

APAP Toxicity

Acetaminophen overdose floods the liver with NAPQI, a poison that your liver normally catches with glutathione. Too much NAPQI uses up all the glutathione, then kills liver cells. NAC (the antidote) gives your liver fresh glutathione so it can stop the damage—but only if you give it early.

THE ONE-LINE TRUTH

When you take too much acetaminophen, your liver makes NAPQI (a poison) faster than glutathione (your liver's natural protector) can clean it up, so NAPQI kills liver cells.

The chain — how it unfolds

1. Hours 0 to 24: no symptoms or mild nausea, vomiting, feeling unwell. — why: NAPQI is building up and glutathione is being used up, but liver cells are just starting to die. Not enough liver damage has happened yet to release big amounts of enzymes or cause the liver to lose function. Nausea and vomiting come from acetaminophen irritating your stomach and triggering the vomiting center in your brain.
2. Hours 24 to 72: pain under your right ribs, sky-high liver enzymes (ALT and AST in the thousands), rising INR. — why: Liver cells around the central vein (zone 3) are dying and breaking open, spilling ALT and AST into your bloodstream. Pain happens because your liver is swelling and stretching its outer covering (the capsule). INR rises because your liver can't make clotting factors anymore.
3. Hours 72 to 96: peak liver damage with yellowing of the skin and eyes (jaundice) (yellow skin and eyes), confusion (encephalopathy), bleeding problems (coagulopathy), kidney failure, lactic acidosis (acid from oxygen-starved tissues) (acid buildup in the blood). — why: So many liver cells are dead that the liver stops doing its jobs. It can't clear bilirubin (a yellow pigment from broken-down red blood cells), so you turn yellow. It can't convert ammonia to urea, so ammonia builds up in your blood, crosses into your brain, and causes confusion, flapping hand tremor, and coma. It can't make clotting factors, so you bleed and bruise easily, sometimes with serious GI bleeding. It can't keep blood flowing to your kidneys (hepatorenal syndrome), so your kidneys fail and creatinine rises. It can't clear lactic acid or make energy properly (mitochondria are broken), so acid builds up in your blood.

4. Hours 96 and beyond: recovery (liver grows new cells) or death from multiorgan failure (liver, kidneys, brain, clotting all collapse). — why: The liver can grow back if less than half of its cells are dead. Surviving liver cells divide (mitosis) and replace the dead ones over 1 to 3 months. If more than 70 percent of the liver is destroyed, the liver can't regenerate fast enough and you die unless you get a liver transplant.
5. Every clinical finding is a direct result of NAPQI killing liver cells and using up glutathione. — why: Nothing is random. Nausea is the toxin irritating your gut and brain. Pain is your swollen liver stretching its capsule. High liver enzymes are dead cells spilling their insides. Bleeding is lost clotting factors. Confusion is ammonia poisoning your brain. Kidney failure is lost blood flow from a failing liver. Low blood sugar is lost ability to make glucose. Yellow skin is bilirubin buildup. All trace back to one upstream break: NAPQI overwhelming glutathione and killing liver cells.
6. Treatment is time-sensitive: NAC (N-acetylcysteine) restores glutathione if given within 8 hours (nearly 100 percent effective); it still helps after 24 hours but works less well. — why: NAC is the building block your liver uses to make glutathione. It refills your liver's glutathione stores so your liver can neutralize remaining NAPQI. NAC also improves blood flow and oxygen delivery to liver cells and calms down inflammation. Early NAC prevents liver damage. Late NAC reduces severity but cannot reverse cells that are already dead.
7. Diagnosis: measure blood acetaminophen level at 4 hours after you took the drug and plot it on the Rumack-Matthew nomogram. Levels greater than 150 micrograms per milliliter at 4 hours or greater than 75 at 8 hours predict liver damage. — why: The nomogram is a chart that compares your blood acetaminophen level to the time since you took the drug. It tells the doctor how likely you are to get liver damage before any symptoms show up. If your level is above the line, you get NAC treatment immediately, even if you feel fine.
8. Risk factors that make toxicity worse: chronic alcohol use (induces CYP2E1, making more NAPQI), malnutrition (depletes glutathione), medications that induce P450 enzymes (phenytoin, rifampin, carbamazepine), and fasting (lowers glutathione stores). — why: Chronic alcohol use turns on the enzymes that make NAPQI, so you make more poison from the same dose. Malnutrition and fasting mean you have less glutathione to start with, so NAPQI overwhelms your liver faster. Enzyme-inducing drugs also ramp up NAPQI production. These patients can get severe liver damage from lower acetaminophen doses (as low as 4 grams per day).

