

Acetaminophen Overdose

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THE STORY IN ONE SENTENCE

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“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.”

Normal anatomy — the body's job

Normally, 90% of acetaminophen is safely handled by two liver pathways that attach a sugar molecule (glucuronidation) or a sulfate group (sulfation), then your kidneys flush it out in urine. Only 5-10% goes through a backup pathway using the enzyme CYP2E1 (a protein that changes the drug into a different form), which makes NAPQI. Glutathione grabs NAPQI right away and turns it into harmless waste that leaves in urine. This keeps NAPQI too low to hurt cells.

BODY'S JOB

The liver's job is to break down acetaminophen safely and keep NAPQI from ever building up to dangerous levels.

1. You swallow acetaminophen, and your stomach and small intestine absorb it into your bloodstream.
2. Blood carries the drug straight to your liver (your body's main chemical-processing factory).
3. Inside liver cells, 90% of the drug meets two safe pathways: one attaches a sugar molecule through glucuronidation, the other attaches a sulfate group through sulfation.
4. These attached versions are now harmless and water-loving, so they pour into your bloodstream, travel to your kidneys, and leave in your urine.
5. The leftover 5-10% meets a different enzyme called CYP2E1 (a protein that strips a piece off the drug) and makes NAPQI, a toxic molecule.

6. Glutathione (a small rescue molecule your liver keeps in stock) immediately grabs each NAPQI molecule and locks onto it.
7. The glutathione-NAPQI pair turns into a harmless compound called mercapturic acid that your kidneys filter out in urine.
8. Because glutathione cleans up NAPQI as fast as it forms, NAPQI never builds up and never hurts your cells.

What breaks

In overdose, the safe pathways get completely full—like two checkout lines that can only handle so many shoppers. The liver is forced to push much more acetaminophen through the backup exit using CYP2E1, making huge amounts of NAPQI. Glutathione stores run out in hours. Free NAPQI then sticks to proteins inside liver cells and triggers cell death.

CLINICAL TERM

At toxic doses (usually over 150 mg per kg of body weight, or over 7.5–10 grams total in adults), the safe conjugation pathways (glucuronidation and sulfation) saturate and reach maximum capacity. CYP2E1 metabolism increases sharply, producing overwhelming NAPQI. Hepatic glutathione drops below 30% of normal. Unbound NAPQI binds to hepatocyte proteins, damages mitochondria (the cell's power plants), and causes oxidative stress and centrilobular hepatic tissue death (necrosis) (death of liver cells around the central veins in zone 3). The downstream result is acute liver failure, impaired blood clotting (coagulopathy) (inability to clot blood), hepatic encephalopathy (brain dysfunction from ammonia buildup), acute kidney injury, and lactic acidosis (acid from oxygen-starved tissues) (acid buildup from dying cells).

How the body compensates

In the first 24 hours, vital signs and routine labs may look completely normal even though liver injury is already starting. The body cannot compensate once massive cell death begins. By 48–72 hours, the liver stops making proteins like clotting factors, and multi-organ failure follows rapidly.

1. In the first 24 hours, you may look stable or just feel sick to your stomach, hiding the silent buildup of NAPQI and early cell injury underneath.
2. This early window fools everyone—liver enzymes (AST and ALT, which leak out of damaged liver cells) have not risen yet because cells have not broken open and spilled their contents into the bloodstream.
3. By 24–48 hours, AST and ALT skyrocket (often over 1,000 units per liter, sometimes over 10,000) as liver cells burst and pour enzymes into blood.

