

Anemia of Chronic Disease

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THE STORY IN ONE SENTENCE

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“Anemia of chronic disease means long-lasting inflammation—from rheumatoid arthritis (joint disease), cancer, chronic kidney disease, or lingering infection—tells the liver to make extra hepcidin (a hormone that traps iron inside cells), so even though your body has plenty of iron stored, the bone marrow (the factory inside your bones that makes blood) cannot get to it and red blood cell production drops.”

Normal anatomy — the body's job

Normally, iron moves in a controlled cycle. Old red blood cells break down in the spleen (an organ that filters blood) and release iron. The gut absorbs iron from food. Transferrin (a blood protein) carries iron to bone marrow. Bone marrow uses iron plus erythropoietin (a kidney hormone) to make new red blood cells every day. Hepcidin (a liver hormone) fine-tunes this cycle by blocking iron release from storage cells and gut cells when the body senses enough iron or when infection is present. In health, hepcidin stays low enough that iron flows freely to meet the bone marrow's daily demand of roughly 20 to 25 milligrams of iron to replace the 1 percent of red cells that die each day.

BODY'S JOB

If you do not understand this normal iron cycle and hepcidin's gatekeeper role first, the lab pattern of anemia of chronic disease—low serum iron but normal or high ferritin—will seem like a contradiction instead of a logical lockdown.

1. Old red blood cells (which live about 120 days) reach the end of their life and break apart in the spleen and liver.

2. Macrophages (immune cells that eat old cells) digest the hemoglobin inside those old red cells and release iron into the bloodstream.
3. In the gut, cells in the small intestine absorb iron from food (especially heme iron from meat and fortified grains) and release it into the blood.
4. Transferrin (a protein made by the liver) binds iron in the blood and carries it like a taxi to the bone marrow.
5. Bone marrow stem cells take in iron from transferrin and combine it with a protein called globin to build hemoglobin (the molecule that carries oxygen inside red cells).
6. The kidneys sense tissue oxygen levels; when oxygen is low, kidney cells release erythropoietin (a hormone) into the blood.
7. Erythropoietin binds receptors on bone marrow stem cells and pushes them to become red blood cells, which takes about five days.
8. The liver makes hepcidin (a 25-amino-acid hormone) in small amounts and releases it into the blood to fine-tune iron balance.

What breaks

Chronic inflammation—from diseases like rheumatoid arthritis, cancer, chronic kidney disease, or long-lasting infection—triggers immune messenger proteins (cytokines, especially IL-6) that tell the liver to make excess hepcidin. High hepcidin blocks iron from leaving storage cells and gut cells, so serum iron drops even though total body iron is normal or high. At the same time, inflammation and kidney disease lower erythropoietin (the hormone that drives red blood cell production). The result is a double hit: the bone marrow gets less iron and less growth signal, so red blood cell production falls and anemia develops slowly over weeks to months.

CLINICAL TERM

Inflammatory cytokines (primarily interleukin-6, or IL-6, along with tumor tissue death (necrosis) factor-alpha and interleukin-1) bind receptors on liver hepatocytes and up-regulate hepcidin gene (HAMP) transcription via the JAK-STAT3 signaling pathway. Elevated hepcidin binds ferroportin (the only known cellular iron-export channel, encoded by SLC40A1) on the surface of gut enterocytes, reticuloendothelial macrophages, and hepatic storage cells, causing ferroportin internalization and lysosomal degradation. This blocks dietary iron absorption in the duodenum and traps recycled iron inside macrophages that have phagocytosed senescent red cells. Concurrently, inflammatory cytokines (IL-1, TNF-alpha, interferon-gamma) and severe waste buildup in the blood (uremia) (waste buildup in chronic kidney disease) suppress erythropoietin synthesis in renal peritubular interstitial cells and reduce bone marrow erythroid progenitor sensitivity to erythropoietin by down-regulating the erythropoietin receptor and inducing apoptosis of erythroid precursors. The downstream laboratory signature is normocytic (mean corpuscular volume 80 to 100 femtoliters) or mildly microcytic anemia that develops gradually, with a blunted reticulocyte response (absolute reticulocyte count typically less than 100 times 10 to the ninth per liter, or reticulocyte percentage less than 2 percent in the face of anemia) and the classic iron panel: low serum iron (typically less than 50 micrograms per deciliter), low or low-normal total iron-binding capacity (TIBC, reflecting suppressed transferrin synthesis as a negative acute-phase reactant), normal or elevated ferritin (greater than 100 nanograms per milliliter—iron is trapped in storage and ferritin itself rises as a positive acute-phase reactant), and low transferrin saturation (serum iron divided by TIBC, typically less than 20 percent). Every lab abnormality points backward to this single upstream break: cytokine-driven hepcidin excess and erythropoietin deficiency.

How the body compensates

The body tolerates slowly developing anemia much better than acute blood loss because plasma volume expands to keep blood pressure normal, and tissues extract more oxygen from each red cell (the oxygen-dissociation curve shifts right by raising 2,3-DPG inside red cells). Vital signs—heart rate, blood pressure, respiratory rate—can stay in normal range even when hemoglobin drifts down to 9 or 10 grams per deciliter. This compensation is protective in the short term but dangerous because it masks the severity of anemia and lets clinicians miss coexisting true iron deficiency (which can layer on top and requires oral or intravenous iron) or

the moment when cardiac output can no longer increase enough to meet tissue oxygen demand.

