

Acetaminophen Overdose

Acetaminophen overdose kills liver cells because huge doses flood a backup pathway that makes NAPQI (a poison), your glutathione (the cleanup molecule) gets used up, and NAPQI then sticks to liver cells and kills them.

THE ONE-LINE TRUTH

When you take too much acetaminophen, your liver turns it into NAPQI (a poison), which kills liver cells after the body's protector molecule—glutathione—runs out.

The chain — how it unfolds

1. Hours 0–8: Acetaminophen is absorbed from your gut into your bloodstream, travels through your body, and arrives at the liver. — why: Peak drug level in blood happens 30 minutes to 2 hours after you swallow the pills (immediate-release) or up to 4 hours (extended-release). The drug is already being broken down, but NAPQI is still low and glutathione is still plentiful, so you feel nothing yet.
2. Hours 8–24: Glutathione drops below 30% of normal; NAPQI sticks to liver cell proteins; early cell injury begins, but you have no symptoms or just feel sick to your stomach and tired. — why: NAPQI binds to mitochondria (the power plants of the cell) and other cell parts, wrecking their ability to make energy and triggering cell death. Liver enzymes (AST and ALT) have not leaked into the bloodstream in big amounts yet, so they stay near normal. Nausea and vomiting come from stomach irritation and effects on the chemoreceptor trigger zone (the vomiting center in your brainstem, the lower part of your brain that controls basic body functions).
3. Hours 24–72: Right-upper-belly pain, skyrocketing AST and ALT (often 3,000–20,000 units per liter), rising bilirubin, and rising INR. — why: Liver cells around the central veins (zone 3, where CYP2E1 is highest) die in huge numbers and spill their contents—AST, ALT, and other enzymes—into the blood. The liver swells with fluid, stretching its capsule (outer wrapper) and causing right-upper-belly pain. Bilirubin rises because damaged cells cannot package and flush it out. INR begins to rise because the liver cannot make new clotting factors (factor VII has a half-life of only 6 hours, so it drops fast).

4. Hours 72–96: Peak liver injury—yellowing of the skin and eyes (jaundice) (yellow skin and eyes), bleeding (INR over 3–6, spontaneous bleeding), confusion or coma from ammonia buildup, kidney failure (creatinine rising, urine dropping), lactic acidosis (acid from oxygen-starved tissues) (blood pH below 7.35, lactate over 3–5 millimoles per liter), and low blood sugar (glucose below 70 mg per deciliter). — why: The liver has lost 50–90% of working cells. It cannot make clotting factors, so INR soars and you bleed from gums, gut, or any puncture site. It cannot convert ammonia to urea, so ammonia crosses into the brain and causes confusion or coma. It cannot package bilirubin, so yellowing of the skin and eyes (jaundice) deepens. It cannot make new glucose, so blood sugar drops. It cannot clear lactate, so acid builds up. The kidneys fail because back-pressure in liver blood vessels and body-wide inflammation squeeze kidney vessels shut (hepatorenal syndrome) and because NAPQI directly injures kidney tubule cells (the tiny tubes in the kidneys that filter waste and make urine).
5. Day 4 and beyond: Either recovery begins—AST and ALT level off then fall, INR improves, mental fog clears—or total liver failure marches to multi-organ failure, brain swelling, infection, and death without emergency liver transplant. — why: If fewer than 70% of liver cells died, the survivors regrow (the liver can rebuild itself). Enzyme levels drop, the liver starts making proteins again, and you survive. If more than 70–80% died, the liver cannot regrow fast enough. Brain swelling (cerebral swelling (edema)) develops from ammonia damage and swelling of astrocytes (brain support cells that feed and protect nerve cells). Infection risk soars because the liver makes immune proteins and clears bacteria from blood. Without transplant, brain herniation (brain tissue pushed through skull openings, crushing vital centers) or septic shock (infection causing blood pressure to crash) causes death.
6. NAC (N-acetylcysteine, the antidote) breaks the domino chain if given within 8–10 hours by refilling glutathione, grabbing NAPQI, and providing raw material for the safe pathways. — why: NAC is a building block for glutathione. It refills liver glutathione in 2–4 hours, letting the liver detoxify leftover NAPQI before it sticks to proteins. NAC also acts as a direct antioxidant (a molecule that mops up damaging oxygen particles) and improves blood flow in the liver. It works in over 95% of patients if started within 8 hours, drops to 70% effectiveness at 10–16 hours, and is minimal after 24 hours—though late NAC may still lower death risk in total liver failure by improving oxygen delivery and calming inflammation.