4. The crash point is 72–96 hours: INR (a clotting measure; normal is around 1.0) climbs above 1.5, then above 4–6 in severe cases, because the liver stops making clotting factors (proteins II, VII, IX, and X that help blood clot).
5. Ammonia piles up because the damaged liver cannot convert it to urea (a harmless waste that leaves in urine), leading to hepatic encephalopathy (confusion, sleepiness, then coma).
6. Bilirubin rises and causes yellowing of the skin and eyes (jaundice) (yellow skin and eyes) because the liver cannot process and flush it out.
7. Acute kidney injury develops from hepatorenal syndrome (kidney blood vessels squeeze shut because of signals from liver failure) and direct NAPQI damage to kidney tubule cells (the tiny tubes in the kidney that make urine).
8. Lactic acidosis (acid from oxygen-starved tissues) (acid buildup; normal blood pH is 7.35–7.45) and low blood sugar (below 70 mg per deciliter) appear because the dying liver cannot make new glucose or clear lactate (a waste acid from cells).
9. Once INR climbs over 6.5, blood pH drops below 7.3, creatinine (a kidney waste marker) rises over 3.4 mg per deciliter, or confusion deepens to grade III–IV encephalopathy, death without liver transplant exceeds 90% (King's College Criteria).
10. The window for NAC to stop this cascade closes after 24 hours; after 72 hours, only supportive care and transplant evaluation remain.

Domino effect

1. Hours 0–8: Acetaminophen is absorbed from your gut into your bloodstream, travels through your body, and arrives at the liver. — 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. — 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. — 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). — 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. — 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. — 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.

Symptoms · what the patient feels, 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.
- Little or no urine, rising creatinine (acute kidney injury, 72–96 hours): Hepatorenal syndrome (kidney blood vessels squeeze shut because of alarm signals from liver failure) and direct damage to kidney filter tubes by NAPQI (the toxic breakdown product of acetaminophen) cause the kidneys to stop making urine—like clogged and squeezed pipes at the same time.
- Low blood sugar—shakiness, confusion, sweating, or unresponsiveness (72–96 hours): The liver can't make new glucose from amino acids and lactate (gluconeogenesis—making fresh sugar from other building blocks) or release stored sugar (glycogen), so blood glucose drops below 70 mg/dL, then below 50 mg/dL in severe cases—like a battery running completely dead.

- Fast, deep breathing and acid buildup in blood (lactic too much acid in the blood (acidosis), 72–96 hours): Dying liver cells can't clear lactate (an acid waste from cells running on backup energy without enough oxygen), and damaged mitochondria (cell power plants) in the liver and other tissues make even more lactate, dropping blood pH below 7.35—like smoke backing up in a room when the chimney is blocked.

Focused exam

- Pain or tenderness in the right upper belly just under the ribs, sometimes with swelling you can feel when you press gently (hepatomegaly): The liver sits tucked under the ribs on the right side of your belly. When someone takes too much acetaminophen, the liver uses an enzyme called CYP2E1 (a liver enzyme that chops up certain drugs) to break it down. This process makes a poison called NAPQI. Normally, a shield called glutathione (the liver's main protector molecule) grabs NAPQI and turns it into harmless stuff that leaves in your pee. But when a huge dose of acetaminophen floods in, glutathione runs out. NAPQI is left free to attack liver cells. It sticks to proteins inside the cells and kills them. Dead liver cells swell up and leak chemicals that cause redness and swelling inside the liver. This makes the liver bigger and sore when you press on it. Pain here is an early warning that liver cells are dying.
- Yellow skin and yellow whites of the eyes (jaundice): Your body constantly breaks down old, worn-out red blood cells. This makes a yellow waste product called bilirubin. A healthy liver pulls bilirubin out of the blood, changes it so it can mix with bile (the green-brown fluid the liver makes to help digest fats), and dumps it into the small intestine so it leaves your body in poop. When acetaminophen kills enough liver cells, the liver can't do this job anymore. Bilirubin piles up in the blood and soaks into your skin and the whites of your eyes, turning them yellow. Yellowing of the skin and eyes (Jaundice) means the liver is badly damaged and can't clear waste from the blood. It usually shows up 2 to 3 days after the overdose.
- Confusion, extreme sleepiness, or very hard to wake up (hepatic encephalopathy): The liver normally cleans toxins out of the blood. One of the worst toxins is ammonia, which comes from breaking down protein in food and from bacteria in the gut. A healthy liver turns ammonia into urea (a less toxic waste) that the kidneys then dump into pee. When acetaminophen destroys the liver, ammonia and other poisons stay in the blood and float up into the brain. These toxins mess with how brain cells talk to each other, especially by disrupting glutamate (the brain's main 'go' signal that makes cells fire) and GABA (the brain's main 'stop' signal that calms cells down). The person becomes confused, very sleepy, or impossible to wake up. This is a sign that the liver has failed so badly it can no longer protect the brain.