1. {'step': 'The body dilutes blood by retaining slightly more plasma (the liquid part of blood), so hemoglobin concentration falls but total blood volume and blood pressure stay near normal.', 'why': 'Hemoglobin is measured in grams per deciliter—if the denominator (plasma volume) grows, the numerator (red cell mass) can shrink and the patient will not feel faint because blood pressure depends on total volume, not red cell count.'}
2. {'step': 'Red cells increase 2,3-diphosphoglycerate (2,3-DPG), a molecule inside the cell that shifts the oxygen-dissociation curve to the right.', 'why': 'A right shift means hemoglobin releases oxygen more easily at any given tissue oxygen level, so tissues can pull more oxygen off each hemoglobin molecule that passes by; this partly compensates for fewer red cells per liter.'}
3. {'step': 'Cardiac output rises modestly—heart rate and stroke volume (the amount of blood pumped per beat) increase slightly—to deliver more blood per minute.', 'why': 'If each liter of blood carries less oxygen, pumping more liters per minute can keep total oxygen delivery near normal; patients may not notice a resting heart rate that has crept from 70 to 85 beats per minute.'}
4. {'step': 'These adaptations keep the patient comfortable at rest, which is the dangerous middle—vital signs look reassuring, so the clinical team may delay workup or treatment while the anemia worsens.', 'why': 'A patient who feels fine sitting in the clinic but becomes short of breath climbing one flight of stairs is already using maximum cardiac reserve; that is not stable, that is one step from decompensation.'}
5. {'step': 'The crash point to watch for: coexisting absolute iron deficiency (ferritin truly low, less than 30 nanograms per milliliter, or less than 100 in the setting of inflammation—meaning storage is empty, not just locked) that you miss because you assume all low serum iron is functional.', 'why': 'Anemia of chronic disease and true iron deficiency often coexist—especially in inflammatory bowel disease (gut bleeding plus inflammation), chronic kidney disease (poor absorption plus inflammation), or malignancy (bleeding plus inflammation); the clue is ferritin trending down or a very low transferrin saturation (less than 15 percent) despite treatment of the underlying disease.'}
6. {'step': 'Another crash point: heart failure or starved blood flow (ischemia) (not enough blood reaching the heart muscle) in a patient with coronary artery disease whose heart cannot increase output further.', 'why': 'Anemia increases cardiac workload because the heart must pump faster and harder; if coronary arteries are already narrowed, the heart muscle may not get enough oxygen for that extra work, triggering chest pain, heart attack, or sudden heart failure.'}

7. {'step': 'Erythropoiesis-stimulating agents (ESAs such as epoetin alfa, darbepoetin, or methoxy polyethylene glycol-epoetin beta) can raise hemoglobin in chronic kidney disease or cancer-related anemia, but they carry risk of clot formation (thrombosis) (blood clots), stroke, heart attack (myocardial infarction), tumor progression, and death if dosed to a target hemoglobin above 11 to 12 grams per deciliter.', 'why': 'FDA black-box warnings (2007, reaffirmed 2010), KDIGO 2012 anemia guideline, and KDOQI 2006 updates all recommend starting ESA only when hemoglobin is less than 10 grams per deciliter and avoiding a target above 11.5 grams per deciliter; higher targets thicken blood and increase clot risk without clear benefit.'}
8. {'step': 'Watch trends—serial hemoglobin, reticulocyte count, ferritin, and transferrin saturation over weeks—not single snapshots, because a stable hemoglobin of 9 grams per deciliter today that was 11 two months ago signals ongoing loss of compensation.', 'why': 'A flat trend after treatment of the underlying inflammation suggests functional iron deficiency (high hepcidin still blocking iron mobilization) or true deficiency (stores are empty); either may require intravenous iron (especially in chronic kidney disease and heart failure, where oral iron is poorly absorbed) per KDIGO, AHA/ACC heart failure guidelines, and iron-deficiency society consensus.'}
9. {'step': 'If the underlying inflammatory disease is treated successfully—such as achieving remission in rheumatoid arthritis with a TNF-alpha inhibitor, clearing chronic infection, or removing a tumor—hepcidin falls, iron is released from storage, erythropoietin production recovers, and hemoglobin usually climbs back toward normal over four to eight weeks without transfusion.', 'why': 'This proves the anemia was functional, not structural; the bone marrow was capable all along but was blocked by the cytokine storm—turn off the storm, unlock the gate, and the factory runs again.'}

Domino effect

1. Chronic inflammation—from rheumatoid arthritis (immune attack on joints), inflammatory bowel disease (Crohn disease or ulcerative colitis), cancer, chronic kidney disease, or persistent infection (such as osteomyelitis, tuberculosis, or endocarditis)—releases cytokines (especially interleukin-6, tumor tissue death (necrosis) factor-alpha, and interleukin-1) into the bloodstream. — Cytokines are messenger proteins that coordinate the immune response; they also trigger a coordinated iron-withholding response, an ancient defense meant to starve invading bacteria and cancer cells of the iron they need to grow.
2. Cytokines bind receptors on liver cells (hepatocytes) and activate the JAK-STAT3 signaling pathway, which turns on the hepcidin gene (HAMP). — Interleukin-6 is the strongest trigger; it binds the IL-6 receptor, activates Janus kinase (JAK), which phosphorylates signal transducer and activator of transcription 3 (STAT3), and STAT3 enters the nucleus and ramps up hepcidin production—this is why IL-6 blockade (such as tocilizumab in rheumatoid arthritis) can improve anemia.

