

Drug used for anemia

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BCPS

Introduction

Anemia definitions

Anemia is defined for patient care as a reduction in one or more of the major red blood cell (RBC) measurements obtained as a part of the complete blood count (CBC): hemoglobin concentration, hematocrit, or RBC count. A low hemoglobin concentration and/or low hematocrit are the parameters most widely used to diagnose anemia, with the following cutoffs:

Females – Hemoglobin <11.9 g/dL (119 g/L) or hematocrit <35 percent

Males – Hemoglobin <13.6 g/dL (136 g/L) or hematocrit <40 percent

Additional information about how these values are determined and variation in cutoff values includes the following:

Hemoglobin – Hemoglobin is reported as the concentration of hemoglobin in whole blood. When measured by an electronic counter, hemoglobin concentration is directly determined, while hematocrit is calculated from other parameters. For this reason, many physicians prefer to use hemoglobin to define and describe anemia. Values may be expressed as grams of hemoglobin per 100 mL (g/dL) or per liter (g/L).

Hematocrit – Hematocrit (HCT), also called packed cell volume (PCV), is the percentage of blood volume occupied by RBCs. It can be measured directly following centrifugation of a blood sample.

RBC count – RBC count is the number of RBCs contained in a specified volume of whole blood, usually expressed as millions of cells per microL of whole blood.

General signs and symptoms of anemia include fatigue, palpitations, shortness of breath, pallor, dizziness, and insomnia.

- Pregnancy
- During a healthy pregnancy, maternal red cell mass increases, but plasma volume increases to a greater degree, causing a relative decrease in hemoglobin and HCT. By the criterion of RBC mass, the individual is not anemic, but hemoglobin, HCT, and RBC count frequently decrease to anemic levels. The terms "physiologic" or "dilutional" anemia have been applied to this setting, although these individuals are not actually anemic and do not require evaluation as long as their hemoglobin remains
 - ≥ 11 g/dL in the first trimester,
 - ≥ 10.5 g/dL in the second trimester,
 - ≥ 10.5 g/dL in the third trimester.

- Smoking causes an increase in hemoglobin, HCT, and RBC count due to increased levels of carbon monoxide, which reduces oxygen delivery. Thus, individuals who smoke or have significant exposure to secondary smoke or other sources of carbon monoxide may have HCT higher than normal. A study of blood donors who smoke found a significant correlation between the patients' blood carboxyhemoglobin and hemoglobin values.
- Medications/drugs
 - Certain medications can increase the hemoglobin concentration; examples include androgens and sodium-glucose co-transporter 2 (SGLT2) inhibitors.
 - Hemoconcentration – Individuals with dehydration or hypovolemia related to vomiting or diarrhea will have a relative increase in hemoglobin and HCT due to hemoconcentration. Anemia will become apparent after volume replacement. This is particularly a problem in patients with severe burns, in whom substantial RBC loss may be masked by exudative loss of plasma volume until fluid resuscitation has occurred
 - High altitude – Persons living at high altitude have higher values than those living at sea level due to relative hypoxia

Anemia causes:

1-chronic blood loss,

2-Diseases (bone marrow abnormalities, hemolysis, infections, malignancy, endocrine deficiencies, renal failure, and a number of other disease states).

3-A large number of drugs cause toxic effects on blood cells, hemoglobin production, or erythropoietic organs, which, in turn, may cause anemia.

4-Nutritional anemias are caused by dietary deficiencies of substances such as iron, folic acid, and vitamin B12 (cyanocobalamin) that are necessary for normal erythropoiesis.

5-a genetic predisposition to anemia, such as sickle cell disease, thalassemia

- Role of blood in oxygen delivery — Blood delivers oxygen to the tissues, and the vast majority of oxygen delivered is bound to hemoglobin in RBCs. Thus, anemia has the potential to reduce oxygen delivery and, most importantly, end-organ oxygen utilization. However, most patients are able to increase tissue oxygen delivery as well as the extraction of oxygen from the RBCs over a range of hemoglobin concentrations. The major physiologic considerations relevant to anemic patients are the degree to which oxygen delivery to the tissues is adequate, the extent of oxygen extraction at the tissue level, and whether compensatory mechanisms for maintaining oxygen delivery and utilization will become overwhelmed or deleterious

- Oxygen delivery (DO₂) is determined by the formula:
- $DO_2 = \text{cardiac output} \times \text{arterial oxygen content}$
- In healthy patients, DO₂ can generally be raised by increasing cardiac output (via increased heart rate or stroke volume). In critically ill patients, DO₂ may become more dependent on arterial oxygen content, and end-organ oxygen utilization can become pathologically dependent upon DO₂ (supply dependence).

