

# Aplastic Anemia

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## THE STORY IN ONE SENTENCE

The bone marrow factory stops making red cells, white cells, and platelets — usually because the body's own immune cells attack the stem cells or toxic chemicals and drugs destroy them.

“Aplastic anemia is when the bone marrow shuts down completely and stops making all three kinds of blood cells at once.”

## Normal anatomy — the body's job

Bone marrow is the soft tissue inside your bones—especially your hips, spine, ribs, and the long bones of your arms and legs. It holds hematopoietic stem cells (the master cells that can become any blood cell). These stem cells live in a support neighborhood called the stromal microenvironment—a network of nurturing cells, tiny blood vessels, and chemical signals (growth factors like erythropoietin, G-CSF, and thrombopoietin) that tell stem cells when to divide and what to become. Every day, healthy marrow makes about 200 billion red blood cells (to replace old ones that die after 120 days), 100 billion white blood cells (neutrophils only live 6 to 8 hours, so they need constant replacement), and 100 billion platelets (which last 7 to 10 days). Think of the marrow as a busy factory with three assembly lines running at once, all fed by the same pool of stem cells. Keep that normal picture in your head—every finding in aplastic anemia is a direct result of this factory shutting down.

## BODY'S JOB

If you do not understand the normal job first, the cluster of findings—low counts in all three cell lines, normal spleen size, fatigue, infections, and bleeding—will seem like random problems instead of one single broken upstream process.

1. Stem cells in the marrow divide and begin to specialize (commit to becoming red cells, white cells, or platelets).

2. Chemical signals (erythropoietin from the kidneys, G-CSF from immune cells, thrombopoietin from the liver) guide which cell type to make and how many.
3. Immature cells mature inside the marrow over several days, building the machinery they need (hemoglobin for red cells, enzymes and granules for white cells, clotting proteins for platelets).
4. Mature cells are released into the bloodstream through tiny marrow blood vessels (sinusoids) to do their jobs throughout the body.
5. Old or damaged cells are removed by the spleen and liver, and the cycle repeats every day to keep your blood counts stable.

## What breaks

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One broken thing upstream—destruction or failure of the stem cells—explains all the findings you see downstream.

**CLINICAL TERM**

The hematopoietic stem cell population in the bone marrow is destroyed or suppressed. In about 70% of cases, the cause is autoimmune: the patient's own cytotoxic T lymphocytes (CD8+ killer T cells) attack the stem cells. These T cells release interferon-gamma and tumor tissue death (necrosis) factor-alpha, which trigger apoptosis (programmed cell death) in the stem cells and block the signals that tell stem cells to divide. Other causes include direct toxic injury—chloramphenicol (an antibiotic) shuts down protein synthesis in dividing marrow cells; sulfonamides and NSAIDs trigger immune-mediated marrow suppression; viruses like hepatitis A, B, C, and parvovirus B19 infect and kill stem cells; ionizing radiation breaks DNA in dividing cells; benzene (a chemical in gasoline, solvents, and industrial products) forms toxic metabolites that damage DNA and kill stem cells. Inherited conditions like Fanconi anemia (cells cannot repair DNA cross-links) and dyskeratosis congenita (cells have abnormally short telomeres and die early) also destroy the stem cell pool over time. That single upstream break—stem cell loss—does not stay local. The downstream consequence is low counts of all blood cells (pancytopenia): all three blood cell lines drop together because they all depend on the same stem cell factory. Anemia (low red cells, hemoglobin often below 10 g/dL) causes tissue low oxygen (hypoxia), fatigue, and pale skin (pallor). Dangerously low infection-fighting cells (Neutropenia) (low neutrophils, often below 500 cells per microliter in severe cases) opens the door to life-threatening bacterial and fungal infections. A low platelet count (Thrombocytopenia) (low platelets, often below 20,000 per microliter) causes spontaneous bleeding—pinpoint bleeding spots (petechiae) (tiny red dots on the skin), purple bleeding blotches (purpura) (larger bruises), mucosal bleeding (nosebleeds, bleeding gums), and risk of intracranial bleeding (hemorrhage). Read every finding backward from that one broken stem cell factory upstream.

## How the body compensates

The body has no way to replace the stem cells once they are gone, so it tries to stretch what little blood cell production remains. Vital signs and routine labs can look stable for weeks while the marrow silently fails. Your job is to see the crash point coming before it happens—because once severe infection or bleeding starts, the window to save the patient closes fast.

1. The heart pumps faster and harder (mild a fast heart rate (tachycardia), increased stroke volume) to deliver oxygen to tissues even though red blood cells are low. Blood vessels in the skin and gut constrict slightly to redirect flow to the brain, heart, and kidneys. This keeps blood pressure and oxygen delivery near-normal for weeks, so the patient may only feel tired and weak rather than dizzy or short of breath at rest.