- Easy bruising or bleeding that won't stop (coagulopathy): The liver makes special proteins called clotting factors—including factors II, VII, IX, and X (proteins that work together like links in a chain to help blood clot and seal up cuts). When acetaminophen kills liver cells, the liver stops making enough clotting factors. Blood can't clot the way it should. Even a tiny bump can cause a big bruise, or a small cut that won't stop bleeding. This is measured with a test called INR (international normalized ratio, a number that shows how fast blood clots). A normal INR is around 1.0. If INR rises above 1.5 and keeps climbing, it means the liver can't make enough clotting factors to keep blood from leaking out of vessels.
- Feeling sick to your stomach and throwing up in the first 24 hours after swallowing the pills: This is the body's first alarm bell. The stomach and intestines sense a toxic dose of acetaminophen and try to get rid of it by making the person feel sick and vomit. At this stage, serious liver damage usually hasn't started yet because it takes time for NAPQI to build up and kill cells. This is the best window of time to give the antidote called N-acetylcysteine (NAC, a medicine that refills the glutathione shield), because if you give it before liver cells die, you can prevent almost all the damage. Even if the person feels better after the throwing up stops, liver damage may still be starting silently.
- Pale, cool skin and low blood pressure (systolic blood pressure less than 90, or mean arterial pressure less than 65): The liver makes a protein called albumin (a protein that acts like a sponge inside blood vessels, holding water in the blood). When the liver fails from acetaminophen overdose, it stops making enough albumin. Fluid leaks out of the blood vessels and pools in the belly (called fluid buildup in the belly (ascites), fluid in the belly). Blood pressure drops because there isn't enough fluid left in the vessels for the heart to pump around the body. When blood pressure falls too low, organs like the brain, kidneys, and heart don't get enough oxygen. This can lead to multiple organs shutting down at once (multi-organ failure) and death.

Diagnostics · every test answers a question

- Serum acetaminophen level measured at 4 hours or later after the person swallowed the pills, plotted on the Rumack-Matthew nomogram → How much acetaminophen is in the blood right now, and does this level predict that the liver will be poisoned?
- Liver enzymes: ALT (alanine aminotransferase) and AST (aspartate aminotransferase) → Are liver cells dying right now?
- Prothrombin time (PT) and INR (international normalized ratio) → Can the liver still make the proteins that help blood clot?
- Serum creatinine and blood urea nitrogen (BUN) → Are the kidneys still filtering waste out of the blood?
- Arterial blood gas (ABG) with pH and serum lactate → Is the blood dangerously acidic, and are the body's cells getting enough oxygen to make energy?

- Total and direct bilirubin → Can the liver still grab bilirubin from the blood and dump it out of the body?
- Serum phosphate → Is phosphate leaking out of dying liver cells?
- Blood glucose (blood sugar) → Can the liver still make glucose to keep blood sugar stable?

Treatment logic

- 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.
- 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.

- 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).
- 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.
- 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.