ARTERIAL OXYGEN DELIVERY (DO_2)

DO_2

=

CO

HR

x

SV

preload

cardiac
function

afterload

x

$1.34 \times [Hb] \times SpO_2$

+

$0.003 \times PaO_2$

CaO_2

Oxygen delivery

Hemoglobin

Amount of dissolved O_2 in the blood

$$DO_2 = \dot{Q} \times (Hb \times SaO_2 \times 1.34 + (PaO_2 \times 0.003))$$

Cardiac output

Arterial O_2 saturation

Treatment of anemia

1-Blood transfusion
2-medications

1-Blood transfusion

- Restrictive transfusion strategy for most stable patients — For most patients, we recommend using a restrictive transfusion strategy (ie, giving less blood; transfusing at a lower hemoglobin level; and aiming for a lower target hemoglobin level) rather than a liberal transfusion strategy (ie, giving more blood; transfusing at a higher hemoglobin level) based on the results of multiple clinical trials. (Related Pathway(s): Anemia: Indications for red blood cell transfusion in hospitalized adults.) For most hemodynamically stable medical and surgical patients, we recommend considering transfusion at a hemoglobin of 7 to 8 g/dl

Major exceptions to the use of a threshold of 7 to 8 g/dL, where evidence is insufficient to guide therapy, include the following:

Symptomatic patients may be transfused at higher hemoglobin levels to treat symptoms. We agree with the premise that symptomatic anemia should be treated with transfusion in patients with hemoglobin <10 g/dL, regardless of the hemoglobin level, provided that the symptoms are severe enough and are clearly related to the anemia rather than the underlying condition. It is reasonable to defer transfusion for some symptomatic individuals with a hemoglobin between 7 and 10 g/dL; an example would be a young person without comorbidities or coronary artery disease whose hemoglobin is 8 g/dL, is not expected to decline further, and/or is expected to increase their hemoglobin within one or two weeks.

Patients with acute coronary syndromes have not been adequately evaluated in clinical trials and may require higher thresholds for transfusion. Acute coronary syndrome – The optimal transfusion threshold in the setting of acute coronary syndromes (ACS; ie, acute myocardial infarction [MI], unstable angina) remains unresolved. Our practice in patients with ACS is to transfuse when hemoglobin is <8 g/dL and to consider transfusion when the hemoglobin is between 8 and 10 g/dL. If the patient has ongoing ischemia or other symptoms, we maintain the hemoglobin ≥ 10 g/dL

Threshold-based transfusion is not appropriate for patients requiring massive transfusion, such as in the setting of trauma or serious gastrointestinal bleeding.

- Pre-existing coronary artery disease — A transfusion threshold of 8 g/dl
- Heart failure — Anemia and heart failure (HF) often coexist for a variety of reasons (eg, cytokine changes, dilutional anemia, medical therapy for HF). The approach to transfusion (including more restrictive thresholds for asymptomatic individuals and transfusion for symptoms if hemoglobin is <10 g/dL).
- Intensive care unit/septic shock — Restrictive transfusion appears to be safe in medical patients in an intensive care unit (ICU), with the possible exception of patients with ischemic heart disease/acute coronary syndrome. The use of a threshold of 7 g/dL in hemodynamically stable patients in the ICU is supported by data from the Transfusion Requirements in Critical Care (TRICC) trial.
- - Non-cardiac surgery — Results of a randomized trial in patients undergoing hip surgery suggest that it is reasonable to use a lower threshold restrictive strategy of 8 g/dL for patients who have undergone surgery, in the absence of symptoms of anemia, even in elderly patients with underlying cardiovascular disease or cardiovascular risk factors.
- Cardiac surgery — Transfusion thresholds in cardiac surgery have been evaluated in multiple randomized trials. A 2018 meta-analysis of data from these trials suggested that a restrictive transfusion strategy with a hemoglobin threshold of 7.5 to 8 g/dL appears to be reasonable in patients undergoing cardiac surgery with cardiopulmonary bypass.

