

Acetaminophen poison

Acetaminophen poisoning kills liver cells when NAPQI overwhelms glutathione. The antidote N-acetylcysteine (NAC) must start within 8 hours—timing saves lives. Doctors use the Rumack-Matthew chart to decide who needs treatment.

THE ONE-LINE TRUTH

When you swallow too much acetaminophen, a poison called NAPQI piles up faster than your liver's shield (glutathione) can grab it. NAPQI sticks to liver cells and kills them.

The chain — how it unfolds

1. Stage 1 (0 to 24 hours): nausea, vomiting, feeling unwell, or no symptoms at all — why: Acetaminophen is absorbed from the stomach and small intestine into the bloodstream within 30 minutes to 2 hours. It travels to the liver. The liver breaks it down, making NAPQI faster than glutathione can neutralize it. Glutathione stores run out within 8 to 12 hours. NAPQI starts sticking to liver cell proteins, but not enough cells have died yet to spill enzymes into the blood. Liver enzyme tests (AST and ALT) stay normal. The patient feels little or nothing, or has mild nausea from acetaminophen irritating the stomach lining. This deceptive calm is the danger—patients feel okay and delay seeking care, missing the narrow window when the antidote works best.
2. Stage 2 (24 to 72 hours): pain in the right upper belly, rising AST and ALT, sometimes nausea goes away — why: NAPQI sticks to the mitochondria (the power plants inside liver cells) and other proteins, stopping the cell from making energy. The cell swells, the membrane ruptures, and the cell dies. Dying liver cells spill their enzymes—AST and ALT—into the blood. Levels often shoot up into the thousands (normal is under 40). Right upper belly pain comes from the liver swelling with inflammation and fluid. The tight capsule that wraps the liver stretches, and stretch receptors in the capsule send pain signals. Nausea may go away because the stomach has cleared the drug, fooling the patient into thinking they are recovering. In reality, liver cell death is accelerating.

3. Stage 3 (72 to 96 hours): sudden massive liver failure with yellow skin, bleeding that will not stop, confusion, acid buildup, and kidney shutdown — why: Huge numbers of liver cells die—often 70 to 90 percent of functioning cells are gone. The liver loses its ability to make things and process waste. It stops making clotting factors (proteins II, VII, IX, X needed for blood to clot), so INR rises and bleeding happens from the nose, gums, gut, or needle sites. It stops processing bilirubin (a yellow breakdown product of old red blood cells), so bilirubin piles up in the blood and skin and eyes turn yellow (jaundice). It stops clearing ammonia (made by gut bacteria breaking down protein), so ammonia crosses the blood-brain barrier and poisons astrocytes (brain support cells that feed and protect neurons), causing confusion, sleepiness, or coma (hepatic encephalopathy). Dead liver cells dump lactate (a waste product from cells dying without oxygen) and the liver can no longer clear it, so lactate and acid pile up in the blood and pH drops (lactic too much acid in the blood (acidosis)). Kidneys fail from two hits: direct toxin damage to the filtering tubes (acute tubular tissue death (necrosis)) and signals sent by the failing liver that make kidney blood vessels squeeze shut, cutting off blood flow (hepatorenal syndrome). The patient is now in multi-organ failure.
4. Stage 4 (4 days to 2 weeks): recovery or death — why: If NAC was given early and liver cell death is limited (less than 50 to 70 percent of cells lost), the liver can grow back. Liver cells (hepatocytes) can divide and multiply, unlike many other organs. New cells grow and restore function over 1 to 3 weeks. AST and ALT fall, INR normalizes, bilirubin clears, and the patient recovers fully with no long-term damage. If damage is too severe (more than 70 to 80 percent of cells lost), the liver cannot regenerate fast enough. Multiple organs fail—liver, kidneys, brain, clotting system, lungs. Only a liver transplant can save the patient. Without transplant, death comes from brain swelling (cerebral swelling (edema) from ammonia and fluid shifts), bleeding that cannot be stopped, or infection (the liver makes immune proteins, so liver failure leaves the patient defenseless). Mortality without transplant is 50 to 90 percent once encephalopathy and impaired blood clotting (coagulopathy) appear together.
5. None of this is random — why: Every finding—nausea, rising liver enzymes, bleeding, confusion, kidney failure—traces directly back to glutathione running out and allowing NAPQI to kill liver cells. It is one upstream break cascading downstream in a predictable sequence. Nausea comes from stomach irritation and early toxin signals. Rising AST and ALT come from dying cells spilling enzymes. Bleeding comes from loss of clotting factor production. Confusion comes from ammonia the liver cannot clear. Kidney failure comes from toxins and liver signals shutting down kidney blood flow. Each domino falls because the one before it fell.