Spot it — what you see, and why

- Nausea and vomiting (first 24 hours): Acetaminophen (the pain medicine) and the toxic byproduct NAPQI (a poison made when the liver tries to break down too much acetaminophen) irritate the stomach lining and trigger a special zone in the brainstem called the chemoreceptor trigger zone—the brain's 'vomit switch'—causing nausea and vomiting even before the liver is badly damaged.
- Right upper quadrant pain—sharp or aching pain under the right ribs (24–72 hours): As liver cells die from the poison, they swell up like water balloons. This stretches the liver's outer wrapper (the hepatic capsule), which has pain nerves. Think of it like a balloon stretching inside a tight box—it hurts.
- Yellowing of the skin and eyes (Jaundice)—yellowing of the skin and whites of the eyes (48–96 hours): The damaged liver cannot process bilirubin (a yellow pigment left over when old red blood cells are broken down). Bilirubin piles up in the blood and seeps into the skin and the whites of the eyes, turning them yellow—like staining a white shirt with mustard.
- Confusion, sleepiness, or coma—hepatic encephalopathy (72–96 hours): The failing liver cannot clean ammonia (a toxic waste from gut bacteria and digested protein) out of the blood. Ammonia crosses into the brain and poisons brain cells, causing confusion, disorientation, a flapping hand tremor called asterixis, and eventually coma—like trying to think clearly in a room full of toxic fumes.
- Easy bruising, bleeding gums, or blood in vomit or stool (72–96 hours): The liver makes clotting factors (special proteins like II, VII, IX, and X that help blood form clots). When the liver fails, it stops making these proteins, so the blood cannot clot properly. Even small bumps cause bruises, gums bleed, and bleeding can start inside the stomach or intestines.
- Decreased urine output and dark urine (72–96 hours): The kidneys can fail in two ways: hepatorenal syndrome (blood vessels in the kidneys squeeze shut because the liver is failing) and direct tubular injury (the kidney's filter tubes are poisoned by toxins the liver cannot clear anymore). Less urine is made, creatinine (a kidney waste marker) rises in the blood, and urine turns dark like cola.

Red flags — act now

- Confusion, asterixis (flapping hand tremor when arms are held out), or altered mental status—warns of hepatic encephalopathy and liver failure happening now
- INR greater than 6.5 or any bleeding without injury (bleeding gums, blood in vomit or stool, large bruises)—shows the blood cannot clot and death risk is very high
- Rising creatinine or low urine output (oliguria) (less than 400 mL of urine per day, about 1.5 cups)—signals acute kidney injury and hepatorenal syndrome

- Lactic acidosis (acid from oxygen-starved tissues) (lactate above 4 mmol/L) or blood pH below 7.3—means the cell's energy system is failing; meets criteria for emergency liver transplant
- Low blood sugar (Hypoglycemia) that does not respond to sugar given through the IV—shows the liver has lost the ability to make glucose; this is late-stage liver failure