3. The liver releases large amounts of hepcidin (a 25-amino-acid hormone) into the bloodstream. — Hepcidin is the master regulator of iron; normally the liver makes just enough to keep iron balance stable, but inflammation can raise hepcidin ten-fold or more.
4. High hepcidin binds ferroportin (the only cellular iron-export channel, a protein on the surface of gut cells, liver storage cells, and macrophages) and causes ferroportin to be pulled inside the cell and destroyed in lysosomes. — Without ferroportin on the cell surface, iron cannot leave storage sites or gut cells to enter the bloodstream—it is locked in a cage; this happens within hours of cytokine exposure.
5. Gut absorption of dietary iron drops to nearly zero because duodenal enterocytes (the cells that absorb iron from food) have no ferroportin channels left to push iron into the blood. — Even if you eat iron-rich food or take oral iron supplements, that iron gets trapped inside gut cells and is lost when those cells slough off every few days—oral iron cannot overcome high hepcidin.
6. Macrophages (immune cells in the spleen, liver, and bone marrow that eat old red blood cells) recycle about 20 milligrams of iron per day from dead red cells, but high hepcidin traps that iron inside the macrophages so it cannot re-enter the bloodstream. — This is the biggest iron source—much more than diet—so blocking macrophage iron export causes serum iron to plummet within days; the iron is still in your body, just locked away.
7. Serum iron (the amount of iron floating in blood) falls, often to less than 50 micrograms per deciliter (normal is roughly 60 to 170 micrograms per deciliter). — Transferrin (the blood protein that taxis iron to the bone marrow) has fewer iron atoms to bind, so transferrin saturation (serum iron divided by total iron-binding capacity) drops, typically below 20 percent (normal is 20 to 50 percent).
8. At the same time, inflammation suppresses liver production of transferrin (a negative acute-phase reactant), so total iron-binding capacity (TIBC, which measures total transferrin) is low or low-normal instead of rising. — In true iron deficiency (when stores are empty), the body makes extra transferrin to hunt for any iron it can find, so TIBC rises above 400 micrograms per deciliter; in anemia of chronic disease, TIBC stays low (often 200 to 300 micrograms per deciliter) because the body is not looking for iron—it is hiding iron—so a low TIBC is the key lab clue that the anemia is inflammatory.
9. Ferritin (the storage protein for iron) appears normal or elevated in blood tests—often 100 to 800 nanograms per milliliter—even though functional iron (iron available for red cell production) is low. — Ferritin is both a storage marker and a positive acute-phase reactant—it rises with inflammation independent of iron stores—and it also reflects iron trapped inside macrophages; a high ferritin in anemia of chronic disease means the vault is full but the key (ferroportin) is gone.

- 10.** At the same time, inflammatory cytokines (especially interleukin-1, tumor tissue death (necrosis) factor-alpha, and interferon-gamma) and severe waste buildup in the blood (uremia) (waste buildup in chronic kidney disease) suppress erythropoietin production in kidney peritubular cells and reduce bone marrow sensitivity to erythropoietin. — Erythropoietin is the hormone that tells bone marrow stem cells to become red blood cells; cytokines down-regulate the erythropoietin gene (EPO) and cause apoptosis (programmed cell death) of erythroid precursors in the marrow, so even if some iron were available, it would not be used efficiently—this is the second hit.
- 11.** Bone marrow receives less iron (because hepcidin locked it away in macrophages and gut cells) and less erythropoietin signal, so red blood cell production (erythropoiesis) slows; fewer new red cells are made each day than the roughly 200 billion that die of old age (about 1 percent of the 25 trillion red cells in your body). — Red blood cells live approximately 120 days; normally the marrow replaces them at the same rate they die, but when production drops below the destruction rate, hemoglobin falls by roughly 0.5 to 1 gram per deciliter per month.
- 12.** The bone marrow tries to compensate by releasing reticulocytes (immature red cells, about one day old, still containing bits of ribosomal RNA) into the bloodstream early, but this reticulocyte response is blunted. — A healthy marrow responding to anemia would push reticulocyte count above 2 percent (or absolute count above 100 times 10 to the ninth per liter); in anemia of chronic disease, reticulocyte count stays low (often less than 1.5 percent or 80 times 10 to the ninth per liter) because the marrow lacks both iron and erythropoietin drive—this low reticulocyte count is the hallmark of underproduction anemia and distinguishes it from red blood cell destruction (hemolysis) (red cell destruction) or bleeding, both of which would push reticulocyte count high.
- 13.** Hemoglobin drifts down over weeks to months, typically stabilizing in the range of 9 to 11 grams per deciliter (rarely lower unless another process—such as true iron deficiency, vitamin B12 or folate deficiency, or blood loss—is layered on top). — The anemia is self-limited because once hemoglobin falls, tissue low oxygen (hypoxia) (low oxygen delivery) eventually triggers some erythropoietin release via low oxygen-inducible factor (HIF) and feeds back to slow the decline; the new steady state is a mild to moderate anemia that persists as long as the underlying inflammation persists.
- 14.** Red cells are normocytic (mean corpuscular volume 80 to 100 femtoliters) or mildly microcytic (mean corpuscular volume 75 to 80 femtoliters if iron restriction is severe or prolonged). — In early or mild anemia of chronic disease, red cell size is normal because the marrow still has enough iron to fill each cell; if inflammation persists for months, iron becomes so scarce that new red cells are smaller (microcytic), but they are rarely as small as in true iron deficiency (where mean corpuscular volume often drops below 70 femtoliters).

