

Acute Liver Failure

When something kills most of your liver cells fast—acetaminophen overdose, a virus, or a toxin—your liver stops making the proteins that stop bleeding and stops cleaning ammonia (a brain poison), so you bleed and get confused at the same time, usually within days to weeks.

THE ONE-LINE TRUTH

Acute liver failure means most of your liver cells suddenly die within 26 weeks, stopping the liver from making clotting proteins (so you bleed easily) and clearing ammonia (so your brain becomes confused)—in someone whose liver was healthy before.

The chain — how it unfolds

1. Impaired blood clotting (Coagulopathy) (blood clotting failure) develops. — why: Massive hepatocyte death stops synthesis of vitamin K-dependent clotting factors (II, VII, IX, X) and factor V, so prothrombin time (PT, the time it takes blood to clot in a lab test) and INR (international normalized ratio, a standardized clotting score) rise above 1.5 within days. Bleeding risk increases from every needle stick, from the lining of the stomach and intestines (gastrointestinal mucosa), from the nose and gums, and from any site of trauma.
2. Hepatic encephalopathy (altered mental status and brain dysfunction) begins and progresses. — why: The dying liver cannot run the urea cycle to convert ammonia—produced in the gut by bacteria breaking down protein—into urea. Ammonia rises in the blood, crosses the blood-brain barrier, and poisons astrocytes (star-shaped brain support cells). Astrocytes swell and release glutamine, which further raises osmotic pressure inside the skull. Clinically this produces confusion (grade I), lethargy and asterixis, a flapping tremor of the hands (grade II), stupor, meaning very hard to wake (grade III), and coma (grade IV) over hours to days.
3. Low blood sugar (Hypoglycemia) (dangerously low blood sugar) occurs. — why: The liver normally maintains blood glucose between meals by breaking down stored glycogen into glucose (glycogenolysis) and making new glucose from lactate, amino acids, and glycerol (gluconeogenesis). When hepatocytes die, both pathways shut down and blood glucose drops below 70 mg/dL, sometimes to below 40 mg/dL, starving the brain of its primary fuel and worsening encephalopathy and risk of seizures.

4. Cerebral swelling (edema) (brain swelling) and intracranial high blood pressure (hypertension) (high pressure inside the skull) develop in severe cases. — why: High serum ammonia—often above 150–200 $\mu\text{mol/L}$ —plus inflammatory cytokines (tumor tissue death (necrosis) factor-alpha, interleukin-6) and astrocyte swelling cause the brain to swell. Intracranial pressure rises above 20–25 mmHg (normal is 5–15). If unchecked, this compresses the brainstem through the foramen magnum (the opening at the base of the skull), causing brain herniation, loss of brainstem reflexes (pupil response to light, gag reflex, cough reflex), and death.
5. Low blood pressure (Hypotension) (low blood pressure) and circulatory shock emerge. — why: Systemic vasodilation from nitric oxide and prostacyclin (vasodilator molecules released by dying hepatocytes) combined with third-spacing—fluid leaking from blood vessels into tissues—from low albumin (below 2.5 g/dL, normal is 3.5–5.0) drops systemic vascular resistance (the resistance arteries provide to blood flow). Mean arterial pressure falls below 65 mmHg. The heart initially compensates by increasing cardiac output, but eventually myocardial depression (heart muscle dysfunction from circulating toxins) and hypovolemia (low blood volume) cause distributive shock (from vasodilation) and hypovolemic shock (from fluid loss).
6. Acute kidney injury (AKI) develops. — why: Low blood pressure (Hypotension) reduces renal blood flow (perfusion) pressure (blood pressure reaching the kidneys) below the autoregulation threshold—around 80 mmHg systolic—causing prerenal waste buildup in the blood (azotemia) (rising blood urea nitrogen and creatinine from inadequate kidney blood flow). In 40–50% of cases, hepatorenal syndrome type 1 develops: intense renal vasoconstriction (kidney blood vessel narrowing) triggered by splanchnic vasodilation and activation of the renin-angiotensin-aldosterone and sympathetic nervous systems. Creatinine rises above 1.5–2.0 mg/dL and urine output falls below 400 mL per day.
7. Infection and sepsis become common complications. — why: Loss of liver synthesis of complement proteins (C3, C4), opsonins (immune proteins that tag bacteria for destruction), and acute-phase reactants (infection-fighting proteins) plus increased gut permeability (leaky gut allowing bacteria to enter the bloodstream via the portal vein) plus invasive lines—central venous catheters, urinary catheters, breathing tubes—create the perfect environment for pneumonia, spontaneous bacterial bloodstream infection, urinary tract infection, and invasive fungal sepsis, especially from *Candida* species. This occurs in 25–50% of patients and often worsens shock and triggers multiorgan failure.