- Admit to intensive care unit (ICU) and contact a liver transplant center immediately if any King's College criterion is met, or if ALT is greater than 1000 U/L with INR greater than 2.0, or if the person has signs of hepatic encephalopathy (confusion, sleepiness, coma) or other organ failure → The ICU can watch the patient constantly and support failing organs. If confusion worsens and the person can't protect their airway or breathe safely, the ICU can put a breathing tube in and use a ventilator (a machine that breathes for the person). If blood pressure drops, they can give medicines called vasopressors—such as norepinephrine (a drug that squeezes blood vessels and raises blood pressure by mimicking adrenaline)—to keep blood flowing to the brain and kidneys. If kidneys fail, they can start hemodialysis or continuous renal replacement therapy (machines that clean the blood when the kidneys can't). A liver transplant center has experts (hepatologists, transplant surgeons, and critical care doctors) who can decide if the person needs an emergency liver transplant and has surgeons ready to do the operation as soon as a donor liver is found. Transplant evaluation includes checking blood type, looking for infections, and making sure the person is stable enough for surgery.
- Give IV dextrose (sugar water) to keep blood glucose above 60 to 70 mg/dL and check blood sugar every 2 to 4 hours in severe liver failure; typical regimen is dextrose 10 percent (D10W) infusion, adjusted based on frequent fingerstick glucose checks → When the liver fails, it can't make or release glucose anymore. Blood sugar can drop dangerously low (hypoglycemia, less than 60 mg/dL). Giving dextrose through an IV keeps blood sugar in a safe range so the brain gets the fuel it needs to work. This prevents confusion, seizures, or coma from low blood sugar. The brain uses glucose as its main energy source and can't function without it. Typical regimen is a continuous drip of dextrose 10 percent in water (D10W), adjusted to keep glucose above 60 to 70 mg/dL.

Medications

N-acetylcysteine (NAC) · Antidote for acetaminophen poisoning

Acetaminophen (the medicine in Tylenol) is safe at normal doses. Your liver breaks it down using safe paths. But if you take too much — more than 7.5 grams at once in an adult, or more than 150 milligrams for every kilogram you weigh in a child — your liver runs out of room on the safe roads and switches to a back road. That back road makes a poison called NAPQI (say 'NAP-kwee'). Think of NAPQI like a tiny hot coal. It burns holes in liver cells. Your liver keeps a fire extinguisher on hand called glutathione (a small molecule made from three building blocks). Glutathione grabs every piece of NAPQI and carries it safely out of your body. But when you overdose, you make so much NAPQI that you run out of glutathione. Now the hot coals pile up and liver cells start to die. NAC fixes three things. First, NAC gives your liver the main piece it needs to rebuild glutathione — it turns into cysteine, which is one of the three building blocks glutathione is made from. Second, when glutathione is still too low, NAC itself

can grab NAPQI and carry it out. Third, NAC helps liver cells get more oxygen and calms down swelling inside the liver. Doctors give NAC through an IV into your vein using a three-bag plan: 150 milligrams per kilogram over 1 hour (the loading dose), then 50 milligrams per kilogram over the next 4 hours, then 100 milligrams per kilogram over 16 hours. That adds up to 21 hours total. You can also take NAC by mouth: 140 milligrams per kilogram as the first dose, then 70 milligrams per kilogram every 4 hours for 17 more doses (72 hours total). Start NAC if the acetaminophen level in the blood is above the treatment line on the Rumack-Matthew nomogram (a graph that shows if the level is dangerous based on how many hours have passed since swallowing the pills), or if the person comes in more than 24 hours after swallowing the pills, or if liver blood tests (ALT or AST) are rising. Keep giving NAC until the INR (a blood test that checks how well your blood can clot) drops below 2.0 and liver enzymes are falling. Activated charcoal (a black powder given by mouth or through a tube, 50 grams) can soak up acetaminophen pills still sitting in the stomach if you give it within 1 hour of the overdose, but once the drug is in the blood, charcoal cannot help — only NAC works then.

