

Anemia of Chronic Disease

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.

THE ONE-LINE TRUTH

Chronic inflammation raises hepcidin (a liver hormone that locks iron inside storage cells) so the bone marrow cannot reach that iron to build red blood cells, even though total body iron is normal or high.

The chain — how it unfolds

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. — why: 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). — why: 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. — why: 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. — why: 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. — why: 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. — why: 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). — why: 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. — why: 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.

Spot it — what you see, 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.

Red flags — act now

- 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)

Treat it — in this order

1. 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.
2. 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).
3. 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.
4. 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.
5. 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.

Your top priorities at the bedside

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 — why: 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 — why: 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 — why: 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