Spot it — what you see, and why

- **Yellowing of the skin and eyes (Jaundice) (yellow skin, eyes, and under the tongue):** When liver cells die suddenly, they can no longer attach a sugar molecule (glucuronic acid) to bilirubin—a yellow-orange waste from broken-down old red blood cells—and cannot push it into bile. Both forms of bilirubin (the unattached and the attached) pile up in the blood. Once bilirubin levels go above about 3 (measured in mg/dL), the yellow waste spills into body tissues, staining the skin, the whites of the eyes, and the tissue under the tongue a yellow-orange color.
- **Confusion, sleepiness, or coma (hepatic encephalopathy):** The dying liver cannot clean poisons—especially ammonia from digested protein, sulfur-containing compounds called mercaptans, and metals like manganese—out of the blood. These toxins cross into the brain, poison the support cells (astrocytes) and nerve cells (neurons), and scramble the brain's chemical signals. At first the person gets confused and may sleep during the day and stay awake at night (grade I). Next comes extreme sleepiness and a flapping hand tremor (grade II). Then stupor—the person only wakes up if you cause pain (grade III). Finally, coma—no response at all (grade IV).
- **Easy bruising, tiny red spots on the skin, bleeding gums, nosebleeds, or blood in vomit or stool:** The liver makes most of the proteins (clotting factors II, V, VII, IX, and X) that stop bleeding. When the liver fails, these proteins vanish from the blood. Blood tests show the prothrombin time (PT) and INR (international normalized ratio) climb above 1.5—often as high as 2 to 6 or more. Now even tiny injuries—brushing teeth, inserting an IV, placing a feeding tube—cause bleeding that won't stop. Platelet counts also drop (often below 100,000 per microliter) because the spleen traps them and the liver stops making thrombopoietin (the hormone that tells bone marrow to make platelets), adding even more bleeding risk.
- **Pain or tenderness below the right rib cage:** When liver cells die quickly and the liver swells up with inflammation, the outer fibrous bag around the liver (called Glisson's capsule) stretches tight. This capsule is packed with pain nerves. The stretch causes a constant dull ache or sharp tenderness just below the right ribs. Taking a deep breath or pressing on the area makes the pain worse.
- **Nausea, vomiting, and complete loss of appetite:** Poisons like ammonia and waste products that should have been cleared by the liver, plus inflammatory messenger molecules (interleukin-1 and tumor tissue death (necrosis) factor-alpha), flood the bloodstream. These chemicals directly trigger the vomiting center in the brainstem (the chemoreceptor trigger zone in a spot called the area postrema) and shut down the appetite control centers in the hypothalamus (a deep brain region). The result is persistent nausea, frequent vomiting, and zero desire to eat.

- Flapping hand tremor when arms are held out (asterixis): High ammonia levels in the blood (usually above 100 micromol per liter) disrupt the circuits in the deep brain (thalamus and basal ganglia) that keep muscles contracted steadily. When you ask the person to hold their arms straight out with wrists bent back (like stopping traffic), the hands suddenly flap downward and then jerk back up every one to two seconds. This repeating flap is a sensitive sign that hepatic encephalopathy has reached grade II or higher.

Red flags — act now

- Stupor (arousable only to painful stimuli) or coma (no response to pain)—this is grade III or IV hepatic encephalopathy and signals high risk of brain swelling (cerebral swelling (edema)), pressure inside the skull rising above 20 mmHg, and the brain herniating (getting squeezed through the skull base). The person needs a breathing tube placed immediately, transfer to the ICU, and (in transplant centers) a device to monitor brain pressure.
- INR above 4.0 or active bleeding from the gut (vomiting blood, black tarry stool, or bright red blood from the rectum)—this means the blood has almost no clotting ability and bleeding can be deadly. Fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa must be given, and if bleeding is ongoing, a camera scope (endoscopy) must look inside the gut to find and stop the source.
- Blood sugar below 60 mg/dL despite continuous IV dextrose (sugar solution)—this means the liver has lost almost all ability to make new glucose (gluconeogenesis) or release stored glucose (glycogenolysis). Less than 10 percent of liver cells are still working. Without an emergency liver transplant, death is imminent.
- Creatinine above 2.0 mg/dL or climbing more than 0.3 mg/dL per day, plus very little urine —this strongly suggests hepatorenal syndrome type 1 or death of kidney tubule cells (acute tubular tissue death (necrosis)). Both mean multiple organs are failing. Without a liver transplant, 70 to 80 percent of patients will die.
- Blood pressure so low that it requires vasopressor drugs (norepinephrine or vasopressin) through an IV to keep mean arterial pressure at or above 65 mmHg—this is distributive shock and multiorgan dysfunction syndrome. The person must go to the ICU immediately for close monitoring and be evaluated urgently for emergency liver transplant. Without transplant, fewer than 20 out of 100 patients survive.