2. The kidneys sense low oxygen and release more erythropoietin (EPO), a hormone that normally tells the marrow to make more red cells. But in aplastic anemia the stem cells are gone, so EPO rises high in the blood (often >100 mU/mL, normal is 4–30) with no response—the signal is loud but the factory is closed. Measuring EPO does not diagnose aplastic anemia, but a high level with low reticulocytes (immature red cells, usually <1% or <40,000 per microliter) confirms the marrow is not responding.
3. Platelets drop slowly at first because they live 7–10 days, so the body uses up the existing pool before bleeding starts. Once the count falls below 50,000 per microliter, you see easy bruising and pinpoint bleeding spots (petechiae) (tiny red dots on the skin, especially the lower legs). Below 20,000, mucosal bleeding (nosebleeds, bleeding gums, heavy periods) becomes common. Below 10,000, spontaneous bleeding into the brain, gut, or lungs becomes a real risk—this is a medical emergency.
4. Neutrophils drop fast because they only live 6–8 hours, so even a few days without marrow production causes dangerously low infection-fighting cells (neutropenia). Once the absolute neutrophil count (ANC) falls below 1,500 per microliter, infection risk rises. Below 500 (severe dangerously low infection-fighting cells), the patient has almost no defense against bacteria (especially gut bacteria like *E. coli*, *Klebsiella*) and fungi (*Candida*, *Aspergillus*). Fever in a patient with ANC below 500 is a medical emergency (febrile dangerously low infection-fighting cells)—broad-spectrum antibiotics must start within one hour, because sepsis can kill within hours.
5. That compensated middle phase is dangerous because it hides how close the patient is to the edge. The team can miss that the marrow has no reserve left. A patient may walk into clinic feeling only 'a bit more tired than usual,' yet have a hemoglobin of 7 g/dL, platelets of 15,000, and neutrophils of 300—one infection or one fall away from death.
6. The crash points to watch for are: (1) Severe infection—sepsis from gut bacteria (*E. coli*, *Pseudomonas*, *Klebsiella*), mouth bacteria (*Streptococcus viridans*), or fungi (*Candida* bloodstream infection, *Aspergillus pneumonia*) when ANC is below 500. (2) Life-threatening bleeding—intracranial bleeding (hemorrhage) (bleeding into the brain, often fatal), gastrointestinal bleeding, or pulmonary bleeding when platelets are below 10,000. (3) Clonal evolution—the damaged marrow sometimes starts making abnormal cells with new mutations, and 10–15% of untreated or partially treated aplastic anemia cases evolve into myelodysplastic syndrome (MDS, pre-leukemia) or acute myeloid leukemia (AML) over months to years.

7. Treatment itself carries major risks. Immunosuppressive therapy (ATG—horse or rabbit antithymocyte globulin—plus cyclosporine) works in about 60–70% of patients but takes 3–6 months to show a response, and during that time infection and bleeding risks remain high. Allogeneic stem cell transplant (from a matched sibling or unrelated donor) can cure, but 20–30% of patients develop graft-versus-host disease (GVHD—the donor immune cells attack the patient's skin, gut, liver, and other organs), 5–10% reject the graft, and severe infections during the first 100 days post-transplant (when counts are near zero) can be fatal.
8. Watch trends over days and weeks—how fast are counts dropping, how often does the patient need red cell or platelet transfusions, are infections becoming more frequent. Do not rely on one snapshot. A patient with stable vital signs but hemoglobin dropping 1 g/dL per week, platelets falling from 40,000 to 15,000 over two weeks, and a new fever is not stable—they are on a downhill slope toward decompensation.
9. Always think one step ahead: if this patient's neutrophils drop another 200 in the next few days, will they be able to fight off even a simple urinary tract infection? If platelets fall another 5,000, will a small bump cause a brain bleed? The goal is to intervene—start treatment, transfuse, give growth factors (G-CSF for neutrophils), admit for close monitoring—before the crash, not after.

## Domino effect

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1. Hematopoietic stem cells in the bone marrow are destroyed or suppressed. — Cytotoxic T lymphocytes attack the stem cells (autoimmune, most common cause, about 70% of cases), or drugs (chloramphenicol, sulfonamides, NSAIDs), viruses (hepatitis, parvovirus B19), chemicals (benzene), radiation, or inherited defects (Fanconi anemia, dyskeratosis congenita) directly kill or poison the stem cells. The factory that makes all blood cells shuts down at the source.
2. Production of red blood cells, white blood cells, and platelets all drop together (pancytopenia). — All three cell lines come from the same pool of stem cells. When the stem cells are gone, every assembly line in the marrow factory stops at once—this is why you see low counts in all three types, not just one.