- 15.** Every lab finding—low serum iron, low or low-normal TIBC, normal to high ferritin, low transferrin saturation, low reticulocyte count, normocytic or mildly microcytic red cells—points backward to the single upstream break: cytokine-driven hepcidin excess and erythropoietin suppression. — None of the findings is random; each is a direct physiologic consequence of iron sequestration and blunted red cell production, so reasoning from the broken mechanism to the lab pattern makes diagnosis and management logical instead of a memory exercise—recognize the pattern, treat the underlying inflammation, and consider intravenous iron or erythropoiesis-stimulating agents only when inflammation control is inadequate or the patient has coexisting true deficiency or symptomatic anemia (per KDIGO 2012 for chronic kidney disease, AHA/ACC 2022 for heart failure, and NCCN 2023 for cancer-related anemia).

Symptoms · what the patient feels, and why

- Fatigue and tiring quickly during activities that used to feel easy (like climbing stairs or walking a few blocks): Red blood cells carry oxygen to every part of your body. When you have fewer red cells (low hemoglobin), your muscles and brain get less oxygen than they need. Your cells try to make energy without enough oxygen—a slower, messier backup method—and they build up waste products like lactate. That makes you feel tired and weak much faster than normal.
- Pale skin, pale inside the eyelids, or pale nail beds: Hemoglobin is the red pigment inside red blood cells. When your hemoglobin drops, your blood becomes lighter in color. The tiny blood vessels in your skin and the inside of your eyelids carry less red pigment, so those areas look pale or washed-out instead of pink.
- Shortness of breath when you move around or exercise: Your body senses that tissues are not getting enough oxygen, so the breathing control center in your brainstem tells your lungs to breathe faster and deeper. This helps push more oxygen in, but it makes you feel out of breath even though your lungs themselves are working fine.
- Fast heartbeat (your heart pounds or races, especially when you are active): When each drop of blood carries fewer red cells, your heart has to pump faster to move more blood every minute so your organs still get the oxygen they need. You feel your heart beating hard or fast because it is working overtime to make up for the low red cell count.
- Feeling dizzy or lightheaded, especially when you stand up quickly: With fewer red cells, your blood is thinner and your brain may not get a strong enough surge of oxygen-rich blood when you change position. Also, many chronic diseases can make you a little dehydrated, so blood pressure dips when you stand, and less blood reaches your brain for a moment—that feels like dizziness.

- **Headache (usually a dull, steady ache):** Your brain needs a constant supply of oxygen. When oxygen levels drop, the blood vessels in your brain widen to let more blood through. That stretching of the vessel walls triggers pain sensors around them, causing a headache.
- **Cold hands and feet:** Your body is smart: it sends blood first to the most important organs—your heart, brain, and kidneys. To do that, it tightens the blood vessels in your skin and fingers and toes so less warm blood reaches them. That is why your hands and feet feel cold.
- **Your underlying disease feels worse (for example, more joint pain if you have rheumatoid arthritis, or more trouble breathing if you have kidney disease):** Anemia means less oxygen reaches tissues that are already sick or inflamed, so symptoms from your main illness get worse. On top of that, the same inflammation chemicals (cytokines) that cause anemia also ramp up pain signals and make you feel more tired and achy all over.
- **New chest pain or much worse shortness of breath (especially at rest) if you already have heart disease or heart failure:** Your heart muscle needs a lot of oxygen to keep pumping. If your coronary arteries are already narrowed by fatty plaques and your hemoglobin drops, your heart cannot get the oxygen it needs—this is called starved blood flow (ischemia) (starving the heart muscle). That causes chest pain (angina) or can trigger fluid backup in the lungs (heart failure), making you short of breath even when you are sitting still.
- **Fainting (syncope):** If anemia gets very severe or drops suddenly, your brain may not receive enough oxygen to stay awake. Fainting means your body's backup systems—faster heart rate, faster breathing—have failed to keep your brain fed. It is a sign you are close to serious trouble and need urgent help.