Spot it — what you see, and why

- Nausea and vomiting (first 24 hours): Acetaminophen and its early breakdown pieces irritate the stomach lining and trigger the chemoreceptor trigger zone (the vomit alarm center in the brainstem—the part of your brain that decides when you need to throw up).

- Feeling tired, weak, and generally unwell (first 24 hours): Your body senses the poison and early cell stress, so it triggers a general 'sick' alarm—you feel bad all over but can't point to one spot that hurts.
- Right-upper-belly pain and tenderness (24–72 hours): Massive liver cell death makes the liver swell with fluid and inflammation, stretching Glisson's capsule (the tight wrap around the liver—like blowing up a balloon inside a tight bag), and that stretch hurts.
- Yellowing of the skin and eyes (Jaundice)—yellow skin, yellow whites of the eyes, and yellow mucous membranes (48–96 hours): Dying liver cells can't process bilirubin (a yellow waste from old red blood cells being recycled) or push it into bile, so bilirubin piles up in the blood and stains the skin and eyes yellow—like spilling yellow dye into water.
- Confusion, sleepiness, flapping hand tremor when arms are held out, or coma (72–96 hours): Hepatic encephalopathy (brain malfunction from liver failure) happens because the dying liver can't convert ammonia (a toxic gas made by gut bacteria and protein breakdown) into urea (a safe waste your kidneys can dump), so ammonia crosses into the brain and messes up the astrocytes (brain support cells) and nerve signals—like static jamming a radio.
- Bleeding—from gums, easy bruising, tiny red spots on skin, blood in vomit or stool (72–96 hours): Impaired blood clotting (Coagulopathy) (poor clotting) happens because the liver can't make clotting factors (proteins numbered II, VII, IX, X) and proteins C and S, so the INR (a clotting test) rises above 3 or even 6, and blood can't clot—like trying to patch a leak without glue.

Red flags — act now

- INR over 3.0 or climbing fast, especially with any bleeding (gums, bruises, or blood in vomit or stool)
- Confusion, sleepiness, flapping tremor, or hard to wake (hepatic encephalopathy—brain shutting down)
- Creatinine rising or urine output less than 0.5 mL per kg per hour (kidneys failing)
- Blood pH below 7.30 or lactate over 3.5 mmol/L on blood gas (severe lactic acidosis (acid from oxygen-starved tissues)—body turning dangerously acidic)
- Blood sugar below 60 mg/dL despite giving sugar by IV (liver can't make or release glucose)

Treat it — in this order

1. N-acetylcysteine (NAC) intravenous: 150 milligrams per kilogram over 1 hour (loading dose), then 50 milligrams per kilogram over 4 hours, then 100 milligrams per kilogram over 16 hours (21-hour protocol per FDA; some centers use extended or repeat courses if ALT remains elevated or liver injury is severe) → NAC is the antidote. It gives the liver the building blocks to make more glutathione, which is the shield that catches NAPQI and turns it into harmless stuff the kidneys can dump into pee. When you give NAC, you refill the shield so NAPQI stops killing liver cells. The sooner you give NAC after the overdose, the more liver cells you save. If you give NAC within 8 hours, almost no one develops liver failure. Even if you give NAC late—after 10, 24, or even 36 hours—it may still help by calming down inflammation (reducing the body's overactive immune response that can damage cells), improving blood flow to the liver, and acting as an antioxidant (a chemical that reduces damage from harmful molecules called free radicals). NAC reduces death and the need for liver transplant even when started late. Current guidelines recommend continuing NAC until the person is clinically well, ALT is falling, and INR is less than 2.0.
2. Measure serum acetaminophen level at 4 hours after swallowing the pills (or immediately if the person comes in later than 4 hours) and plot it on the Rumack-Matthew nomogram; start NAC right away if the level is at or above the treatment line (150 mcg/mL at 4 hours), or if the time or amount swallowed is unclear, or if there is any evidence of liver injury (elevated ALT) → The Rumack-Matthew nomogram is a graph that predicts whether enough acetaminophen got into the blood to overwhelm the liver's glutathione shield. You measure the acetaminophen level at 4 hours or later (or right away if the person arrives later) and find that number on the graph. If the level is at or above the treatment line—150 mcg/mL at 4 hours, 75 mcg/mL at 8 hours, 37.5 mcg/mL at 12 hours—it means glutathione will run out and NAPQI will start killing liver cells unless you give NAC. Treating based on the nomogram prevents liver failure even if the person feels totally fine at that moment. If you don't know exactly when or how much acetaminophen was taken, or if the person took extended-release acetaminophen (which absorbs slowly over many hours), start NAC right away and figure it out later, because waiting can cost lives. Current practice is to start NAC immediately and not wait for the level to come back if the history suggests a toxic dose.