Thresholds for red blood cell transfusion in adults

Condition	Hemoglobin threshold for transfusion
Symptomatic patient (eg, myocardial ischemia, hemodynamic instability)	10 g/dL*[1]
Hospitalized patient	
Preexisting coronary artery disease	8 g/dL*
Acute coronary syndromes, including acute MI	8 to 10 g/dL¶[2]
ICU (hemodynamically stable)	7 g/dL*[3,4]
Gastrointestinal bleeding (hemodynamically stable)	7 g/dL*[5,6]
Orthopedic surgery	8 g/dL*[1]
Cardiac surgery	7.5 g/dL*[7,8]
Ambulatory outpatient	
Oncology patient in treatment	7 to 8 g/dL¶
Palliative care setting	As needed for symptoms; hospice

Complications of blood transfusions

ACUTE COMPLICATIONS

IMMUNOLOGIC

- Allergic reactions
- Febrile non-haemolytic transfusion reactions
- Anaphylactic reaction
- Transfusion related acute lung injury
- Acute haemolytic transfusion reaction

NON-IMMUNOLOGIC

- Bacterial contamination/sepsis
- Transfusion associated circulatory overload
- Clotting abnormalities
- Metabolic complications: citrate toxicity, hyperkalaemia, hypocalcaemia, hypothermia, etc

Others: Air embolism

DELAYED/LONG-TERM COMPLICATIONS

IMMUNOLOGIC

- Delayed haemolytic transfusion reaction
- Delayed serologic transfusion reaction
- Allo-immunization
- Transfusion associated Graft Versus Host Disease
- Post transfusion purpura