Focused exam

- **Mild pale skin (pallor) (paleness) of skin, nail beds, and the inside lining of the lower eyelid (conjunctiva):** When inflammation from diseases like rheumatoid arthritis or cancer stays active for weeks to months, the liver releases a hormone called hepcidin. Hepcidin locks iron inside immune cells (macrophages) so the bone marrow cannot use that iron to build hemoglobin, the oxygen-carrying protein in red blood cells. With fewer red cells in the blood, the skin and mucous membranes lose their pink color and look pale.
- **Normal-sized or slightly enlarged spleen felt under the left rib cage:** Chronic inflammation keeps the spleen working harder than usual to filter old red cells. It stays normal-sized or just slightly bigger. A spleen that is much larger suggests a different problem, such as red cells breaking apart too fast (hemolysis) or bone marrow making too many cells (myeloproliferative disorder). A normal spleen size points toward anemia of chronic disease, not those other conditions.

- Signs of the long-term disease causing the inflammation—swollen, warm joints in rheumatoid arthritis; belly pain and mouth sores in inflammatory bowel disease; unintentional weight loss and muscle wasting in cancer: Anemia of chronic disease never stands alone. It always comes from another disease that is causing long-term inflammation. Finding and treating that root disease is the only way to bring hepcidin levels down and let the bone marrow make red cells again.
- Heart rate at rest is normal (60 to 100 beats per minute), or faster than 100 beats per minute only when walking or exercising: Because anemia of chronic disease builds slowly over weeks to months, the heart has time to adapt by pumping more blood with each beat. If the heart is racing even at rest, the anemia is likely severe (hemoglobin below 7 grams per deciliter) or there is a separate heart problem that needs urgent attention.
- No bleeding from gums, no tiny red or purple dots on the skin (petechiae), no blood in stool or vomit, no heavy menstrual bleeding: Anemia of chronic disease is not caused by losing blood. If you see signs of bleeding, the patient may also have iron deficiency anemia from blood loss in the gut or from heavy periods. The two types of anemia often occur together in people with chronic diseases.
- Feeling tired or short of breath only during moderate activity like climbing stairs, but not at rest: When hemoglobin is mildly to moderately low (8 to 10 grams per deciliter), the body compensates by having the heart pump more blood and by red cells releasing oxygen more easily to tissues. If the patient is short of breath lying down or sitting still, the anemia is severe or there is a lung or heart problem that needs urgent evaluation.

Diagnostics · every test answers a question

- Complete blood count (CBC) with red cell indices (MCV, MCH, MCHC) and reticulocyte count → Is the bone marrow making enough new red blood cells to try to fix the anemia, or is production slowed down by inflammation?
- Iron studies panel: serum iron, total iron-binding capacity (TIBC), serum ferritin, and transferrin saturation → Is iron missing from the body, or is iron present but trapped inside cells by inflammation?
- C-reactive protein (CRP) and red blood cell (erythrocyte) sedimentation rate (ESR) → Is there active inflammation in the body driving hepcidin production?
- Serum creatinine and estimated glomerular filtration rate (eGFR) → Are the kidneys working well enough to make erythropoietin, the hormone that signals the bone marrow to produce red blood cells?
- Peripheral blood smear reviewed under a microscope → Do the red cells look normal, or is there a pattern that suggests a different cause of anemia?
- Serum vitamin B12 and folate levels → Is a vitamin deficiency contributing to the anemia?

- Soluble transferrin receptor (sTfR) and sTfR/log ferritin ratio (if iron studies are unclear) → Is there hidden iron deficiency even though ferritin is high from inflammation?

Treatment logic

- Treat the underlying chronic disease with disease-specific therapy: disease-modifying antirheumatic drugs (methotrexate, TNF inhibitors) for rheumatoid arthritis, antibiotics for chronic infections, aminosalicylates or biologics (infliximab, adalimumab) for inflammatory bowel disease, chemotherapy or immunotherapy for cancer → Controlling the root disease lowers the levels of interleukin-6 (IL-6) and other inflammatory signaling molecules. Lower IL-6 means the liver makes less hepcidin. When hepcidin drops, iron is released from immune cells back into the bloodstream, and the bone marrow can use that iron to build hemoglobin. This fixes the cause of anemia of chronic disease.
- Give iron supplementation—oral ferrous sulfate 325 milligrams once daily, or intravenous iron (iron sucrose 200 milligrams, ferric carboxymaltose 750 to 1000 milligrams)—if transferrin saturation is below 20 percent and ferritin is below 100 nanograms per milliliter, suggesting coexisting iron deficiency → Iron supplementation provides the raw material the bone marrow needs to build hemoglobin once hepcidin levels fall from treating the underlying disease. Intravenous iron bypasses the gut, where hepcidin blocks absorption, and is preferred when inflammation is high or the gut is damaged (inflammatory bowel disease, chronic kidney disease).
- Give erythropoiesis-stimulating agents (ESAs: epoetin alfa 50 to 100 units per kilogram subcutaneously three times weekly, or darbepoetin alfa 0.45 micrograms per kilogram once weekly) for anemia in chronic kidney disease (eGFR below 60) or chemotherapy-induced anemia, targeting hemoglobin 10 to 11.5 grams per deciliter per KDIGO and ASCO/ASH guidelines → ESAs replace erythropoietin that damaged kidneys are not making. They signal the bone marrow to increase red blood cell production even when hepcidin is trapping iron. This bypasses part of the iron block by pushing the marrow harder.
- Give packed red blood cell transfusion (1 unit raises hemoglobin by about 1 gram per deciliter) for severe symptomatic anemia—hemoglobin below 7 grams per deciliter with chest pain, fainting, shortness of breath at rest, confusion, or active bleeding—per AABB restrictive transfusion guidelines → Transfused red cells immediately restore oxygen-carrying capacity, preventing tissue low oxygen (hypoxia) (not enough oxygen reaching organs) and damage to the heart, brain, and kidneys.