3. Activated charcoal 50 grams by mouth or through a tube into the stomach (nasogastric tube) if the person arrives within 1 hour (possibly up to 2 hours for very large doses or extended-release acetaminophen) after swallowing the acetaminophen, and only if the person is awake and can protect their airway → Activated charcoal is like a super-sticky sponge made of carbon with millions of tiny holes. If you give it within 1 hour after someone swallows acetaminophen, the charcoal sticks to the acetaminophen pills or liquid still sitting in the stomach and intestines. This stops the body from absorbing the acetaminophen into the blood. Less acetaminophen absorbed means less NAPQI poison gets made in the liver, so fewer liver cells die. Charcoal works best if given in the first hour, and possibly up to 2 hours if the person took a very large dose (greater than 30 grams) or extended-release acetaminophen (which dissolves slowly).
4. Check liver enzymes (ALT, AST), INR or PT, creatinine, and total bilirubin at baseline and then every 12 to 24 hours until the numbers return to normal or the person is listed for liver transplant → Checking these labs every 12 to 24 hours shows whether NAPQI is still killing liver cells and whether the liver and kidneys are starting to fail. Rising ALT and AST (often peaking between 3000 and 10,000 U/L or higher) mean liver cells are still dying. Rising INR above 1.5 means the liver can't make clotting proteins anymore. Rising creatinine above 1.5 to 2.0 mg/dL means the kidneys are shutting down. Rising bilirubin means the liver can't clear yellow waste from the blood. These numbers guide decisions about moving the patient to the intensive care unit (ICU), calling a liver transplant center, deciding how long to continue NAC, and checking for complications like bleeding, low blood sugar, or infection.
5. Apply King's College Criteria to decide if the person needs emergency evaluation for liver transplant: arterial pH less than 7.3 after giving enough IV fluids to support circulation (fluid resuscitation), OR all three of (INR greater than 6.5 AND creatinine greater than 3.4 mg/dL AND grade III or IV hepatic encephalopathy, meaning severe confusion or coma) → These criteria identify patients whose liver has failed so badly that they will almost certainly die without a new liver. A pH less than 7.3 after fluid resuscitation means the blood is dangerously acidic and the body can't fix it on its own. The combination of very high INR (blood won't clot), very high creatinine (kidneys failing), and severe confusion or coma (brain poisoned by ammonia and other toxins) means the liver has lost all its main jobs. Meeting the pH criterion alone, or meeting all three of the other criteria, means the liver is too destroyed to recover and must be replaced with a donor liver to save the person's life. About 80 to 90 percent of people who meet these criteria will die without a transplant. Other factors that suggest poor prognosis include lactate greater than 3.5 mmol/L after fluids, phosphate greater than 3.75 mg/dL at 48 to 96 hours, and worsening INR despite NAC. Some centers also use the MELD score (Model for End-stage Liver Disease) or other scoring systems to help decide who needs transplant.

Your top priorities at the bedside

1. Start the NAC intravenous infusion within 8 hours of the overdose if possible—150 milligrams per kilogram over 1 hour, then 50 milligrams per kilogram over 4 hours, then 100 milligrams per kilogram over 16 hours. — why: NAC (N-acetylcysteine) replaces glutathione (the body's protector molecule that neutralizes NAPQI poison). When started within 8 hours, NAC stops nearly all liver damage. Even after 8 hours, NAC still helps by reducing inflammation and improving blood flow to the liver.
2. Draw serum acetaminophen level at 4 hours after ingestion (or immediately if the patient arrives late), then check ALT (alanine aminotransferase, a liver enzyme), AST (aspartate aminotransferase, another liver enzyme), INR (international normalized ratio, a clotting test), creatinine (a kidney test), and bilirubin (a liver waste product). — why: The 4-hour level plotted on the Rumack-Matthew nomogram tells us if the dose is toxic. ALT and AST rising above 1,000 means liver cells are dying. INR over 1.5 means the liver is not making clotting proteins. Creatinine rising means kidneys are failing from the toxin or low blood flow.
3. Monitor for anaphylactoid reactions (flushing, itching, hives, wheezing, low blood pressure) during the NAC loading dose, especially in the first 15 to 60 minutes. — why: NAC releases histamine (an allergy chemical) in some patients, causing flushing, itching, and sometimes dangerous low blood pressure or trouble breathing. This is not a true allergy—it is dose and rate related. Slowing or stopping the infusion for 30 minutes usually fixes it.