6. The body tries to compensate where it can — why: Early on, surviving liver cells work overtime to keep making clotting factors and processing bilirubin and ammonia, so INR and bilirubin stay normal at first. Kidneys concentrate urine to save water and keep blood pressure up. The brain tolerates low levels of ammonia for a short time by shifting it into other pathways. But these compensations hide the severity until liver cell numbers drop below a critical point—usually 70 to 80 percent lost—and compensation collapses suddenly. INR shoots up, bilirubin climbs, confusion sets in, and kidneys fail all at once. The crash is dramatic because the body was masking the damage until it could not anymore.
7. Trace backward from each finding to the root cause — why: Every treatment targets one point in the cascade. Activated charcoal (if given within 1 to 2 hours of ingestion) binds acetaminophen in the gut so it cannot be absorbed into the bloodstream. NAC (N-acetylcysteine) refills glutathione stores and gives the liver the building blocks to make more glutathione, so NAPQI gets neutralized. NAC also acts as a direct antioxidant and improves blood flow to the liver. NAC works best if started within 8 hours of ingestion—survival is over 95 percent. If started after 24 hours, survival drops to 60 to 70 percent because too many cells have already died. Liver transplant replaces the organ when cell death is too far gone—usually considered when INR is above 6.5, pH is below 7.3, creatinine is above 3.4, or encephalopathy is grade 3 or 4 (the King's College Criteria for transplant). Treatment logic follows the biology: stop absorption, refill the shield, replace the organ if needed.
8. Timing is everything — why: Acetaminophen poisoning is one of the most treatable overdoses—if caught early. NAC started within 8 hours prevents liver failure in over 95 percent of cases. After 24 hours, the window narrows. After 48 hours, much of the damage is done. The Rumack-Matthew nomogram helps decide who needs treatment based on blood acetaminophen level at 4 hours after ingestion. A level above 150 micrograms per milliliter at 4 hours means high risk and NAC should start immediately. The nomogram cannot be used for extended-release acetaminophen or for patients who took multiple doses over time (chronic overdose)—these patients need clinical judgment and NAC is often given if any doubt exists. The key teaching: treat early, treat based on the level and the nomogram, and do not wait for symptoms or liver enzyme elevation. By the time AST and ALT rise, glutathione is already gone and liver cells are dying. The antidote works by preventing damage, not reversing it once it has happened.

Spot it — what you see, and why

- Nausea and vomiting (Stage 1, first 24 hours): Acetaminophen and the pieces your liver breaks it into irritate the lining of your stomach. At the same time, they trigger the area postrema (the brain's vomit switch at the back of the brainstem that watches for poisons in the blood). This double hit makes you feel sick and throw up.

- Feeling better or no symptoms at all (Stage 2, 24 to 72 hours): All the acetaminophen has been soaked up and broken down, so your stomach feels better. Behind the scenes, liver cells are dying, but not enough damage has happened yet to make you feel sick. This quiet window tricks people into thinking they are fine—but the liver is still being destroyed.
- Pain and tenderness in the right upper belly (Stage 2 to 3): Dying liver cells cause the liver to swell with fluid and inflammation. Your liver sits inside a tight bag called the capsule. When the liver swells, it stretches the capsule—and the capsule has pain nerves. The liver cannot expand much inside your ribcage, so the stretching hurts.
- Yellow skin and whites of the eyes (jaundice, Stage 3, 72 to 96 hours): Dead liver cells cannot clean up bilirubin (a yellow waste dye made when old red blood cells break down). Bilirubin builds up in your blood and leaks into your skin and the whites of your eyes, turning them yellow.
- Confusion, extreme sleepiness, or not responding (encephalopathy, Stage 3): The failing liver cannot turn ammonia (made by gut bacteria and when you digest protein) into urea (a harmless waste). Ammonia piles up in the blood, crosses into your brain, and poisons astrocytes (the support cells that feed brain cells). This causes brain swelling and messes up neurotransmitters (the chemical messengers that let brain cells talk), leading to confusion, sleepiness, or even coma.
- Easy bruising, bleeding gums, or bleeding from the stomach or gut (Stage 3): Dying liver cells stop making clotting factors (the proteins that help blood clot), especially the ones that need vitamin K (factors II, VII, IX, and X). A test called INR goes up, meaning blood takes much longer to clot. Even small bumps cause big bruises, and your mouth and gut lining bleed on their own.

Red flags — act now

- INR greater than 1.5 or liver enzymes (ALT or AST) climbing into the thousands—signals severe liver cell death and loss of clotting proteins
- Confusion, sleepiness, or flapping hand tremor when arms are held out (asterixis)—signs ammonia is poisoning the brain
- Blood lactate greater than 3.5 after giving fluids, or blood pH less than 7.30—means massive cell death and very high risk of dying
- Kidney function worsening (rising creatinine) or urine output dropping below 0.5 mL per kilogram per hour—acute kidney injury on top of liver failure
- Reported swallowing more than 10 grams total (or 150 mg per kg of body weight), or blood acetaminophen level plotting above the treatment line on the Rumack-Matthew nomogram—high risk for liver damage if the antidote NAC is not given quickly

