, [hemolytic anemia](#), [sickle cell anemia](#), and pernicious anemia, the most important of them being deficiency and sickle cell anemia with together 60% of market share because of highest prevalence as well as higher treatment costs

compared with other types.^[13] Treatment for anemia depends on cause and severity. Vitamin supplements given orally ([folic acid](#) or vitamin B₁₂) or intramuscularly ([vitamin B₁₂](#)) will replace specific deficiencies.^[1]

Apart from that, iron supplements, antibiotics, immunosuppressant, bone marrow stimulants, corticosteroids, gene therapy and iron chelating agents are forms of anemia treatment drugs, with immunosuppressants and corticosteroids accounting for 58% of the market share. A paradigm shift towards gene therapy and monoclonal antibody therapies is observed.^[13]

Oral iron

[\[edit\]](#)

Nutritional iron deficiency is common in developing nations. An estimated two-thirds of children and of women of childbearing age in most developing nations are estimated to have iron deficiency without anemia with one-third of them having an iron deficiency with anemia.^[96] Iron deficiency due to inadequate dietary iron intake is rare in men and postmenopausal women. The diagnosis of iron deficiency mandates a search for potential sources of blood loss, such as gastrointestinal bleeding from ulcers or colon cancer.^[citation needed]

Mild to moderate iron-deficiency anemia is treated by oral iron supplementation with [ferrous sulfate](#), [ferrous fumarate](#), or [ferrous gluconate](#). Daily iron supplements have been shown to be effective in reducing anemia in women of childbearing age.^[97] When taking iron supplements, stomach upset or darkening of the feces are commonly experienced. The stomach upset can be alleviated by taking the iron with food; however, this decreases the amount of iron absorbed. [Vitamin C](#) aids in the body's ability to absorb iron, so taking oral iron supplements with orange juice is of benefit.^[98]

In the anemia of chronic kidney disease, [recombinant erythropoietin](#) or [epoetin alfa](#) is recommended to stimulate RBC production, and if iron deficiency and inflammation are also present, concurrent [parenteral iron](#) is also recommended.^[99]

Injectable iron

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In cases where oral iron has either proven ineffective, would be too slow (for example, pre-operatively), or where absorption is impeded (for example in cases of inflammation), [parenteral iron](#) preparations can be used. Parenteral iron can improve iron stores rapidly and is also effective for treating people with postpartum haemorrhage, inflammatory bowel disease, and chronic heart failure.^[100] The body can absorb up to 6 mg iron daily from the gastrointestinal tract. In many cases, the patient has a deficit of over 1,000 mg of iron which would require several months to replace. This can be given concurrently with [erythropoietin](#) to ensure sufficient iron for increased rates of [erythropoiesis](#).^[101]

Blood transfusions

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Blood transfusions in those without symptoms is not recommended until the hemoglobin is below 60 to 80 g/L (6 to 8 g/dL).^[1] In those with [coronary artery disease](#) who are not actively bleeding transfusions are only recommended when the hemoglobin is below 70 to 80g/L (7 to 8

g/dL).^[10] Transfusing earlier does not improve survival.^[102] Transfusions otherwise should only be undertaken in cases of cardiovascular instability.^[103]

A 2012 review concluded that when considering blood transfusions for anaemia in people with advanced cancer who have fatigue and breathlessness (not related to cancer treatment or haemorrhage), consideration should be given to whether there are alternative strategies can be tried before a blood transfusion.^[104]

Vitamin B₁₂ intramuscular injections

[\[edit\]](#)

In many cases, vitamin B₁₂ is used by [intramuscular injection](#) in severe cases or cases of malabsorption of dietary-B₁₂. Pernicious anemia caused by loss of intrinsic factor cannot be prevented.^[105] If there are other, reversible causes of low vitamin B₁₂ levels, the cause must be treated.^[106]

Vitamin B₁₂ deficiency anemia is usually easily treated by providing the necessary level of vitamin B₁₂ supplementation.^[107] The injections are quick-acting, and symptoms usually go away within one to two weeks.^[107] As the condition improves, doses are reduced to weeks and then can be given monthly. Intramuscular therapy leads to more rapid improvement and should be considered in patients with severe deficiency or severe [neurologic](#) symptoms.^[107] Treatment should begin rapidly for severe neurological symptoms, as some changes can become permanent.^[32] In some individuals lifelong treatment may be needed.^[32]

Erythropoiesis-stimulating agents

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The objective for the administration of an [erythropoiesis-stimulating agent](#) (ESA) is to maintain hemoglobin at the lowest level that both minimizes transfusions and meets the individual person's needs.^[108] They should not be used for mild or moderate anemia.^[102] They are not recommended in people with [chronic kidney disease](#) unless hemoglobin levels are less than 10 g/dL or they have symptoms of anemia. Their use should be along with parenteral iron.^{[108][109]} The 2020 Cochrane Anaesthesia Review Group review of erythropoietin (EPO) plus iron versus control treatment including placebo or iron for preoperative anaemic adults undergoing non-cardiac surgery ^[110] demonstrated that patients were much less likely to require red cell transfusion and in those transfused, the volumes were unchanged (mean difference -0.09, 95% CI -0.23 to 0.05). Pre-operative hemoglobin concentration was increased in those receiving 'high dose' EPO, but not 'low dose'.^[citation needed]

Hyperbaric oxygen

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Treatment of exceptional blood loss (anemia) is recognized as an indication for [hyperbaric oxygen](#) (HBO) by the [Undersea and Hyperbaric Medical Society](#).^{[111][112]} The use of HBO is indicated when [oxygen](#) delivery to tissue is not sufficient in patients who cannot be given [blood transfusions](#) for [medical](#) or [religious](#) reasons. HBO may be used for medical reasons when threat of [blood product](#) incompatibility or concern for [transmissible disease](#) are factors.^[111] The beliefs of some religions (ex: [Jehovah's Witnesses](#)) may require they use the HBO method.^[111] A 2005 review of the use of HBO in severe anemia found all publications reported positive results.^[113]

Preoperative anemia

[\[edit\]](#)

An estimated 30% of adults who require non-cardiac surgery have anemia.^[114] In order to determine an appropriate preoperative treatment, it is suggested that the cause of anemia be first determined.^[115] There is moderate level medical evidence that supports a combination of iron supplementation and erythropoietin treatment to help reduce the requirement for red blood cell transfusions after surgery in those who have preoperative anemia.^[114]

Epidemiology

[\[edit\]](#)

Anemia affects 27% of the world's population with iron-deficiency anemia accounting for more than 60% of it.^[116] A moderate degree of iron-deficiency anemia affected approximately 610 million people worldwide or 8.8% of the population.^[14] It is somewhat more common in females (9.9%) than males (7.8%).^[14] Mild iron-deficiency anemia affects another 375 million.^[14] Severe anaemia is prevalent globally, and especially in sub-Saharan Africa^[117] where it is associated with infections including malaria and invasive bacterial infections.^[118]