3. Hemoglobin falls below 10 g/dL (normal is 12–16 for women, 14–18 for men), often down to 6–8 g/dL in severe cases. Reticulocytes (immature red cells) are low (<1% or <40,000 per microliter), showing the marrow is not trying to replace the lost red cells. — Red blood cells live about 120 days. With no new red cells being made, the old ones die off naturally and are not replaced. Oxygen-carrying capacity drops, so tissues become oxygen-starved (hypoxic) (starved for oxygen). The patient feels exhausted, looks pale (especially in the palms, nail beds, and inside the eyelids), may have headaches, dizziness, and shortness of breath with mild activity. The heart beats faster (tachycardia) to pump the remaining red cells around faster and try to deliver enough oxygen.
4. Absolute neutrophil count (ANC) falls below 1,500 per microliter (normal is 1,500–8,000), then often below 500 in severe cases (severe dangerously low infection-fighting cells (neutropenia)). — Neutrophils only live 6–8 hours in the bloodstream—they are the first responders to bacterial and fungal infections, so they must be replaced constantly. With no new neutrophils made, the immune defense collapses within days. Bacteria from the gut (*E. coli*, *Klebsiella*, *Pseudomonas*), mouth (*Streptococcus viridans*), and skin (*Staphylococcus aureus*) break through, and fungi (*Candida*, *Aspergillus*) invade. The patient gets recurrent infections—fever, mouth sores (oral ulcers), skin infections, pneumonia, bloodstream infections (sepsis)—and infections spread fast because there are no neutrophils to wall them off.
5. Platelet count falls below 50,000 per microliter (normal is 150,000–400,000), then often below 20,000 or even below 10,000 in severe cases. — Platelets live 7–10 days. With no new platelets made, the clotting system fails. The patient sees easy bruising (purpura—purple patches on the skin), pinpoint bleeding spots (petechiae) (tiny red or purple dots, like pinpoints, especially on the lower legs and inside the mouth), nosebleeds (epistaxis), bleeding gums, heavy or prolonged menstrual periods (menorrhagia), and blood in the urine (hematuria) or stool (melena, bright red blood in the stool (hematochezia)). Below 10,000, spontaneous bleeding into the brain (intracranial bleeding (hemorrhage)), lungs (pulmonary bleeding), or gut becomes a life-threatening risk.
6. The spleen and liver stay normal size (no an enlarged spleen (splenomegaly), no an enlarged liver (hepatomegaly)) on physical exam. — The problem in aplastic anemia is not overproduction or buildup of abnormal cells (like in leukemia, lymphoma, or myelofibrosis) and not extra destruction of cells in the spleen (like in destroying red blood cells (hemolytic) anemia). The problem is absence of cell production—the marrow is empty or nearly empty, so there is nothing extra to fill or enlarge the spleen. A normal-sized spleen is an important clue that helps separate aplastic anemia from other causes of low counts of all blood cells (pancytopenia).

7. Bone marrow biopsy shows hypocellular marrow (cellularity <25%, often <10% in severe cases) with mostly fat cells and very few blood cell precursors. The remaining cells look normal (no blasts, no abnormal shapes), ruling out leukemia or myelodysplastic syndrome at the time of diagnosis. — With the stem cells gone, the marrow space is replaced by fat (adipocytes). The biopsy confirms the diagnosis and rules out other causes of low counts of all blood cells (pancytopenia)—leukemia (which would show packed marrow full of immature blast cells), myelodysplastic syndrome (which shows abnormal, dysplastic cells), and myelofibrosis (which shows scar tissue replacing the marrow).
8. The patient presents with fatigue, pale skin (pallor) (pale skin), easy bruising and bleeding (petechiae, nosebleeds, heavy periods), and recurrent infections (fever, mouth sores, pneumonia). Every symptom traces back to the broken marrow upstream. — Fatigue and pale skin (pallor) come from tissue low oxygen (hypoxia) (low red cells mean not enough oxygen reaches the muscles, brain, and organs). Bruising, pinpoint bleeding spots (petechiae), and bleeding come from failed clotting (low platelets mean the body cannot plug small leaks in blood vessels). Recurrent infections come from absent immune defense (low neutrophils mean bacteria and fungi break through unchecked). All three problems happen at once because all three cell types depend on the same stem cell factory, and that factory is shut down.

## Symptoms · what the patient feels, and why

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- Fatigue and getting tired quickly during activity: The bone marrow stops making enough red blood cells. Red cells carry oxygen using a protein called hemoglobin (it's like tiny oxygen trucks in your blood). When you don't have enough red cells, your muscles and brain don't get the oxygen they need, so you feel exhausted even doing normal things like walking upstairs.
- Pale skin, pale inside of eyelids, and pale nail beds: Hemoglobin is what makes blood red. When red blood cells drop, there's less red color flowing through your skin and the thin tissues inside your mouth and eyelids. So you look washed out or pale instead of pink.
- Easy bruising and tiny red or purple dots on the skin (petechiae): The bone marrow stops making enough platelets (tiny cell fragments that plug holes in blood vessels like quick-dry cement). Without enough platelets, even a light bump causes a bruise. Tiny blood vessels leak and make pinpoint red spots, especially on the legs and arms.
- Bleeding gums, nosebleeds, or very heavy menstrual periods: Platelets normally rush to any break in a blood vessel and form a plug to stop bleeding. When platelet counts are low, bleeding in the nose, mouth, or uterus doesn't stop quickly. The blood just keeps oozing because there aren't enough platelets to seal the leak.

- Getting infections over and over (like skin infections, pneumonia, or mouth sores): The bone marrow stops making enough white blood cells called neutrophils (the soldiers that kill bacteria and fungi). Without these infection fighters, germs can invade your skin, lungs, or mouth and cause infections that keep coming back or get serious fast.
- Fever with no clear cause: When your neutrophil count drops very low (below 500 cells per microliter—normal is 1,500 or higher), bacteria can sneak into your bloodstream and spread through your body. Your immune system can't fight back well, so you get a fever even though doctors can't always find exactly where the infection started.
- Shortness of breath during activity or even at rest: When hemoglobin falls very low (below 7 grams per deciliter—normal is 12–16), your heart beats faster trying to deliver enough oxygen. But if the anemia is severe, even a racing heart can't keep up. Your brain senses low oxygen and makes you feel like you can't catch your breath.
- Severe bleeding from the stomach, intestines, bladder, or inside the skull: When platelet counts crash below 10,000 to 20,000 per microliter (normal is 150,000 or more), blood vessels can start leaking on their own—even without an injury—because there are almost no platelets to patch the tiny breaks. Bleeding in the gut causes black or bloody stool; bleeding in the brain causes sudden headache, confusion, or weakness.
- Dizziness or feeling lightheaded: Severe anemia means your brain isn't getting enough oxygen. When you stand up or move around, blood pressure shifts and the low oxygen delivery makes you feel woozy or like the room is spinning.
- Fast or pounding heartbeat (palpitations): Your heart tries to make up for low oxygen by pumping faster and harder. You feel your heart racing or thumping in your chest, especially when you're active or lying down quietly at night.