- Monitor complete blood count with reticulocyte count, serum ferritin, transferrin saturation, and inflammatory markers (CRP or ESR) every 4 to 8 weeks during treatment → Lab trends tell you whether the underlying disease is under control. Falling ferritin and CRP mean inflammation is dropping. Rising reticulocyte count and hemoglobin mean the bone marrow is responding. These numbers guide decisions about iron dosing, ESA use, and whether to adjust treatment for the root disease.

Medications

Disease-modifying antirheumatic drugs (DMARDs) · Immunomodulator

DMARDs quiet down the overactive immune system that is attacking the joints in rheumatoid arthritis. When inflammation drops, the body makes less hepcidin (a liver protein that locks iron inside storage cells). With less hepcidin blocking the exits, iron can leave storage and travel to the bone marrow where new red blood cells are built. Common DMARDs include methotrexate, sulfasalazine, and hydroxychloroquine.

1. The drug enters immune cells and blocks enzymes or receptors that make inflammatory chemicals (cytokines like IL-6 and TNF-alpha).
2. With fewer inflammatory signals, the liver receives less instruction to produce hepcidin.
3. Hepcidin levels fall, so the protein ferroportin (the iron exit door on storage cells) stays open.
4. Iron flows out of storage cells in the liver and spleen into the bloodstream.
5. Transferrin (the iron taxi protein) carries iron to the bone marrow.
6. Bone marrow uses the iron to build hemoglobin inside new red blood cells, raising the red blood cell count over weeks to months.

SAFETY WATCH

Infection risk rises because the immune system is dampened; watch for fever, cough, or painful urination and call the doctor right away. · Liver damage (rare)—blood tests every 8 to 12 weeks check liver enzymes; stop the drug if levels climb. · Low white blood cell or platelet counts (rare)—regular blood counts detect this early. · Nausea or mouth sores with methotrexate—folic acid 1 mg daily prevents most side effects. · Eye damage with hydroxychloroquine (very rare)—eye exam every 12 months after 5 years of use.

Oral iron supplementation (ferrous sulfate, ferrous gluconate, ferrous fumarate) · Iron replacement

Iron pills give the body extra iron to fill the gap when blood tests show true iron deficiency (transferrin saturation below 20 percent or ferritin below 30 ng/mL). The small intestine

absorbs iron into the bloodstream, transferrin carries it to the bone marrow, and the marrow uses it to build hemoglobin—the oxygen-carrying protein inside red blood cells. Each pill delivers 65 mg of elemental iron (the usable form).

1. Stomach acid dissolves the iron tablet into ferrous iron (Fe^{2+}), the form the body can absorb.
2. Cells in the duodenum (first part of the small intestine) pull iron across their wall using a transporter protein called DMT1.
3. Iron enters the bloodstream and immediately binds to transferrin, the blood's iron taxi.
4. Transferrin delivers iron to the bone marrow, where red blood cell precursors are growing.
5. Inside each developing red blood cell, iron is inserted into the center of hemoglobin molecules.
6. Over 4 to 8 weeks, hemoglobin levels rise by about 1 g/dL as new iron-filled red blood cells enter circulation.

SAFETY WATCH

Constipation (most common)—black stools are normal and harmless; drink extra water and eat fiber-rich foods. · Nausea or stomach upset—take with food to reduce irritation, though this cuts absorption by half. · Iron overload if taken when not deficient—never take iron without a blood test showing low iron; excess iron deposits in the heart, liver, and pancreas. · Drug interactions—iron blocks absorption of thyroid hormone (levothyroxine), antibiotics (fluoroquinolones, tetracyclines), and osteoporosis drugs (bisphosphonates); separate doses by at least 2 hours. · Poisoning risk in children—keep bottles locked away; as few as 5 adult tablets can be fatal to a toddler.

Intravenous (IV) iron (iron sucrose, ferric carboxymaltose, iron dextran) · Iron replacement

IV iron delivers a large dose of iron directly into the bloodstream, bypassing the small intestine where hepcidin blocks absorption. Macrophages (clean-up immune cells) in the liver and spleen grab the IV iron particles, break them down, and release iron into the blood. Transferrin carries the iron to the bone marrow to build hemoglobin. IV iron is used when oral iron fails (either the gut cannot absorb it or side effects are intolerable) or when rapid correction is needed (such as before surgery).