NON IMMUNOLOGIC

- Transfusion transmissible infections
- Thrombophlebitis
- Iron overload

Iron

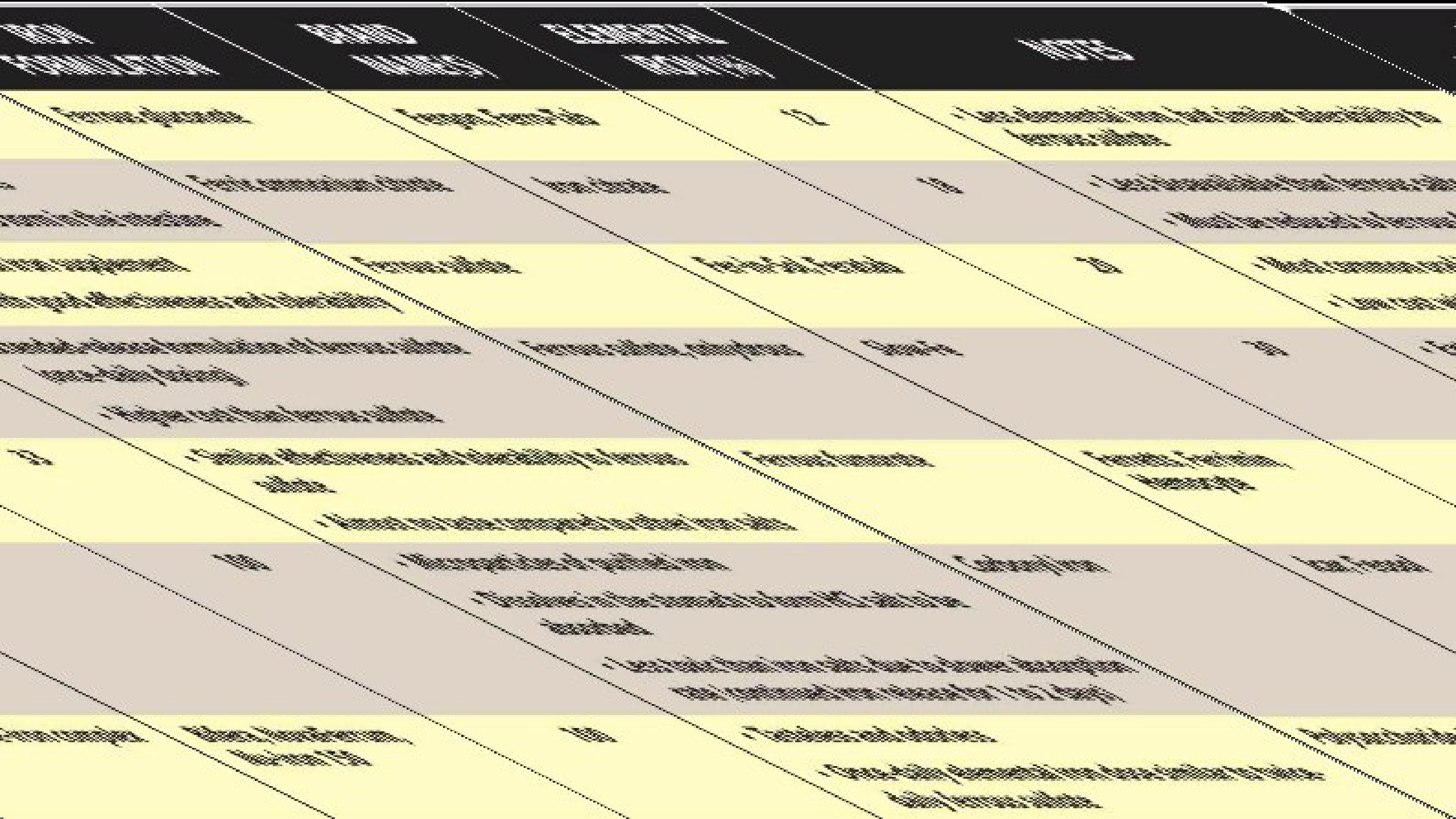


Iron is stored in the intestinal mucosal cells, liver, spleen, and bone marrow as ferritin (an iron–protein complex) and delivered to the marrow for hemoglobin production by transferrin, a transport protein. Iron deficiency, the most common nutritional deficiency, results from a negative iron balance due to depletion of iron stores and/or inadequate intake, such as acute or chronic blood loss, menstruating or pregnant women, or periods of accelerated growth in children. In addition to general signs and symptoms of anemia, iron deficiency anemia may cause pica (hunger for ice, dirt, paper, etc.), koilonychias (upward curvature of the finger and toe nails), and soreness and cracking at the corners of the mouth.

Mechanism of action

Supplementation with elemental iron corrects the iron deficiency. The CDC recommends 150 to 180 mg/day of oral elemental iron administered in divided doses two to three times daily for patients with iron deficiency anemia.

- Pharmacokinetics
- Iron is absorbed after oral administration. Acidic conditions in the stomach keep iron in the reduced ferrous form, which is the more soluble form. Iron is then absorbed in the duodenum. [Note: The amount absorbed depends on the current body stores of iron. If iron stores are adequate, less iron is absorbed. If stores are low, more iron is absorbed.] The relative percentage of iron absorbed decreases with increasing doses. Parenteral formulations of iron, such as iron dextran, sodium ferric gluconate, ferumoxytol, ferric carboxymaltose, and iron sucrose, are also available. While parenteral administration treats iron deficiency rapidly, oral administration may take several weeks.
- Oral formulations in table:



Parenteral Iron Therapy

Iron Product	Replacement Therapy (TSAT < 30% and ferritin < 500 ng/mL)
Iron dextran (high-molecular-weight iron dextran: Dexferrum) (low-molecular-weight iron dextran: INFeD)	IVP: 100 mg IV three times/wk during HD × 10 doses (1 g)
Sodium ferric gluconate complex (Ferrlecit and generic)	125 mg IV three times/wk during HD × 8 doses (1 g)
Iron sucrose (Venofer)	100 mg IV three times/wk during HD × 10 doses (1 g) For non-HD CKD, 200 mg IV × 5 doses
Ferumoxytol (Feraheme)	510 mg at up to 30 mg/s, followed by a second 510-mg IV dose 3–8 days later (all CKD)
Ferric carboxymaltose (Injectafer)	15 mg/kg IV up to 750 mg; may repeat after at least 7 days (maximum 1500 mg of elemental iron per two-dose course)

Adverse effects

Gastrointestinal (GI) disturbances caused by local irritation (abdominal pain, constipation, nausea, diarrhea) and dark stools are the most common adverse effects of oral iron supplements. Parenteral iron formulations may be used in those who cannot tolerate or inadequately absorb oral iron, as well as those receiving erythropoietin with hemodialysis or chemotherapy. Fatal hypersensitivity and anaphylactoid reactions can occur in patients receiving parenteral iron (mainly iron dextran formulations). A test dose should be administered prior to iron dextran. In addition, intravenous iron should be used cautiously in the presence of active infections. [Note: Iron is essential for bacterial growth.]