Treat it — in this order

1. N-acetylcysteine (NAC) intravenous infusion → NAC refills glutathione — the liver's main shield against acetaminophen breakdown products — cuts down damage from reactive oxygen molecules, and helps liver cells survive in acetaminophen overdose. It works best when started within 8-10 hours of taking the drug, but still helps even when started late. Per AASLD guidelines, NAC also improves survival without transplant in early-stage (grade I-II) brain dysfunction from non-acetaminophen acute liver failure.
2. Fresh frozen plasma, prothrombin complex concentrate, or cryoprecipitate — only for active bleeding or before procedures → These blood products replace clotting factors — proteins like II, VII, IX, X, and fibrinogen — that the dead liver cannot make, temporarily fixing the clotting problem to stop bleeding or allow safe procedures like placing a central IV line or brain pressure monitor.
3. Hyperosmolar therapy: mannitol 0.5-1 g/kg IV or 3% saline bolus for brain swelling → These agents increase the concentration of dissolved particles in blood, pulling water out of swollen brain tissue back into the bloodstream by osmosis — water moving from low to high concentration. This lowers pressure inside the skull and reverses brain compression temporarily. Target serum sodium 145-155 mEq/L and serum osmolality below 320 mOsm/kg per AASLD guidelines.
4. Urgent liver specialist consultation and transplant evaluation (King's College Criteria or MELD score) → Early transplant evaluation finds patients who meet criteria for listing. Per King's College Criteria for acetaminophen cases: pH below 7.30 after resuscitation, or INR above 6.5 plus creatinine above 3.4 mg/dL plus grade III-IV brain dysfunction. For non-acetaminophen cases: INR above 6.5, or any three of — age under 10 or over 40, non-A non-B hepatitis or drug reaction, yellowing of the skin and eyes (jaundice) over 7 days before confusion started, INR above 3.5, bilirubin above 17.4 mg/dL. Listing before irreversible multi-organ failure improves survival after transplant.
5. Continuous IV dextrose (D10 or D20) to keep blood glucose above 70 mg/dL → IV sugar replaces the glucose the failing liver cannot produce, preventing low blood sugar from injuring the brain and worsening confusion. Check blood glucose every 1-2 hours.

Your top priorities at the bedside

1. Check mental status every 1 to 2 hours using the Glasgow Coma Scale and document hepatic encephalopathy grade—alert (grade 0), confused (grade I–II), stuporous or only responding to pain (grade III), or no response to pain (grade IV)—and call the provider immediately if the grade worsens. — why: The brain swells (cerebral swelling (edema)) in 75 percent of people with grade III or IV encephalopathy because ammonia and other toxins leak through the blood-brain barrier, pulling water into brain cells. Swelling raises intracranial pressure (pressure inside the skull) above 20 mmHg, cutting off blood flow and causing brain herniation (the brainstem gets squeezed through the skull base), which stops breathing and heartbeat within minutes.
2. Keep the head of the bed elevated 30 degrees at all times, avoid tight cervical collars or neck flexion, keep the room quiet and lights dim, and give sedation medicines only as ordered—never give benzodiazepines like lorazepam or diazepam because they worsen encephalopathy. — why: Elevating the head 30 degrees helps venous blood (blood returning from the brain) drain by gravity, lowering intracranial pressure by 5 to 10 mmHg. Neck flexion kinks the jugular veins (large neck veins), trapping blood in the skull and raising pressure. Loud noise and bright light trigger agitation, which increases brain oxygen demand and worsens swelling. Benzodiazepines (sedative medicines) cannot be cleared by the failing liver and build up, deepening coma and making it impossible to assess mental status.
3. Check blood glucose by fingerstick every 1 to 2 hours and hang continuous IV dextrose (D10 or D20 solution) to keep glucose between 100 and 150 mg/dL—never let it drop below 60 mg/dL. — why: The liver stores glucose as glycogen (a starch) and releases it between meals to keep blood sugar steady. When liver cells die, glycogen stores run out within 12 hours, causing low blood sugar (hypoglycemia) (low blood sugar below 60 mg/dL). The brain uses glucose as its only fuel, so low blood sugar triggers seizures, more brain swelling, and permanent brain damage within 30 minutes.