1. A nurse injects iron complexed with a sugar or carbohydrate shell into a vein over 15 minutes to 1 hour.
2. Macrophages in the liver and spleen recognize the iron particles and swallow them.
3. Inside the macrophage, enzymes strip away the sugar shell and release free iron.
4. Iron enters the bloodstream and binds to transferrin, the iron transport protein.

5. Transferrin delivers iron to the bone marrow, where red blood cell precursors are multiplying.
6. Over 2 to 4 weeks, hemoglobin rises as new red blood cells packed with iron-filled hemoglobin enter the blood.

SAFETY WATCH

Allergic reactions (rare but serious)—flushing, itching, chest tightness, or trouble breathing during the infusion; iron dextran carries the highest risk, so a test dose is given first. · Low blood pressure or dizziness if infused too fast—infusion runs slowly with close monitoring. · Infection risk from deposited iron—bacteria use iron to grow; avoid IV iron during active infection. · Iron overload with repeated doses—blood tests (ferritin, transferrin saturation) guide total dose to prevent excess. · Staining of skin at the injection site (rare)—appears as a brown discoloration that may be permanent.

Erythropoiesis-stimulating agents (ESAs): epoetin alfa, darbepoetin alfa · Erythropoietin analog

ESAs are lab-made copies of erythropoietin, a hormone the kidneys normally make to tell the bone marrow to produce red blood cells. In chronic kidney disease, damaged kidneys make too little erythropoietin, so red blood cell production drops. ESAs are injected under the skin or into a vein to replace the missing hormone. They are also used in cancer patients on chemotherapy when hemoglobin falls below 10 g/dL and symptoms (fatigue, shortness of breath) interfere with daily life. ESAs work only if the body has enough iron; iron stores must be checked and refilled first.

1. The drug is injected under the skin (subcutaneous) or into a vein (intravenous); subcutaneous lasts longer.
2. ESA molecules travel through the bloodstream to the bone marrow.
3. They lock onto erythropoietin receptors on the surface of early red blood cell precursors (colony-forming units and proerythroblasts).
4. The receptor sends a 'grow and divide' signal inside the cell, activating genes that drive red blood cell production.
5. Precursor cells multiply faster, mature into reticulocytes (young red blood cells), and then into fully functional red blood cells.
6. Over 2 to 6 weeks, the red blood cell count and hemoglobin level rise; the goal is hemoglobin 10 to 11.5 g/dL (higher targets increase risk of stroke, heart attack, and blood clots).

SAFETY WATCH

High blood pressure (common)—monitor blood pressure weekly at start; may need blood pressure medication. · Blood clots in veins (deep vein clot formation (thrombosis)) or arteries (stroke, heart attack) if hemoglobin rises above 11.5 g/dL—use the lowest dose that relieves symptoms. · Faster cancer growth or shorter survival in cancer patients—use only if hemoglobin is below 10 g/dL and patient is on chemotherapy; stop when chemotherapy ends. · Pure red cell aplasia (very rare)—the immune system attacks the drug and natural erythropoietin, causing severe anemia; stop ESA immediately if hemoglobin suddenly drops. · Iron deficiency from rapid red blood cell production—check iron labs every month and supplement as needed.

Packed red blood cell (PRBC) transfusion · Blood product replacement

A transfusion delivers healthy red blood cells from a donor directly into the patient's vein, instantly raising the oxygen-carrying capacity of the blood. Each unit of packed red blood cells raises hemoglobin by about 1 g/dL in an average adult. Transfusion is reserved for severe anemia (hemoglobin below 7 g/dL) with symptoms such as chest pain, trouble breathing, dizziness, or confusion, or for active bleeding when the body cannot wait weeks for medications to work. The donor blood is tested for blood type (A, B, AB, O) and Rh factor (positive or negative) and screened for infections (HIV, hepatitis B and C, syphilis).

1. A nurse inserts an IV line into a vein, usually in the arm.
2. A bag of packed red blood cells (about 300 mL, filtered to remove most plasma and white blood cells) is hung and connected to the IV.
3. Red blood cells flow into the patient's circulation over 1.5 to 4 hours (slower if the patient has heart failure to avoid fluid overload).
4. Transfused red blood cells mix with the patient's own cells and immediately begin picking up oxygen in the lungs and delivering it to organs and muscles.
5. Hemoglobin rises by about 1 g/dL per unit; symptoms (shortness of breath, rapid heartbeat, fatigue) improve within hours.
6. Transfused red blood cells survive about 60 to 90 days before the spleen removes them, so the benefit is temporary unless the underlying cause is treated.

SAFETY WATCH

Allergic reactions (common: itching, hives; rare: severe trouble breathing, shock)—symptoms during or within hours of transfusion; stop transfusion immediately and call for help. · Fluid overload in patients with heart failure or kidney disease—too much volume causes shortness of breath, leg swelling, and lung crackles; give transfusion slowly and use a diuretic (water pill) if needed. · Infection transmission (very rare with modern screening)—HIV, hepatitis B and C, bacteria; risk is about 1 in 1 to 2 million per unit. · Acute destroying red blood cells (hemolytic) reaction (rare, life-threatening)—fever, back pain, dark urine within minutes if wrong blood type is given; requires emergency treatment. · Iron overload with repeated transfusions (more than 20 units lifetime)—excess iron deposits in heart, liver, pancreas; chelation therapy (drugs that bind and remove iron) may be needed.