## Focused exam

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- Pale skin and pale conjunctiva (inside the lower eyelid): When the bone marrow stops making enough red blood cells, less oxygen reaches the skin and mucous membranes. The result is pale skin (pallor) (pale color), a visible sign that anemia is real and the body is starving for oxygen.
- Pinpoint bleeding spots (Petechiae) (tiny red or purple dots) or bruises on skin without any recent injury: The marrow has stopped making enough platelets (the cells that plug holes in blood vessels). Without platelets, blood leaks into the skin and mucous membranes, creating spots and bruises even when nothing touched the skin.
- Fever or signs of infection (fast breathing, fast heart rate, chills): The marrow has stopped making enough neutrophils (the white blood cells that eat bacteria and fungi). Without these defenders, infections can spread fast and turn into sepsis (life-threatening infection in the bloodstream).

- Normal-sized spleen (not enlarged, cannot feel it below the rib cage): In aplastic anemia, the spleen does not enlarge because it is not trying to make extra blood cells. A big spleen points to a different problem like leukemia or a disease where red cells are being destroyed.
- No swollen lymph nodes in the neck, armpits, or groin: Aplastic anemia is not cancer. Swollen lymph nodes suggest leukemia, lymphoma, or an infection like mononucleosis instead.
- Mouth sores or bleeding gums: Low neutrophils let bacteria and fungi grow wild in the mouth. Low platelets mean the fragile tissue in the mouth bleeds easily. Both happen together in aplastic anemia.

## Diagnostics · every test answers a question

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- Complete blood count (CBC) with differential and reticulocyte count → Are all three cell types low, and is the marrow even trying to make new red cells?
- Peripheral blood smear (looking at blood cells under a microscope) → Do the blood cells look normal, or are there cancer cells or weird-shaped cells?
- Bone marrow biopsy and aspirate (taking a sample from inside the hip bone) → Is the marrow empty or packed with abnormal cells?
- Flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH) clone (CD55 and CD59 markers) → Is there a population of red cells missing protective proteins, which means PNH is causing or accompanying the marrow failure?
- Cytogenetic analysis (karyotype) of bone marrow cells → Are there broken or rearranged chromosomes that point to myelodysplastic syndrome or inherited marrow failure?
- Viral serologies: hepatitis A, B, C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), HIV, parvovirus B19 → Did a virus trigger the immune system to attack the bone marrow?
- Chromosomal breakage test (diepoxybutane or mitomycin C stress test) and telomere length assay → Is this inherited bone marrow failure (like Fanconi anemia or dyskeratosis congenita) or acquired (immune-mediated)?
- Serum vitamin B12 and folate levels → Could a vitamin deficiency explain the low blood counts instead of true marrow failure?

## Treatment logic

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- Allogeneic hematopoietic stem cell transplant from a matched sibling or matched unrelated donor → Replaces the patient's destroyed or attacked stem cells with healthy donor stem cells. The new stem cells settle in the marrow and restart normal production of red cells, white cells, and platelets permanently. This is the only cure.

- Immunosuppressive therapy: horse or rabbit anti-thymocyte globulin (ATG) plus cyclosporine, often with eltrombopag (a pill that signals the marrow to make more platelets) → Stops cytotoxic T cells (immune cells that kill other cells) from attacking the stem cells. When the attack stops, surviving stem cells can grow back and restart blood cell production. About 60–70% of patients respond within 3–6 months.
- Red blood cell transfusions and platelet transfusions, with iron chelation (deferasirox or deferoxamine) if ferritin rises above 1000 ng/mL → Red cell transfusions bring hemoglobin up temporarily so tissues get enough oxygen and the heart does not fail from overwork. Platelet transfusions keep the platelet count above 10,000/ $\mu$ L (or above 50,000/ $\mu$ L before procedures) to prevent life-threatening bleeding in the brain or gut.
- Preventive (Prophylactic) antibiotics (like levofloxacin or ciprofloxacin) and antifungals (like fluconazole or posaconazole) when absolute neutrophil count is below 500 cells/ $\mu$ L → Prevents bacterial and fungal infections that can turn deadly fast when neutrophils are too low to fight back. If fever develops, switch immediately to empiric broad-spectrum antibiotics (like cefepime or piperacillin-tazobactam) to cover *Pseudomonas* and other aggressive bacteria.
- Granulocyte colony-stimulating factor (G-CSF, like filgrastim) during active severe infection → Pushes any remaining marrow precursors to churn out neutrophils faster, raising the count temporarily to help fight infection. Used only during life-threatening infection, not routinely.
- Use white blood cell (leukocyte)-reduced, irradiated blood products; avoid platelet or red cell transfusions from family members if transplant is planned → White blood cell (Leukocyte) reduction removes white cells from donor blood, lowering the chance of alloimmunization (making antibodies against donor tissue types). Irradiation kills donor lymphocytes so they cannot attack the patient (transfusion-associated graft-versus-host disease). Avoiding family donors keeps the immune system naïve to family antigens, protecting the transplant option.
- Eltrombopag (a thrombopoietin receptor agonist) added to immunosuppression or as single agent in refractory disease → Signals the marrow to make more platelets and may also stimulate stem cells to divide. Improves blood counts in about 40% of patients who did not respond to ATG and cyclosporine alone.