Folic acid (folate)

The primary use of folic acid is in treating deficiency states that arise from inadequate levels of the vitamin. Folate deficiency may be caused by

- 1) increased demand (for example, pregnancy and lactation),
- 2) poor absorption caused by pathology of the small intestine,
- 3) alcoholism,
- 4) treatment with drugs that are dihydrofolate reductase inhibitors (for example, methotrexate and trimethoprim), drugs that directly inhibit DNA synthesis (for example, azathioprine and zidovudine), or drugs that reduce folate absorption (for example, phenytoin and phenobarbital).

A primary result of folic acid deficiency is megaloblastic anemia (large-sized red blood cells), which is caused by diminished synthesis of purines and pyrimidines. This leads to an inability of erythropoietic tissue to make DNA and, thereby, proliferate. [Note: To avoid neurological complications of vitamin B12 deficiency, it is important to evaluate the basis of the megaloblastic anemia prior to instituting therapy. Both vitamin B12 and folate deficiency can cause similar symptoms.]

Folic acid is rapidly absorbed in the jejunum unless abnormal pathology is present. Oral folic acid administration is nontoxic and at high doses, excess vitamin is excreted in the urine. Rare hypersensitivity reactions to parenteral injections have been reported.

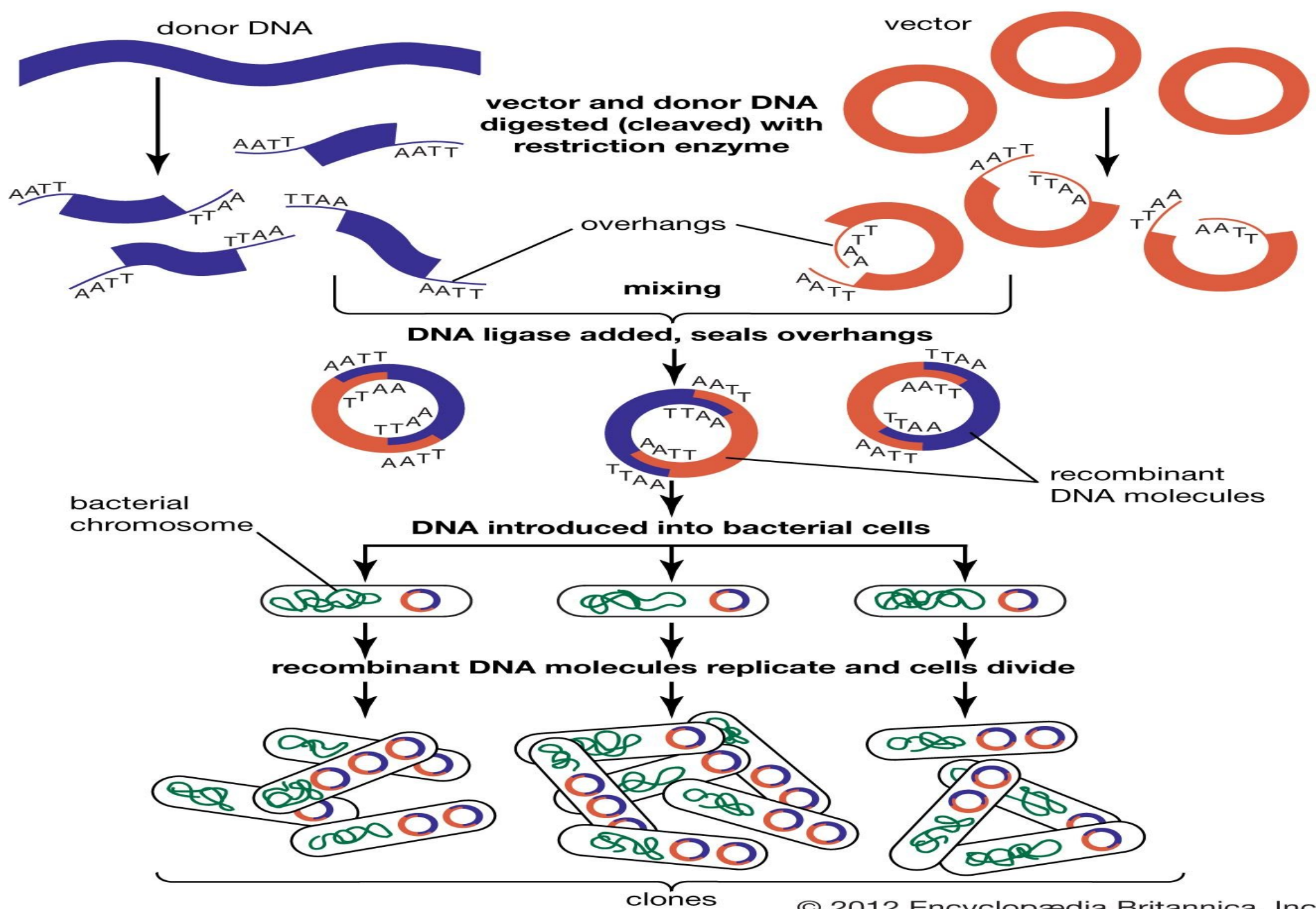
Cyanocobalamin and hydroxocobalamin (vitamin B12)