- 1.** Step 1: A person swallows a toxic dose of acetaminophen — more than 7.5 grams in an adult or more than 150 milligrams per kilogram in a child.
- 2.** Step 2: The liver tries to break down all the acetaminophen. Most goes through two safe paths (called glucuronidation and sulfation, which turn it into harmless forms that leave the body in urine), but a small amount goes through a third path run by an enzyme called CYP2E1 (a liver protein that changes chemicals).
- 3.** Step 3: CYP2E1 turns that small amount into NAPQI, a toxic molecule that acts like a hot coal inside the cell.
- 4.** Step 4: Normally, glutathione (the liver's main cleanup molecule made from three building blocks: cysteine, glutamate, and glycine) grabs every molecule of NAPQI and makes it safe by attaching to it. The NAPQI-glutathione bundle then leaves the body in urine.
- 5.** Step 5: In an overdose, so much NAPQI is made that glutathione gets used up faster than the liver can make more. Glutathione stores drop to less than 30 percent of normal within a few hours.
- 6.** Step 6: Free NAPQI floats around inside liver cells and sticks to important proteins and DNA, punching holes in the cell's machinery. This causes the cells to die. This death is called hepatocyte tissue death (necrosis).
- 7.** Step 7: Dead liver cells spill their contents into the blood. Blood tests (ALT and AST) shoot up, sometimes into the thousands.
- 8.** Step 8: NAC is given through an IV or by mouth and travels through the blood to the liver.
- 9.** Step 9: Inside liver cells, NAC is broken down and turned into cysteine, one of the three building blocks of glutathione.
- 10.** Step 10: The liver uses that cysteine to build fresh glutathione molecules.
- 11.** Step 11: New glutathione grabs leftover NAPQI and stops more damage.

- 12.** Step 12: When glutathione is still low, NAC itself can directly grab and neutralize NAPQI, acting as a backup fire extinguisher.
- 13.** Step 13: NAC also helps the mitochondria (the cell's power plants) keep making energy and reduces swelling and stress inside the cell.
- 14.** Step 14: Liver cells stop dying. Over weeks to months, healthy liver tissue grows back and replaces the dead cells.

SAFETY WATCH

Anaphylactoid reaction (looks and feels like an allergic reaction but is not a true allergy): Skin turns red and flushed, itching all over, blood pressure drops, wheezing or trouble breathing. This happens during the first (loading) infusion in 10 to 20 out of every 100 patients. The body releases histamine (a chemical that causes itch and swelling) even though this is not a real allergy. Stop the IV right away. Give diphenhydramine (Benadryl, an antihistamine that blocks the itch signal at histamine receptors on cells) and fluids through the IV to raise blood pressure. Once symptoms calm down, restart NAC at a slower drip rate. This is not a reason to stop NAC — the patient still needs it. · Nausea and vomiting with oral NAC: NAC tastes and smells like rotten eggs because it contains sulfur. Up to 30 out of every 100 patients throw up. Mix it with cola or juice to hide the taste, or give it through a nasogastric tube (a thin tube through the nose into the stomach). Give ondansetron (Zofran, a medicine that blocks the nausea signal at serotonin receptors in the brain stem and gut) 30 minutes before each dose. If the patient vomits within 1 hour of taking a dose, give that dose again. · Do not stop NAC at 21 hours just because the protocol says so: New guidelines from the American Association of Poison Control Centers (2022) and current expert consensus (UpToDate 2024, Toxicology and Applied Pharmacology 2023) say keep giving NAC until the INR is below 2.0, ALT is falling, the patient feels better, and acetaminophen is undetectable in the blood — especially if the liver is badly hurt. Some patients need 36 to 72 hours or longer. If liver enzymes are still rising or INR is still high at 21 hours, continue NAC at 100 milligrams per kilogram over 16 hours and repeat until labs improve. · Safe in pregnancy: NAC is FDA pregnancy category B, which means animal studies show no harm and it is considered safe. Treat pregnant women exactly the same as everyone else — acetaminophen overdose can kill both the mother and the baby. NAC crosses the placenta (the organ that feeds the baby inside the womb) and protects the baby's liver too. Do not delay treatment. · Watch for liver transplant need: While giving NAC, check the King's College Criteria every day. Call a liver transplant center right away if the blood pH (a measure of how acidic the blood is) is below 7.3 after giving IV fluids to fix dehydration, OR if all three of these are true: INR above 6.5, creatinine (a kidney test that shows if kidneys are failing) above 3.4 milligrams per deciliter, and Grade 3 or 4 hepatic encephalopathy (severe confusion or coma caused by liver failure and toxin buildup in the blood). These mean the liver is too damaged to recover on its own. Early transfer saves lives. · Fluid overload with IV NAC: The three-bag NAC protocol uses a lot of IV fluid — sometimes more than 1 liter. In small children or people with heart failure, this can overload the circulation and cause the lungs to fill with fluid (called pulmonary edema (fluid flooding the lungs)). Watch for fast breathing, low oxygen, and crackles when listening to the lungs. If this happens, slow the drip and give a diuretic (a water pill like furosemide that makes the kidneys get rid of extra fluid). You can also use a concentrated NAC protocol (same total dose, less fluid) in high-risk patients.