## Medications

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### **Anti-thymocyte globulin (ATG) · Polyclonal antibody immunosuppressant**

ATG is made from the blood of horses or rabbits that were exposed to human T-cells (a type of white blood cell). It contains many different antibodies that bind to and destroy T-cells that are attacking the bone marrow stem cells. In aplastic anemia, your own T-cells mistakenly kill the

stem cells that make blood. ATG removes those attacking T-cells, giving the stem cells a chance to survive and grow again.

1. ATG antibodies attach to proteins on the surface of your T-cells (like keys fitting into locks).
2. Once stuck to the T-cell, the antibodies mark it for destruction—your own immune system then clears those marked T-cells away.
3. Some T-cells die directly when ATG binds; others are pulled out of circulation by the spleen and liver.
4. With fewer attack T-cells around, the bone marrow stem cells stop being destroyed.
5. The surviving stem cells begin dividing again, slowly rebuilding red cells, white cells, and platelets over weeks to months.

#### **SAFETY WATCH**

Serum sickness (fever, rash, joint pain, swollen lymph nodes) happens in most patients 7–14 days after the infusion because your body reacts to the horse or rabbit proteins; treat with steroids. · Severe allergic reaction (anaphylaxis) during the infusion—itching, trouble breathing, low blood pressure, fast heart rate—so ATG is always given in a hospital with emergency drugs ready. · Increased risk of serious infections (pneumonia, bloodstream infections, fungal infections) because ATG wipes out many immune cells; patients need antibiotics and antifungals during treatment. · Low platelet count can worsen in the first few days, raising bleeding risk; platelet transfusions are often needed. · Blood clots (deep vein clot formation (thrombosis), pulmonary embolism (a clot lodging in a lung artery)) can occur, especially in patients also getting cyclosporine or steroids.

### **Cyclosporine · Calcineurin inhibitor immunosuppressant**

Cyclosporine blocks a protein inside T-cells called calcineurin (think of it as a switch that turns on T-cell activity). When calcineurin is blocked, T-cells cannot make the chemical signals (cytokines like interleukin-2) they need to multiply and attack. This stops the T-cells from destroying bone marrow stem cells. Cyclosporine works hand-in-hand with ATG: ATG removes the attacking T-cells already present, and cyclosporine prevents new ones from activating.

1. You swallow cyclosporine; it is absorbed in the gut and travels through the bloodstream to every tissue.
2. Cyclosporine enters T-cells and binds to a helper protein called cyclophilin.
3. The cyclosporine-cyclophilin pair then sticks to calcineurin, shutting it off.
4. Without working calcineurin, the T-cell cannot turn on genes for interleukin-2 and other attack chemicals.
5. T-cells become quiet and stop multiplying, so the immune attack on stem cells fades.
6. Stem cells in the marrow are left alone and can slowly recover and make new blood cells.

**SAFETY WATCH**

Kidney damage (cyclosporine narrows blood vessels in the kidneys, reducing filtration)—check creatinine every 2 weeks at first, then monthly; keep the dose as low as possible. · High blood pressure because the drug tightens blood vessels; many patients need blood pressure medicine. · High potassium and low magnesium—monitor blood levels and replace magnesium if needed. · Increased infections (bacterial, viral, fungal) because the immune system is suppressed; watch for fever, cough, sores. · Tremor (shaking hands), headache, and excess hair growth (hirsutism) are common but not dangerous. · Gum overgrowth (gingival hyperplasia)—good dental care helps. · Drug interactions are frequent: many antibiotics, antifungals, and other drugs change cyclosporine levels, so blood levels are checked regularly.

**Eltrombopag · Thrombopoietin receptor agonist**

Eltrombopag mimics a natural hormone called thrombopoietin, which tells stem cells in the bone marrow to wake up and make more blood cells (especially platelets, but also red and white cells). In aplastic anemia, eltrombopag helps the few surviving stem cells work harder. It also appears to have a mild immune-calming effect, though scientists are still studying exactly how. Eltrombopag is always used together with ATG and cyclosporine—it boosts the stem cells while the other drugs stop the immune attack.

1. You swallow eltrombopag on an empty stomach; it is absorbed in the gut (food and minerals block absorption, so timing matters).
2. Eltrombopag travels to the bone marrow and binds to the thrombopoietin receptor (also called c-MPL) on the surface of stem cells.
3. Binding flips a switch inside the cell, turning on genes that promote cell division and survival.
4. Stem cells divide more often, making more daughter cells that mature into platelets, red cells, and white cells.
5. Over weeks to months, blood counts rise as the marrow ramps up production.

**SAFETY WATCH**

Liver injury (elevated liver enzymes, rarely severe hepatitis)—check liver tests every 2 weeks for the first month, then monthly; stop the drug if enzymes rise a lot. · Blood clots (deep vein clot formation (thrombosis), pulmonary embolism (a clot lodging in a lung artery), portal vein clot formation) can happen if platelet counts rise too high or too fast; monitor counts weekly at first. · Cataracts (clouding of the eye lens) have been seen in studies; eye exams are recommended before starting and periodically during treatment. · Bone marrow fibrosis (scar tissue in the marrow) is a rare risk with long-term use. · Take eltrombopag 2 hours before or 4 hours after food, dairy, or minerals (calcium, iron, magnesium, aluminum) because these block absorption and the drug will not work.