Red flags

- Hemoglobin below 7–8 g/dL, or a drop of more than 2 g/dL in one week (suggests sudden bleeding inside the body or red cells breaking apart on top of the chronic anemia)
- New chest pain, severe shortness of breath while resting, or fainting in a person with anemia who also has heart disease (sign the heart is not getting enough oxygen and may be failing)
- Fever, losing weight without trying, drenching night sweats, or swollen lymph nodes along with anemia (raises worry for cancer, tuberculosis, or HIV hiding underneath)
- Hemoglobin keeps falling even after treating the main disease, or does not improve with erythropoietin shots and iron pills (suggests hidden bleeding, red cells being destroyed, or bone marrow taken over by cancer or damaged by medicine)
- Signs of too much iron in the body—ferritin above 1,000 ng/mL, liver swelling, or skin turning bronze—in someone getting many blood transfusions (iron overload can poison the liver, heart, and pancreas)

Nursing priorities

1. Check hemoglobin and hematocrit (the percentage of blood that is red cells) on admission and compare to recent results to detect sudden drops of 2 grams per deciliter or more — A fast drop in hemoglobin signals new bleeding or red blood cell destruction (hemolysis) (red cells breaking apart) layered on top of chronic anemia, which can cause shock (dangerously low blood pressure) and organ damage if not caught and treated quickly with fluids, transfusion, or surgery to stop bleeding

2. Monitor vital signs every 4 hours, watching for heart rate above 100 beats per minute, respiratory rate above 20 breaths per minute, or systolic blood pressure below 90 millimeters of mercury — When hemoglobin is low the heart pumps faster to push the smaller number of red cells around faster and deliver enough oxygen, and the lungs breathe faster to load more oxygen, but if the heart or lungs cannot keep up the blood pressure drops and organs start to fail from lack of oxygen
3. Assess for chest pain, severe shortness of breath at rest, or confusion every shift and report immediately if present — The heart and brain need the most oxygen, so when anemia is severe these organs suffer first—chest pain means the heart muscle is starving for oxygen, shortness of breath at rest means the lungs and heart are failing to compensate, and confusion means the brain is not getting enough oxygen, all of which can lead to heart attack, heart failure, stroke, or death without urgent intervention
4. Place the patient on fall precautions: bed alarm on, call light in reach, non-skid socks, and assist with all walking and transfers — Low hemoglobin means less oxygen reaches the muscles and the balance centers in the inner ear and brain, causing dizziness and muscle weakness, especially when standing up quickly because blood pressure drops, so falls are common and can cause head injury, broken bones, and bleeding that makes anemia worse
5. Administer prescribed disease-specific treatments on time: give methotrexate or biologic injections for autoimmune diseases, antibiotics for infections, chemotherapy for cancer, or erythropoiesis-stimulating agent injections for kidney disease — Hepcidin stays high as long as inflammation continues, so the only way to unlock stored iron and let the bone marrow use it is to treat the root cause of inflammation with drugs that calm the immune system, kill the infection, shrink the tumor, or replace the missing kidney hormone
6. Give oral iron (ferrous sulfate 325 milligrams once daily) or IV iron as ordered, and teach the patient that iron works slowly and may cause dark stools or constipation — Even though total body iron is normal or high in anemia of chronic disease, the iron is trapped inside storage cells by hepcidin, so extra iron—especially IV iron that bypasses the gut and hepcidin block—can give the bone marrow more raw material to build red cells once inflammation starts to drop, though it will not work until the underlying disease is treated
7. Plan nursing care and daily activities in short blocks with rest periods in between, and cluster tasks like bathing, vital signs, and medication administration to avoid exhausting the patient — Red blood cells carry oxygen to muscles, so when hemoglobin is low the muscles run out of oxygen quickly during any activity, causing extreme fatigue and shortness of breath, and the heart has to work much harder, so spreading out activities and allowing rest lets the body recover oxygen levels and prevents dangerous stress on the heart

8. Educate the patient and family that correcting this anemia takes weeks to months because it requires controlling the underlying disease first, not just taking iron pills — Many patients expect anemia to resolve quickly with iron like it does in simple iron deficiency, but in anemia of chronic disease the high hepcidin blocks iron use until inflammation falls, so understanding this prevents frustration and helps the patient stick with the long-term treatment plan for the root disease like rheumatoid arthritis or inflammatory bowel disease

Sources

- KDIGO 2012 Clinical Practice Guideline for Anemia in Chronic Kidney Disease
- American Society of Hematology (ASH) guidelines on anemia management
- FDA Safety Communication on Erythropoiesis-Stimulating Agents
- AABB (American Association of Blood Banks) Clinical Practice Guidelines on Red Blood Cell Transfusion 2016

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