Deficiencies of vitamin B12 can result from either low dietary levels or, more commonly, poor absorption of the vitamin due to the failure of gastric parietal cells to produce intrinsic factor (as in pernicious anemia), or a loss of activity of the receptor needed for intestinal uptake of the vitamin. Nonspecific malabsorption syndromes or gastric resection can also cause vitamin B12 deficiency. In addition to general signs and symptoms of anemia, vitamin B12 deficiency anemia may cause tingling (pins and needles) in the hands and feet, difficulty walking, dementia, and, in extreme cases, hallucinations, paranoia, or schizophrenia. [Note: Folic acid administration alone reverses the hematologic abnormality and, thus, masks the vitamin B12 deficiency, which can then proceed to severe neurologic dysfunction and disease. The cause of megaloblastic anemia needs to be determined in order to be specific in terms of treatment. Therefore, megaloblastic anemia should not be treated with folic acid alone but, rather, with a

The vitamin may be administered orally (for dietary deficiencies), intramuscularly, or deep subcutaneously (for pernicious anemia). Intramuscular hydroxocobalamin is preferred since it has a rapid response, is highly protein bound, and maintains longer plasma levels. In patients with malabsorption, such as in bariatric surgery (surgical treatment for obesity), vitamin B12 supplementation as cyanocobalamin is required daily in high oral doses or monthly by the parenteral route. This vitamin is nontoxic even in large doses. In pernicious anemia, therapy must be continued for life.