**Packed red blood cells (pRBC transfusion) · Blood product / supportive care**

Transfusion of packed red blood cells directly replaces the red cells your marrow cannot make. Red cells carry oxygen from your lungs to every tissue in your body. In aplastic anemia, you do not have enough red cells (anemia), so your heart has to pump harder to deliver oxygen and you feel tired, weak, dizzy, and short of breath. Transfusing red cells quickly raises your oxygen-carrying capacity, relieving symptoms and preventing heart strain while you wait for immunosuppressive therapy or transplant to rebuild your marrow.

1. A unit of red cells (donated blood with plasma and white cells removed) is given through an IV, usually over 2–4 hours.
2. The donor red cells mix with your own blood and flow through your arteries to every tissue.
3. Hemoglobin inside the red cells picks up oxygen in the lungs and releases it in tissues that need it.
4. Your hemoglobin level rises (typically 1 g/dL per unit transfused), and symptoms improve within hours.
5. The transfused cells last about 2–3 months in your circulation, then are cleared by the spleen; you may need repeat transfusions until your marrow recovers.

**SAFETY WATCH**

Transfusion reactions—fever, chills, itching, rash—are usually mild and treated with antihistamines or acetaminophen; rarely, severe allergic or destroying red blood cells (hemolytic) reactions occur (donor and recipient blood must be carefully matched). · Fluid overload (too much volume) can strain the heart and lungs, causing shortness of breath and swelling; transfuse slowly in patients with heart disease and give diuretics if needed. · Iron overload from chronic transfusions (every unit adds  $\approx 200$ – $250$  mg iron); after  $\approx 20$  units, check ferritin levels and consider iron chelation therapy (medicine to remove iron). · Alloimmunization (antibodies against donor red cell or HLA antigens) makes future transfusions less effective and transplant riskier; use white blood cell (leukocyte)-reduced (filtered) blood to lower this risk. · Infections (hepatitis, HIV) are extremely rare in the modern blood supply because all donations are tested, but risk is not zero.

**Platelet transfusion · Blood product / supportive care**

Platelet transfusion directly replaces the platelets your marrow cannot make. Platelets are tiny cell fragments that clump together to form clots and stop bleeding. In aplastic anemia, dangerously low platelet counts (severe a low platelet count (thrombocytopenia)) put you at risk for spontaneous bleeding—nosebleeds, gum bleeding, bruising, and most dangerously, bleeding in the brain (intracranial bleeding (hemorrhage)). Transfusing platelets temporarily raises your count and reduces bleeding risk while the marrow recovers or until transplant.

1. A unit of platelets (collected from one or more donors) is given through an IV over 15–30 minutes.
2. The donor platelets enter your circulation and mix with any platelets you still have.
3. If you cut or bruise yourself, the transfused platelets stick to the damaged vessel wall and to each other, forming a plug.
4. Your platelet count rises immediately (typically 5,000–10,000 per microliter per unit), reducing bleeding risk.
5. Transfused platelets last only 3–5 days in circulation, so you may need transfusions every few days until your marrow recovers.

**SAFETY WATCH**

Alloimmunization (antibodies against donor HLA or platelet antigens) happens in up to 50% of patients after repeated transfusions; once it occurs, transfused platelets are destroyed quickly and do not raise the count—use white blood cell (leukocyte)-reduced and sometimes HLA-matched platelets to reduce this risk. · Transfusion reactions (fever, chills, rash, rarely severe allergic reaction); premedicate with antihistamines and acetaminophen. · Fluid overload (heart strain, lung congestion) if too much volume is given too fast; transfuse slowly in patients with heart or kidney disease. · Infection transmission (hepatitis, HIV, bacteria) is rare but possible; all blood products are tested and filtered. · Minimize platelet transfusions before transplant—only transfuse if the count is dangerously low ( $<10,000/\mu\text{L}$ ) or if active bleeding occurs—because every transfusion increases alloimmunization risk and reduces transplant success.

**Filgrastim (G-CSF) · Granulocyte colony-stimulating factor (growth factor)**

Filgrastim is a man-made copy of a natural hormone called G-CSF (granulocyte colony-stimulating factor). G-CSF tells the bone marrow to make more neutrophils (a type of white blood cell that fights bacteria and fungi). In aplastic anemia, dangerously low neutrophil counts (severe dangerously low infection-fighting cells (neutropenia)) leave you open to life-threatening infections. Filgrastim boosts neutrophil production, raising your count and helping you fight infections while you wait for immunosuppressive therapy or transplant to rebuild the marrow.

1. Filgrastim is injected under the skin (subcutaneous) once daily.
2. It travels through the bloodstream to the bone marrow.
3. Filgrastim binds to G-CSF receptors on the surface of early white cell progenitors (cells that are a few steps away from becoming mature neutrophils).
4. Binding turns on genes that promote cell division, survival, and maturation into neutrophils.
5. Progenitor cells divide faster and more neutrophils are released from the marrow into the blood.
6. Your absolute neutrophil count (ANC) rises, typically within a few days, improving your ability to fight infection.