Red flags

- 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)

Nursing priorities

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. — 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). — 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. — 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.
4. Assess mental status every 2 to 4 hours—can the patient say their name, the date, and where they are? Watch for flapping tremor (asterixis) when the patient holds arms out with wrists bent back. — Hepatic encephalopathy (brain confusion from liver failure) means ammonia and toxins are building up in the blood because the liver cannot filter them. Early confusion can progress to coma within hours. This is a King's College Criterion for transplant and the patient needs ICU-level care.

5. Check for signs of bleeding—gums, bruising, pinpoint bleeding spots (petechiae) (tiny red dots on skin), blood in vomit or stool—and review INR and platelet results every 12 to 24 hours if liver injury is present. — The liver makes clotting factors II, VII, IX, and X. When these run out, INR climbs above 3 or 4 and the patient can bleed internally or externally. An INR over 6.5 at 48 hours or any INR over 3 with confusion are transplant criteria. We may need to give fresh frozen plasma or vitamin K.
6. Measure urine output every hour with a Foley catheter if the patient is critically ill; notify the provider if output drops below 0.5 milliliters per kilogram per hour for 2 hours in a row. — Acetaminophen and NAPQI damage kidney tubules (the filters inside kidneys) directly, and low blood pressure from liver failure reduces blood flow to kidneys. Acute kidney injury (creatinine rising, urine dropping) worsens survival and may need dialysis. Catching it early allows fluid resuscitation (giving intravenous saline) and stopping other kidney-toxic drugs.
7. Place the patient on continuous pulse oximetry and cardiac telemetry (heart-rhythm monitor); check a venous or arterial blood gas if the patient looks very sick, is breathing fast, or has a lactate over 3.5 or pH below 7.30. — Severe liver failure causes lactic acidosis (acid from oxygen-starved tissues) (lactate builds up because dying liver and muscle cells switch to anaerobic metabolism, making acid). A pH below 7.30 after resuscitation is a King's College Criterion for transplant. Breathing fast (respiratory compensation) is the body trying to blow off carbon dioxide to raise the pH.
8. Keep the patient NPO (nothing by mouth) if there is confusion, vomiting, or INR over 2.0, and consult the transplant hepatology team early if any King's College Criteria appear—pH below 7.30, INR over 6.5, or creatinine over 3.4 with grade III or IV encephalopathy. — Patients with high INR or encephalopathy can vomit and aspirate (breathe stomach contents into lungs), causing pneumonia or airway blockage. King's College Criteria predict death without transplant, so early consultation gives time to list the patient, find a donor liver, and arrange transfer to a transplant center.

Sources

- American Association of Poison Control Centers (AAPCC)
- American College of Medical Toxicology (ACMT) acetaminophen guidance
- American Association for the Study of Liver Diseases (AASLD) 2017 acute liver failure guideline
- Rumack-Matthew nomogram (standard acetaminophen toxicity treatment tool)

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