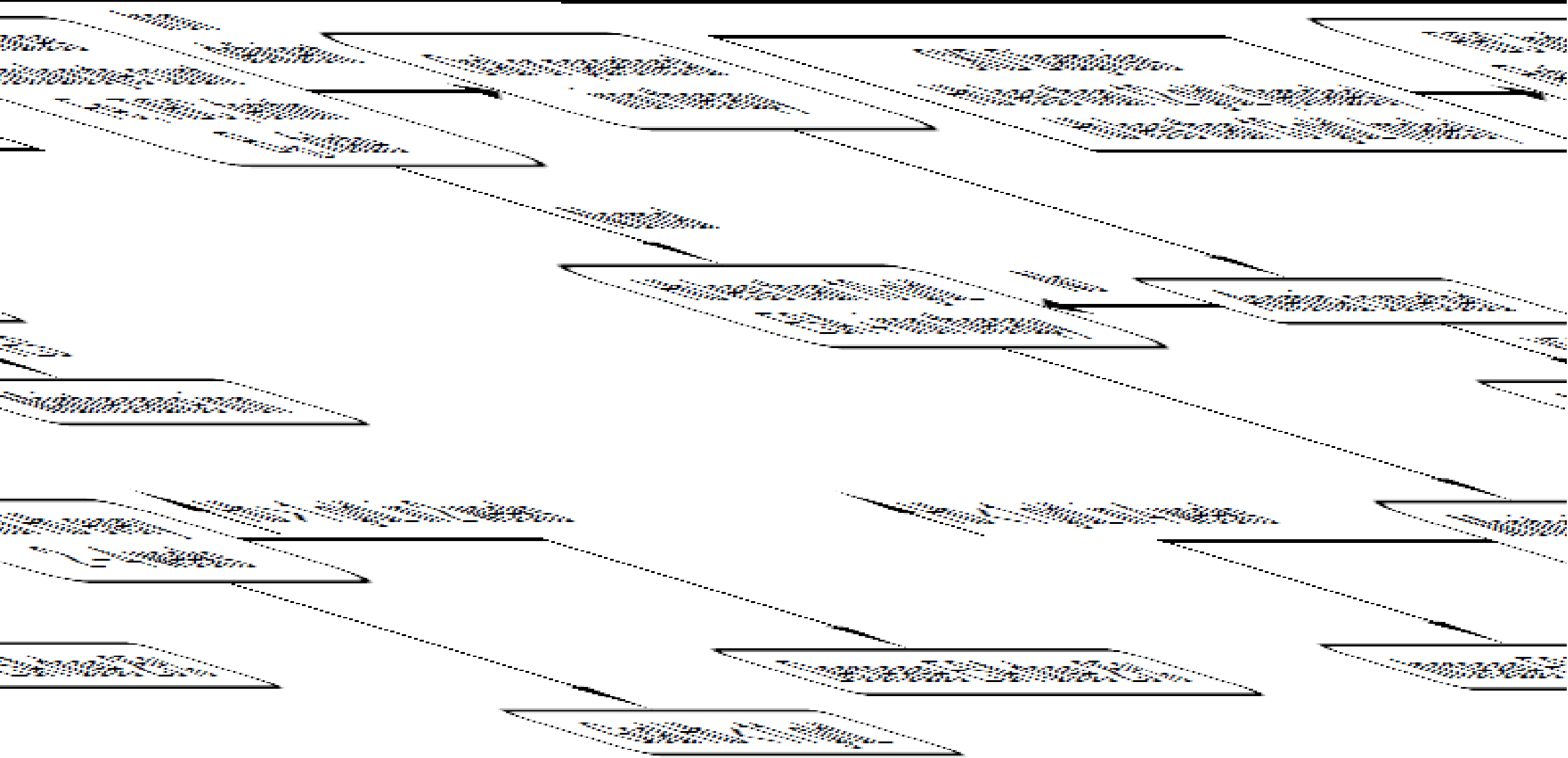
Erythropoietin and darbepoetin

Peritubular cells in the kidneys respond to hypoxia and synthesize and release erythropoietin, a glycoprotein. EPO stimulates stem cells to differentiate into proerythroblasts and promotes the release of reticulocytes from the marrow and initiation of hemoglobin formation. Thus, EPO regulates red blood cell proliferation and differentiation in bone marrow. Human erythropoietin (epoetin alfa), produced by recombinant DNA technology, is effective in the treatment of anemia caused by end-stage renal disease, human immunodeficiency virus infection, bone marrow disorders, prematurity, and malignancy. A long-acting form of erythropoietin, darbepoetin, has a half-life about three times that of epoetin alfa due to the addition of two carbohydrate chains. These agents are well tolerated and are administered intravenously in renal dialysis patients or subcutaneously for other indications. Side effects such as blood pressure elevation and arthralgia may occur in



When epoetin alfa is used to target hemoglobin concentrations over 11 g/dL, serious cardiovascular events (such as thrombosis and severe hypertension), increased risk of death, shortened time to tumor progression, and decreased survival have been observed. The recommendations for all patients receiving epoetin alfa or darbepoetin include a minimum effective dose that does not exceed a hemoglobin level of 12 g/dL, and a hemoglobin level that does not rise by more than 1 g/dL over a 2-week period. Additionally, if the hemoglobin level exceeds 10 g/dL, doses of epoetin alfa or darbepoetin should be reduced or treatment should be discontinued. Neither agent has any value in the acute treatment of anemia due to their delayed onset of action.