**SAFETY WATCH**

Bone pain (aching in the long bones, pelvis, sternum) is very common because the marrow is working harder; treat with acetaminophen or NSAIDs (but NSAIDs can worsen bleeding risk in a low platelet count (thrombocytopenia), so use with caution). · Spleen enlargement (splenomegaly) and rarely spleen rupture can occur; avoid contact sports and heavy lifting. · Worsening of underlying myeloid malignancies (leukemia, myelodysplastic syndrome)—filgrastim should not be used if there is concern for clonal evolution or leukemia. · Allergic reactions (rash, itching, rarely anaphylaxis) can happen. · A low platelet count (Thrombocytopenia) can worsen in some patients (the mechanism is unclear).

**Antibiotics (broad-spectrum, e.g. piperacillin-tazobactam, meropenem, fluoroquinolones) · Antimicrobial agents**

In severe aplastic anemia, very low neutrophil counts (neutropenia, ANC <500/ $\mu$ L) mean you have almost no soldiers to fight bacteria and fungi. Even normal skin and gut bacteria can invade the bloodstream and cause life-threatening infections (sepsis, pneumonia). Broad-spectrum antibiotics kill a wide range of bacteria (both gram-positive like Staph and gram-negative like E. coli and Pseudomonas), protecting you until your neutrophil count recovers. Preventive (Prophylactic) antibiotics (given to prevent infection before it starts) are used when ANC is very low; therapeutic antibiotics are started immediately if you develop fever (febrile dangerously low infection-fighting cells (neutropenia)) because any delay can be fatal.

1. Antibiotics are given by mouth (fluoroquinolones for prevention (prophylaxis)) or IV (piperacillin-tazobactam, meropenem for fever).
2. They travel through the bloodstream to sites of infection.
3. Each antibiotic attacks bacteria in a specific way: beta-lactams (piperacillin, meropenem) break down the bacterial cell wall, causing the bacteria to burst; fluoroquinolones (levofloxacin, ciprofloxacin) block bacterial DNA replication so bacteria cannot multiply.
4. Bacteria die or stop growing, and the infection is controlled.
5. Your immune system (any remaining neutrophils and other immune cells) then clears away the dead bacteria.

**SAFETY WATCH**

Allergic reactions (rash, itching, and rarely severe anaphylaxis, especially with beta-lactams like penicillin); always ask about drug allergies before starting. · Clostridioides difficile (C. diff) diarrhea—broad-spectrum antibiotics kill normal gut bacteria, allowing C. diff to overgrow and cause severe, watery, sometimes bloody diarrhea; stop the antibiotic if possible and treat C. diff. · Kidney injury (some antibiotics like aminoglycosides and vancomycin can damage the kidneys); monitor creatinine. · Drug-resistant bacteria (MRSA, VRE, multidrug-resistant gram-negatives) can develop with prolonged or repeated antibiotic use; use the narrowest effective antibiotic whenever possible. · Drug interactions (many antibiotics change levels of other drugs, especially cyclosporine and eltrombopag); check interactions before prescribing.

**Antifungals (fluconazole, voriconazole, or posaconazole for prevention (prophylaxis); amphotericin B or echinocandins for treatment) · Antimicrobial agents (antifungal)**

In severe dangerously low infection-fighting cells (neutropenia) (ANC <500/ $\mu$ L), you cannot fight fungal infections that healthy people easily control. Fungi like Candida (yeast) and Aspergillus (mold) invade the lungs, sinuses, bloodstream, and organs, causing pneumonia, brain abscesses, and sepsis that can be fatal within days. Antifungals kill or stop fungi from growing. Preventive (Prophylactic) antifungals (fluconazole, posaconazole) are given daily to prevent infection when dangerously low infection-fighting cells is prolonged. If you develop fever despite antibiotics or have signs of fungal infection (persistent fever, lung nodules on CT, sinus pain), stronger antifungals (voriconazole, amphotericin B) are started immediately.

1. Antifungals are given by mouth (azoles like fluconazole, voriconazole) or IV (amphotericin B, echinocandins like caspofungin).
2. They travel through the bloodstream to sites of infection.
3. Each antifungal attacks fungi in a specific way: azoles (fluconazole, voriconazole, posaconazole) block ergosterol production (a building block of fungal cell membranes), causing the membrane to leak and the fungus to die; amphotericin B pokes holes directly in fungal membranes; echinocandins (caspofungin, micafungin) block cell wall synthesis, causing the fungus to burst.
4. Fungi stop growing or die, and the infection is controlled.
5. Your immune system (any remaining neutrophils and macrophages) clears away the dead fungi.

**SAFETY WATCH**

Liver injury (elevated liver enzymes, rarely severe hepatitis)—azoles are the main culprits; check liver tests weekly during treatment. · Kidney injury (amphotericin B is toxic to the kidneys)—give IV fluids and monitor creatinine daily; liposomal formulations are less toxic but very expensive. · QT prolongation (abnormal heart rhythm) with azoles—check an EKG before starting and avoid other QT-prolonging drugs. · Drug interactions are very common with azoles—they inhibit liver enzymes that break down many drugs, raising levels of cyclosporine, eltrombopag, and others; adjust doses and check drug levels. · Electrolyte imbalances (low potassium, low magnesium) with amphotericin B—replace as needed. · Infusion reactions (fever, chills, low blood pressure) with amphotericin B—premedicate with antihistamines, acetaminophen, and sometimes steroids.