Treat it — in this order

1. NAC (N-acetylcysteine)—the antidote. Oral dosing: 140 milligrams per kilogram loading dose, then 70 milligrams per kilogram every 4 hours for 17 more doses (total 72 hours). IV dosing (preferred in the U.S.): 150 milligrams per kilogram over 1 hour, then 50 milligrams per kilogram over 4 hours, then 100 milligrams per kilogram over 16 hours (total 21 hours; continue longer if liver is still failing). → NAC refills the body's glutathione stores (the natural shield inside liver cells that neutralizes NAPQI, the toxic breakdown product of acetaminophen). Fresh glutathione stops NAPQI from latching onto liver cell proteins and killing the cell. NAC works best when started within 8 hours of swallowing—it prevents nearly 100 percent of severe liver damage if given early. NAC still helps even at 24 hours or later by supporting the liver and reducing inflammation, though it cannot undo damage already done.
2. Get a detailed history immediately—What drug did you take? Brand name and any combination ingredients? Exact time swallowed (or best estimate)? Total number of pills or total milligrams? Was it one big dose all at once, or spread over hours (staggered dosing)? Why did you take it—accidental, pain relief, or intentional self-harm? Any alcohol or other drugs taken at the same time? → Knowing the exact dose and time lets you plot the level on the Rumack-Matthew nomogram and decide if NAC is needed. Many over-the-counter cold and pain medicines hide acetaminophen inside (like Nyquil, Percocet, Vicodin)—people often do not realize they took it. Knowing about alcohol or other drugs (especially other liver toxins) tells you if the liver is at higher risk. Knowing intent tells you if the person needs psychiatric evaluation, a safety sitter, and inpatient mental health care after medical treatment.
3. Monitor liver function tests (ALT, AST, bilirubin, PT/INR) and creatinine every 12 to 24 hours once NAC is started. If the patient is in stage 2 or 3, check every 6 to 12 hours. Continue NAC until ALT is falling, INR is below 2.0, and the patient is clearly improving. → Watching the numbers over time tells you if NAC is working. Rising ALT and AST mean liver cells are still dying—keep giving NAC. Falling numbers mean the antidote is protecting the cells that are left and the liver is starting to heal. INR returning toward normal means the liver is making clotting proteins again. If numbers keep climbing despite NAC, the patient needs transplant evaluation.
4. Contact a liver transplant center early—ideally within 24 hours of hospital arrival—if any King's College Criteria are met: arterial pH below 7.30 after fluids, OR INR above 6.5, OR all three of (1) INR above 3.0, (2) creatinine above 3.4 milligrams per deciliter, and (3) grade 3 or 4 hepatic encephalopathy (deep confusion or coma). → Liver transplant replaces the dying liver with a healthy donor organ and is the only cure once acute liver failure has set in. Early referral saves lives because finding a match, arranging surgery, and transporting the patient take time. The King's College Criteria identify patients whose liver will not recover on its own—waiting too long means death.

5. Activated charcoal by mouth—1 gram per kilogram of body weight (maximum 50 grams in adults), given only if less than 1 to 2 hours since swallowing and the person can protect their airway and will not choke → Charcoal is like a sponge—it sticks to acetaminophen still sitting in the stomach and traps it so the drug cannot enter the blood. Less drug absorbed means less NAPQI (the toxic breakdown product that kills liver cells) is made. Charcoal works best within the first hour after swallowing.

Your top priorities at the bedside

1. Start the NAC antidote immediately if the acetaminophen level is above the treatment line on the nomogram, or right away if the patient is confused, jaundiced, or has liver enzymes in the thousands—do not wait for levels if poisoning happened more than 8 hours ago. — why: NAC donates sulfur groups to rebuild glutathione (the liver shield) and directly grabs onto NAPQI poison before it kills more liver cells. It works best within 8 hours of swallowing acetaminophen, but it still helps even 48 to 72 hours later by reducing inflammation and improving blood flow to dying liver tissue.
2. Draw blood for acetaminophen level at least 4 hours after ingestion, and also send INR (clotting time), ALT and AST (liver enzymes), creatinine (kidney function), and basic metabolic panel with bicarbonate and anion gap. — why: Levels drawn before 4 hours are still rising in the gut and blood, so they give false low readings. INR above 1.5 and ALT or AST in the thousands mean massive liver cell death. Creatinine rising means acute tubular tissue death (necrosis) (kidney poisoning). Low bicarbonate and high anion gap mean lactic acidosis (acid from oxygen-starved tissues) from cell death.
3. Monitor for anaphylactoid reactions (flushing, itching, hives, wheezing, low blood pressure) during the first IV NAC loading dose, and stop the infusion temporarily if these appear—then restart at a slower rate once symptoms resolve. — why: The fast IV loading dose releases histamine (an allergy chemical) in about 15 percent of patients, especially in the first 15 to 60 minutes. This is not a true allergy—it is a rate-related reaction. Slowing or pausing the infusion lets histamine levels drop. Do not skip NAC; the benefit outweighs this manageable side effect.