Management of anemia of CKD according to KDIGO and KDOQI guidelines.

CKD = chronic kidney disease; ESA = erythropoiesis-stimulating agent; Fe = iron; Hb = hemoglobin; RBC = red blood cell; TIBC = total iron-binding capacity.

Agents Used to Treat Neutropenia

Myeloid growth factors or granulocyte colony-stimulating factors (G-CSF), such as filgrastim , tbofilgrastim , and pegfilgrastim , and granulocyte-macrophage colony-stimulating factors (GM-CSF), such as sargramostim, stimulate granulocyte production in the marrow to increase neutrophil counts and reduce the duration of severe neutropenia. These agents are typically used prophylactically to reduce the risk of neutropenia following chemotherapy and bone marrow transplantation. Filgrastim and sargramostim can be dosed either subcutaneously or intravenously, whereas tbo-filgrastim and pegfilgrastim are dosed subcutaneously only. The main difference between the available agents is in the frequency of dosing. Filgrastim, tbo-filgrastim, and sargramostim are dosed once a day beginning 24 to 72 hours after chemotherapy, until the absolute neutrophil count (ANC) reaches 5000 to 10,000/ μ L. Pegfilgrastim is a pegylated form of G-CSF, resulting in a longer half-life when compared to the other agents, and is administered 24 hours after chemotherapy, as a single dose, rather than once daily. Monitoring of ANC is typically not necessary with pegfilgrastim. There is no evidence to show superiority of one agent over another in terms of efficacy, safety, or tolerability. Bone pain is a common adverse effect with these agents.

Hydroxyurea

Hydroxyurea is an oral ribonucleotide reductase inhibitor that can reduce the frequency of painful sickle cell crises. In sickle cell disease, hydroxyurea increases fetal hemoglobin (HbF) levels, thus diluting the abnormal hemoglobin S (HbS). Polymerization of HbS is delayed and reduced in treated patients, so that painful crises are not caused by sickled cells blocking capillaries and causing tissue anoxia. A clinical response may take three to six months. Important side effects of hydroxyurea include bone marrow suppression and cutaneous vasculitis. It is important that hydroxyurea is administered under the supervision of a provider experienced in the treatment of sickle cell disease. Hydroxyurea is also used off-label to treat acute myelogenous leukemia, psoriasis, and polycythemia vera.

- Crizanlizumab, a P-selectin inhibitor, was approved by the FDA in 2019 to reduce the frequency of vaso-occlusive crisis (VOC) in adults with SCD. Binding P-selectin on the surface of activated endothelium and platelet cells blocks interactions between endothelial cells, platelets, red blood cells (RBCs), and leukocytes. Approval was based on the SUSTAIN clinical trial, in which crizanlizumab reduced the median annual rate of VOCs leading to health care visits by 45.3% compared with placebo in patients with or without hydroxyurea treatment.
- Voxelotor was also approved by the FDA in 2019. It is indicated for treatment of SCD in adults and adolescents aged 12 years or older. Voxelotor is a hemoglobin S (HbS) polymerization inhibitor that binds to HbS with a 1:1 stoichiometry and exhibits preferential partitioning to RBCs. By increasing the affinity of Hb for oxygen, voxelotor demonstrates dose-dependent inhibition of HbS polymerization. Results showed 51% patients on the higher dose of voxelotor achieved a hemoglobin response compared with 6% with placebo.

Thalassemia major

Treatment for patients with thalassemia major includes the following:

- Long-term transfusion therapy
- Erythroid maturation agents (eg, luspatercept)
- Iron chelation
- Splenectomy
- Allogeneic hematopoietic transplantation

Iron chelation agents
Deferoxamine, deferasirox

luspatercept

Drug is a recombinant fusion protein that diminishes Smad2/3 signaling by binding several endogenous TGF- β superfamily ligands. In a model of beta thalassemia, drug decreased abnormally elevated Smad2/3 signaling and improved hematology parameters associated with ineffective erythropoiesis in mice.

Treatment promoted erythroid maturation through differentiation of late-stage erythroid precursors (normoblasts) in mice.