**Red flags**

- Fever (temperature 100.4°F or 38°C or higher) when your absolute neutrophil count is below 500/ $\mu$ L—this is neutropenic fever and means you could have a life-threatening bloodstream infection (sepsis). You need emergency IV antibiotics right away.
- Platelet count below 10,000/ $\mu$ L—very high risk of bleeding inside your skull (intracranial bleeding (hemorrhage)) or other organs without any warning. You may need an urgent platelet transfusion.
- Sudden severe headache, confusion, slurred speech, one-sided weakness, or vision changes—these can mean bleeding inside your brain from low platelets. This is a medical emergency.
- Blood counts dropping fast over days to weeks—this suggests very severe aplastic anemia or the bone marrow disease is changing into something worse like myelodysplastic syndrome or leukemia. Needs urgent specialist evaluation.
- Chest pain, extreme shortness of breath, or confusion—these mean your heart or brain is starving for oxygen because of severe anemia, and you need immediate care and possibly a blood transfusion.

**Nursing priorities**

1. Monitor temperature every 4 hours and immediately report any reading of 100.4°F (38°C) or higher to the provider, then prepare for stat blood cultures from two sites and rapid start of broad-spectrum IV antibiotics within 1 hour. — Neutropenic fever is the number one cause of death in aplastic anemia. When the absolute neutrophil count (infection-fighting white blood cells) is below 500/ $\mu$ L, bacteria in the blood (bacteremia) can turn into septic shock in 2 to 6 hours. Every hour of delay in antibiotics increases death risk by 10 to 20 percent.

2. Check platelet count daily and inspect skin, gums, and all body fluids for signs of bleeding every shift. Hold all injections, rectal temperatures, and suppositories if platelets are below 20,000/ $\mu$ L. Keep the bed in low position and pad side rails if platelets drop below 10,000/ $\mu$ L. — Platelets plug holes in blood vessels. When platelets fall below 10,000/ $\mu$ L, spontaneous bleeding (bleeding without injury) can happen anywhere—especially in the brain (intracranial bleeding (hemorrhage)). Even small trauma like a needle stick or bumping the head can cause life-threatening bleeding.
3. Use strict neutropenic precautions: private room, all visitors and staff wash hands with soap for 20 seconds or alcohol gel before entering, no fresh flowers or plants, no raw fruits or vegetables, and anyone with cold symptoms stays out. — When neutrophils (bacteria-fighting white blood cells) are very low, normal bacteria from the environment, food, or other people can cause deadly infections. Fungi in soil (from plants) and bacteria on uncooked food are especially dangerous because the body has almost no defense.
4. Transfuse red blood cells when hemoglobin drops below 7 g/dL or sooner if the patient has chest pain, shortness of breath at rest, or heart rate above 110 while lying down. Pre-medicate with acetaminophen and diphenhydramine (an antihistamine) 30 minutes before transfusion, and use leukoreduced (white-blood-cell-filtered) and irradiated blood products. — Hemoglobin carries oxygen to the brain, heart, and muscles. Below 7 g/dL, organs do not get enough oxygen and the heart works too hard (high-output heart failure). Leukoreduced blood prevents reactions and iron overload. Irradiated blood prevents donor white blood cells from attacking the patient (transfusion-associated graft-versus-host disease), which is fatal in immunosuppressed patients.
5. Administer immunosuppressive drugs (anti-thymocyte globulin, cyclosporine, eltrombopag) exactly on schedule, monitor for infusion reactions during ATG (fever, chills, low blood pressure, rash), and check cyclosporine trough levels as ordered to keep levels in therapeutic range. — These drugs stop the immune system from attacking the bone marrow stem cells and give the marrow a chance to recover. ATG is made from horse or rabbit serum and can cause severe allergic reactions (anaphylaxis) or serum sickness. Cyclosporine levels that are too low do not work; levels too high damage the kidneys.
6. Teach and enforce meticulous mouth care with soft toothbrush or foam swabs four times daily, rinse with salt water or baking soda solution, and avoid mouthwashes with alcohol. Inspect the mouth every shift for sores, white patches, or bleeding. — The mouth has millions of bacteria. Mouth sores (mucositis) and bleeding gums are entry points for bacteria into the bloodstream, causing sepsis. Low platelets make gums bleed easily. Gentle mouth care prevents infection and bleeding without causing trauma.

7. Monitor ferritin level every 4 to 6 weeks in patients receiving regular transfusions, and prepare to give iron chelation therapy (deferasirox by mouth or deferoxamine by IV or under the skin) if ferritin rises above 1000 ng/mL. — Each unit of red blood cells contains 200 to 250 milligrams of iron. The body cannot excrete iron, so it deposits in the heart (causing heart failure), liver (causing cirrhosis), and pancreas (causing diabetes). Iron chelators bind iron and let the kidneys remove it, preventing organ damage.
8. Coordinate care with the transplant team if the patient is a transplant candidate: ensure human white blood cell (leukocyte) antigen (HLA) typing is complete for patient and family members, avoid transfusions from family members (to prevent sensitization), and minimize total transfusions when possible. — Allogeneic stem cell transplant (getting healthy bone marrow from a matched donor) is the only cure for aplastic anemia. Each transfusion exposes the immune system to foreign proteins, creating antibodies that can reject the transplant (allosensitization). Transfusions from family donors are especially risky because the patient may reject their cells during transplant.

## Sources

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- American Society of Hematology (ASH) guidelines on aplastic anemia
- British Society for Haematology (BSH) 2016 guidelines for diagnosis and management of aplastic anemia
- National Institutes of Health (NIH) consensus on acquired aplastic anemia
- Aplastic Anemia and MDS International Foundation evidence-based standards

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