Treat it — in this order

1. Activated charcoal 1 gram per kilogram of body weight (up to 50 grams total) by mouth or through a nose-to-stomach tube, given only if the person arrives within 1 to 2 hours of swallowing the acetaminophen → Activated charcoal is like a sponge. It sticks to acetaminophen pills still sitting in the stomach and small intestine, trapping them so they cannot be absorbed into the blood. This lowers the total dose that reaches the liver and cuts down how much NAPQI gets made.
2. Intravenous N-acetylcysteine (NAC) using the 21-hour protocol: loading dose 150 mg/kg in 200 mL sugar water (D5W) over 1 hour, then 50 mg/kg in 500 mL D5W over 4 hours, then 100 mg/kg in 1,000 mL D5W over 16 hours → NAC refills the liver's supply of glutathione, the bodyguard molecule that grabs and neutralizes NAPQI before it can kill more cells. If started within 8 hours of the overdose, NAC prevents almost all liver damage. Even up to 24 hours, it still helps by stopping further cell death.
3. Continue NAC beyond 21 hours if ALT, AST, or INR are still rising or staying high; give another 100 mg/kg over 16 hours and recheck labs every 4 to 6 hours until liver enzymes start falling and INR improves → Some people keep making NAPQI for longer than 21 hours, especially if they took a huge dose or have slow metabolism. Extended NAC keeps glutathione levels high enough to match ongoing toxin production and prevents the injury from getting worse.
4. Apply King's College criteria to decide if the person needs a liver transplant: arterial pH below 7.30 after giving IV fluids, OR all three of these—INR above 6.5, creatinine above 3.4 mg/dL (300 μ mol/L), and grade III or IV confusion (hepatic encephalopathy). If criteria are met, immediately call a liver transplant center for evaluation and possible transfer. → These criteria identify people whose own liver is so destroyed it will never recover. Calling a transplant center early puts the person on the list for a donor liver in time to save their life before other organs shut down for good.

5. Supportive care: IV fluids (normal saline or lactated Ringer's) to keep blood pressure stable and organs supplied with blood; ondansetron 4–8 mg IV for nausea; dextrose infusion if blood sugar drops below 70 mg/dL; transfuse fresh frozen plasma or give prothrombin complex concentrate only if the person is actively bleeding or needs an urgent procedure and INR is dangerously high → Supportive care keeps the body's systems running while NAC works or while waiting for a transplant. It prevents death from low blood pressure, low blood sugar, brain swelling, or uncontrolled bleeding—all complications of liver failure.

Your top priorities at the bedside

1. Start the intravenous N-acetylcysteine (NAC) 21-hour protocol immediately: give loading dose 150 mg per kilogram in 200 mL D5W (sugar water) over 1 hour, then 50 mg per kilogram in 500 mL D5W over 4 hours, then 100 mg per kilogram in 1,000 mL D5W over 16 hours. — why: NAC donates sulfur groups that refill glutathione stores so the liver can detoxify NAPQI before it kills more liver cells. NAC works best when started within 8 hours of ingestion, but it still reduces death even when started late, so never delay—start it while waiting for lab results.
2. Draw blood for acetaminophen level, ALT and AST (liver enzymes), bilirubin, INR and PT (clotting tests), creatinine (kidney test), and basic metabolic panel before starting NAC, then recheck INR, creatinine, ALT, and AST every 12 to 24 hours. — why: The acetaminophen level at 4 hours after ingestion plotted on the Rumack-Matthew nomogram tells if liver damage will happen. Rising ALT above 1,000 units per liter confirms liver injury. INR above 1.5 shows the liver cannot make clotting factors. Rising creatinine means kidney failure is starting.
3. Assess mental status every 2 to 4 hours using the Glasgow Coma Scale or simple questions like 'What is your name?' and 'Where are you?' and check for asterixis by asking the patient to hold both arms out with wrists bent back for 30 seconds and watching for flapping tremor. — why: Hepatic encephalopathy happens when ammonia (a toxin normally removed by the liver) builds up in the blood and poisons brain cells. Confusion or asterixis means liver failure is severe and the patient may need intubation (breathing tube) to protect the airway or urgent liver transplant evaluation.